



FIRST-line support for **A**ssistance in **B**reathing in **C**hildren
(**FIRST-ABC**) Feasibility Study: feasibility study for a
randomised trial of high flow nasal cannula (HFNC) versus
continuous positive airway pressure (CPAP) for non-invasive
respiratory support in critically ill children

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No conflicts of interest to declare.

Signatures

The Chief Investigator, Principal Investigators and Sponsor have discussed this protocol. All have agreed to perform the investigation as written and to abide by this protocol except in case of medical emergency or where departures from it are mutually agreed in writing.

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1 AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
Minor 1	V1.1	20/11/2015	P Ramnarayan R Canter	Minor changes to: <ul style="list-style-type: none"> Criteria to assess response in both treatment algorithms Weaning criteria in both treatment algorithms
1	V2.0	19/02/2016	R Canter P Ramnarayan P Mouncey	<ul style="list-style-type: none"> Added Section 11.4 Updated list of expected adverse events and reporting procedure Minor updates to treatment algorithms
2	V2.1	31/03/2016	R Canter P Ramnarayan	<ul style="list-style-type: none"> Added sections 9.4 and 9.5

2 ABBREVIATIONS

CI	Chief Investigator
CPAP	Continuous Positive Airway Pressure
CRF	Case Report Form
CTU	Clinical Trials Unit
GCP	Good Clinical Practice
GOSH	Great Ormond Street Hospital
GP	General Practitioner
HFNC	High Flow Nasal Cannula
ICF	Informed Consent Form
ISF	Investigator Site File
ICH	International Conference of Harmonisation
NHS	National Health Service
NRES	National Research Ethics Service
NRS	Non-invasive Respiratory Support
PI	Principal Investigator
PICU	Paediatric Intensive Care Unit
PIL	Participant/ Patient Information Leaflet
PSS:PICU	Parental stressor scale: PICU
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
SAE	Serious Adverse Event
SDV	Source Data Verification
SMH	St Mary's Hospital
SOP	Standard Operating Procedure
TMF	Trial Master File
UCL	University College London

3 STUDY SYNOPSIS

Title (Acronym)	Feasibility study for a randomised trial of high flow nasal cannula (HFNC) versus continuous positive airway pressure (CPAP) for non-invasive respiratory support in critically ill children (FIRST-ABC Feasibility Study)
Sponsor name	Great Ormond Street Hospital NHS Foundation Trust
Primary objective	To demonstrate the feasibility of an RCT comparing HFNC with CPAP in critically ill children
Secondary objective (s)	<ol style="list-style-type: none"> 1. To collect data regarding rate of intubation/re-intubation in children receiving HFNC and CPAP 2. To collect data regarding safety such as occurrence of air-leak and nasal/facial trauma in children receiving HFNC and CPAP 3. To collect data regarding secondary outcomes such as effect of the intervention on oxygenation, work of breathing and patient comfort, clinician and parent satisfaction, and length of ICU stay and length of ventilation in children receiving HFNC and CPAP
Study Design	Randomised, open-label feasibility trial
Study Endpoints	Demonstration of feasibility of an RCT
Sample Size	120 patients
Summary of eligibility criteria	<ol style="list-style-type: none"> 1. Term newborn (>36 weeks corrected gestational age) to 15 years inclusive 2. Requiring/expected to require non-invasive respiratory support 3. Satisfying study criteria for hypoxia, respiratory acidosis and respiratory distress
Intervention	High flow nasal cannula therapy versus continuous positive airway pressure
Procedures: Screening & enrolment	Clinical/research teams will screen patients for study eligibility. Clinical/research nurses will consent parents/guardians to enrol patients into the study. A mixed model of consent (prospective and deferred) will be used as appropriate
Baseline assessments	Physiological parameters related to oxygenation, ventilation, and work of breathing
Treatment period	Until clinical improvement as guided by study algorithm
End of Study	Date of PICU discharge of last recruited patient

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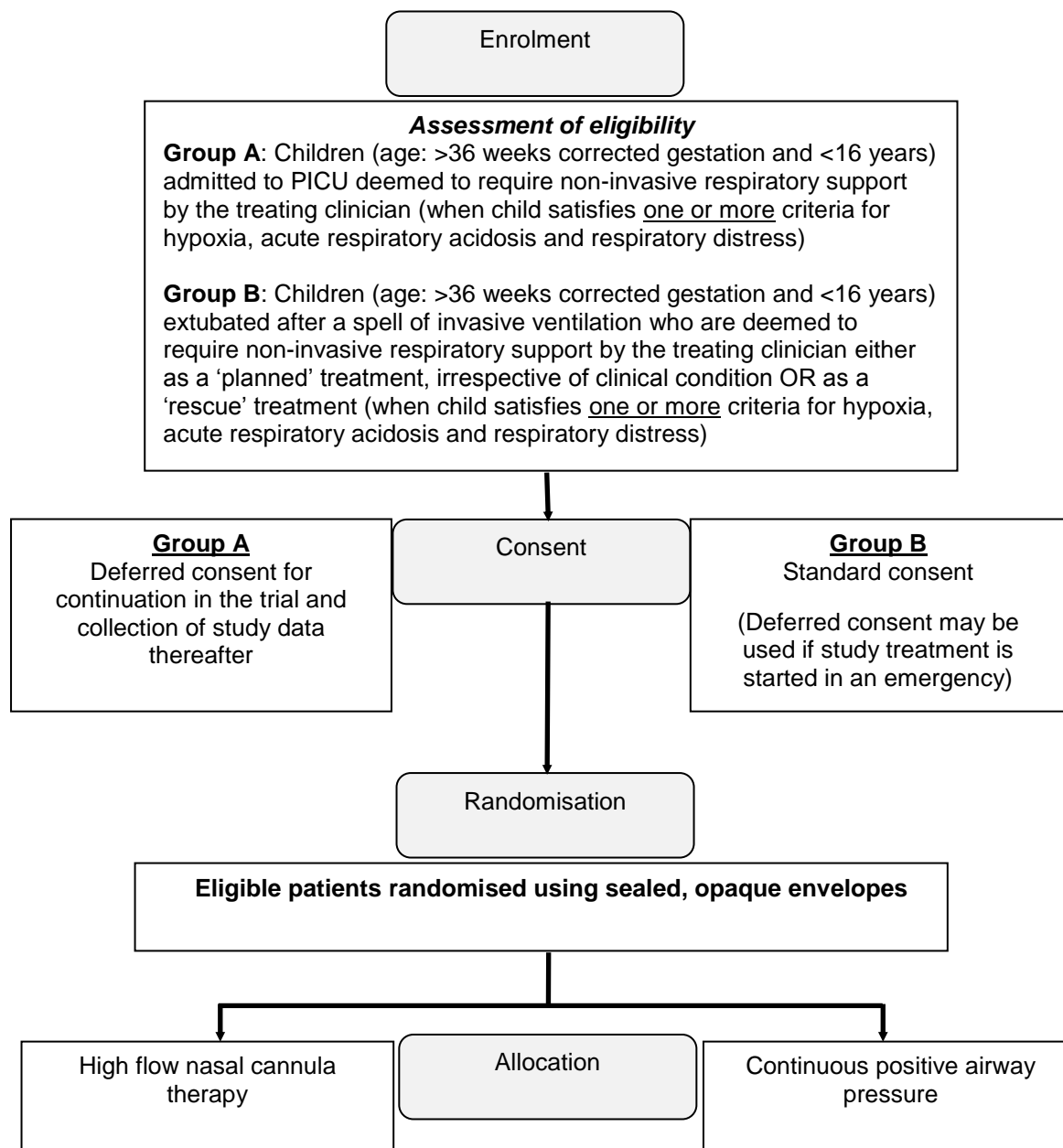
4 SUMMARY

Breathing support is the most common intervention provided to critically ill children in a paediatric intensive care unit (PICU). Although invasive breathing support (delivered through a tracheal tube) is lifesaving, concerns regarding its risks (infection and lung damage) have prompted greater use of non-invasive respiratory support (NRS). However, there is little scientific evidence to guide PICU clinicians on the comparative effectiveness of the commonly used modes of NRS.

In this feasibility study, we are testing whether it is possible to conduct a randomised clinical trial comparing two modes of NRS: continuous positive airway pressure (CPAP), which has been used for over two decades, and high flow nasal cannula (HFNC), a newer method of respiratory support. We do not know for sure how useful HFNC is in critically ill children because there is no published research comparing it with CPAP. However, since HFNC is easier to use and better tolerated by children, many hospitals are now using HFNC instead of CPAP. Before HFNC is widely adopted, a clinical trial to establish its role in the management of critically ill children is urgently needed.

As part of this study, we will randomly allocate children deemed to require NRS by their treating clinician to either HFNC or CPAP. We will mainly assess whether sufficient number of children can be recruited to the trial, whether clinicians are willing to randomise children, and test the proposed treatment pathways for CPAP and HFNC. The trial will run over 6 months, and recruit 120 sick children from three NHS hospitals. We will seek consent from parents/guardians for their children to be included in the study, usually before CPAP or HFNC is started, unless emergency life-saving treatment is required, in which case we will defer consent until there is more time to discuss the study with parents/guardians.

5 STUDY FLOW CHART



6 BACKGROUND

6.1 Introduction

Each year, over 18,000 children are admitted to paediatric intensive care units (PICUs) in the United Kingdom (UK).[1] Irrespective of the primary reason for admission (respiratory or otherwise), respiratory support is the most common intervention undertaken in PICU. National audit data from the UK Paediatric Intensive Care Audit Network (PICANet) demonstrate that nearly 75% of admissions received respiratory support, either invasively (via an endotracheal tube or tracheostomy) and/or non-invasively, during their PICU stay.[2]

Although invasive ventilation is lifesaving, non-invasive respiratory support (NRS) has several advantages, such as the ability to avoid patient sedation, allowing the patient to spontaneously breathe and cough, and minimising the risk of ventilator-associated events.[3] Over the past two decades, concerns regarding ventilator-induced lung injury and nosocomial infections from invasive ventilation have resulted in greater adoption of NRS in adult, paediatric and neonatal intensive care settings. In neonatal and adult intensive care, evidence from randomised controlled trials (RCTs) demonstrates that early use of NRS reduces the need for endotracheal intubation and ventilation, and improves patient outcomes in specific patient subgroups.[4-6] However, a recent Cochrane review highlighted a scarcity of such evidence in the PICU setting.[7]

Despite the lack of evidence from RCTs, NRS is used frequently in critically ill children with acute respiratory failure, either to:

- A. prevent progression to intubation and invasive ventilation (as 'step-up' treatment), or
- B. to prevent re-intubation after being extubated following a spell of invasive ventilation (as 'step-down' treatment).[8]

Data from PICANet suggests that nearly a quarter of all children receiving respiratory support are managed using NRS, either as 'step-up' and/or 'step-down' treatment.

6.2 Current practice

Several modes of NRS are currently available, and are used according to clinician preference rather than based on evidence.

6.2.1 Continuous positive airway pressure (CPAP)

CPAP is the most commonly used first-line mode of NRS. CPAP can be provided via a variety of patient interfaces (e.g. face mask, nasal prongs, helmet); however, its success is crucially dependent on maintaining a constant positive pressure in the patient's airway.[9] In practice, the effective use of CPAP is limited by two main problems: a) the need for a tight-fitting patient interface to avoid leakage of gas from the ventilator circuit, and b) the small but significant risk of serious complications such as pneumothorax or pneumomediastinum. The former causes the patient discomfort/agitation and nasal/facial pressure sores with prolonged use, frequently leading to CPAP treatment failure. The latter usually necessitates close patient monitoring and a high level of skilled nursing input.

6.2.2 High Flow Nasal Cannula therapy (HFNC)

Over the past decade, a novel mode of NRS - heated-humidified high flow nasal cannula therapy (HFNC) - has rapidly gained popularity in the PICU setting. HFNC involves the administration of a mixture of oxygen and air at high gas flow rates (roughly 8-10 times the

patient's normal minute volume). Through a combination of mechanisms such as washout of the nasopharyngeal dead space, lung mucociliary clearance, reduction in airway resistance, and generation of positive airway pressure, HFNC has been shown to be effective in managing acute respiratory failure from various causes.[10] Despite the absence of RCT evidence to support its effectiveness, HFNC has become popular due to its ease of use.[11] HFNC does not require a tight seal around the face/nose, and its patient interface (nasal prongs) appears to be well tolerated by children.[12]

6.3 Current evidence

6.3.1 RCTs

A recent systematic review showed that the clinical effectiveness of HFNC compared with other forms of non-invasive respiratory support, such as CPAP, has not been studied in an RCT performed in the PICU setting.[13] In one small RCT performed in a paediatric cardiac surgical population, children extubated following surgery were randomised to HFNC or standard oxygen therapy – there was no difference in the post-extubation pCO₂ level between the two groups.[14]

RCTs performed in premature newborns and in adult critical care have shown conflicting results. Three unblinded RCTs comparing HFNC with CPAP for respiratory support in premature newborns have been published so far. In a study involving 432 newborns (CPAP: 220; HFNC: 212), Yoder *et al* did not find a significant difference between the groups for the primary outcome of intubation within 72 hours (23/212 [10.8%] vs. 18/220 [8.2%], $p = 0.34$).[15] In an RCT involving 303 ventilated newborns <32 weeks gestation, Manley *et al* showed that HFNC was non-inferior to CPAP for post-extubation respiratory support using a primary outcome of treatment failure within 7 days (34.2% HFNC versus 25.8% CPAP). The non-inferiority margin was set at a wide 20%, which was considered a limitation of the study.[16] Collins *et al* enrolled 132 ventilated newborns <32 weeks gestation into an Australian RCT, and showed no difference between the groups in terms of the primary outcome of extubation failure in the first 7 days (15/67 [22.4%] vs. 22/65 [33.8%]).[17] There is an ongoing multicentre, international RCT in premature newborns comparing HFNC with CPAP as primary respiratory support started immediately after birth; this study is currently recruiting patients in Australia and Norway.[18]

Two large RCTs from adult ICU have been published recently, both comparing HFNC with non-invasive positive pressure ventilation (CPAP or bilevel positive airway pressure, BiPAP). In a trial conducted in French ICUs, 310 adults with hypoxaemic respiratory failure were randomised to three groups: HFNC, standard oxygen using facemask, or to non-invasive ventilation. The primary outcome of proportion of patients intubated at day 28 was not different between the groups (38% for HFNC and 50% for NIV, $p = 0.18$). However, the number of ventilator-free days at day 28 was significantly higher in the HFNC group (24 +/- 8 days vs. 19 +/- 12 days in the NIV group, $p = 0.02$). The hazard ratio for death at 90 days was higher for NIV compared to HFNC (2.50, 95% CI 1.31 to 4.78, $p = 0.006$).[19] In a non-inferiority RCT performed in France involving patients after cardiothoracic surgery, HFNC was not shown to be inferior to BiPAP (treatment failure occurred in 21% of HFNC patients compared to 21.9% of BiPAP patients, $p = 0.003$).[20]

6.3.2 Observational studies

There is evidence from physiological studies to support HFNC use in critically ill children. In one of the first such studies performed in children, Spentzas *et al* showed that HFNC was associated with significant improvement in the respiratory distress score within the first 60-90 minutes of initiation, with sustained improvement demonstrated over the subsequent 8-12

hours. Similarly, oxygen saturation increased significantly within the first 60-90 minutes and continued to rise by 8-12 hours. There was a direct, albeit non-linear, relationship between patient weight and positive pressure generated in the airway during HFNC use. COMFORT score (measuring patient tolerance of the treatment) improved after starting HFNC.[21] In subsequent work, Milesi *et al* showed in infants with bronchiolitis that a gas flow rate of 2 L/kg/min was associated with generation of positive airway pressure throughout the respiratory cycle, and HFNC use resulted in improvement in respiratory distress and effort.[22] Other studies have confirmed these observations. Hough *et al* showed recently that end-expiratory lung volume measured by electrical impedance tomography was higher when infants with bronchiolitis were managed on 8 L/min HFNC flow ($p < 0.01$), with higher gas flow rates showing improvement in respiratory rate, oxygen saturation and oxygen requirement.[23] Similarly, Rubin *et al* showed in a group of 25 critically ill children that a flow rate of 8 L/min (compared to lower gas flow rates) resulted in significant improvement in work of breathing.[24]

Observational studies also support the use of HFNC in critically ill children. Schibler *et al* showed that the rate of intubation/invasive ventilation fell dramatically in their PICU coinciding with the adoption of HFNC over a period of 5 years (2005-2009). The overall rate of intubation/invasive ventilation for children managed on HFNC during this period was 12% (4% for infants with bronchiolitis); there was a significant reduction in the rate of intubation in infants with bronchiolitis from 37% in 2005 to 7% in 2009.[25] In a similar comparison, McKiernan *et al* showed that compared to a winter season in which HFNC was not used, the rate of intubation for infants with bronchiolitis fell from 23% to 9% with the use of HFNC ($p = 0.04$). Median length of ICU stay fell from 6 to 4 days after the introduction of HFNC.[26] In a prospective pilot study in infants with bronchiolitis, Mayfield *et al* showed that response to HFNC could be identified within the first 60 min of treatment, with non-responders less likely to demonstrate a reduction in heart rate and respiratory rate with treatment. Compared to a historical cohort, infants managed on HFNC were four times less likely to need admission to a PICU ($p = 0.04$).[27] Similar findings were observed by Abboud *et al* in bronchiolitis, who showed that a higher pCO_2 level at the time of starting HFNC and lack of reduction in heart rate after starting treatment were both predictive of treatment failure.[28]

However, not all studies have reported beneficial effects with the use of HFNC. In a retrospective study, Metge *et al* showed that no differences could be found between the 19 infants with bronchiolitis who received CPAP in one winter season and the 15 infants who received HFNC in the next winter season in terms of length of stay, oxygenation, maximal heart rate, respiratory rate or rate of intubation.[29] Worryingly, there is evidence from at least one observational study in critically ill adults that HFNC may delay intubation/invasive ventilation and increase mortality.[30] There have also been concerns regarding the complications of HFNC, namely air-leak (pneumothorax/pneumomediastinum), nosocomial infection, and abdominal distension. In a case series of 3 patients, Hegde *et al* reported serious air-leak complications in children ranging from a 2-month old to a 16-year old.[31] A report of pneumocephalus and pneumo-orbitis has also been reported in a premature infant.[32] In 2005, an outbreak of nosocomial infection from an unusual organism (*Ralstonia* species) led to a manufacturer-led device recall of Vapotherm 2000i.[33, 34] Although no further such reports have been published, nosocomial infection remains a risk with the use of HFNC. Abdominal distension is also a reported risk of the treatment, and may compromise the use of HFNC in particular subgroups of patients, such as post-abdominal surgery.[14, 35]

6.4 Rationale for the study

Although HFNC appears to be used widely in critically ill children, there is no RCT evidence to support its clinical effectiveness.

6.4.1 Benefits of HFNC

There are significant clinical benefits associated with the use of HFNC: it appears to be much more comfortable for the child and associated with a low risk of complications. As such, it may have significant advantages as the first-line mode of NRS in terms of a) reducing treatment failure, and therefore the need for invasive ventilation; b) improving patient comfort and the ability for parents to better interact with their child; and c) reducing PICU length of stay by allowing the child to be safely cared for in a ward bed while still receiving respiratory support.

6.4.2 Risks

Concerns exist regarding the safety of HFNC (risk of air-leak syndromes, nosocomial infections, and abdominal distension) and inadvertent adverse effects on patient outcomes (delaying invasive ventilation and prolonging length of ICU or hospital stay).

Before an expensive health technology such as HFNC is adopted more widely, it is crucial that evidence from a well-conducted RCT is available. It is also important that any evidence is generated in a timely fashion, since loss of clinical equipoise regarding the risks and benefits of HFNC is already occurring among clinicians.[36] This randomised feasibility study will compare the two most commonly used modes of non-invasive respiratory support (CPAP and HFNC) in the PICU setting, and serve as a precursor to a future large national RCT.

7 STUDY OBJECTIVES AND OUTCOMES

Objectives	Outcome Measures/Endpoints
<p>Primary Objective</p> <p>Determine the feasibility of an RCT of HFNC versus CPAP in critically ill children</p>	<ol style="list-style-type: none"> 1) Assess the number of eligible patients in Group A (step-up) and Group B (step-down) 2) Assess the acceptability of using a mixed model of consent (prospective and deferred) 3) Assess the feasibility of randomising at least 50% of eligible patients 4) Test the practical aspects of implementing the study protocol in terms of initiation, maintenance and weaning of the study intervention 5) Assess whether a modified COMFORT score (COMFORT score minus the respiratory component) can be used to measure patient tolerance to CPAP/HFNC 6) Assess the feasibility of using the Parental Stressor Scale: PICU (PSS:PPICU) to measure parental stress 24 hours after the initiation of CPAP/HFNC
<p>Secondary Objectives</p> <p>Determine the rate of intubation</p> <p>Determine the rate of treatment failure</p> <p>Assess safety</p> <p>Assess physiological effects</p> <p>Assess effects on patient outcome</p>	<ol style="list-style-type: none"> 1) Proportion of children randomised to the intervention or control who need intubation (Group A) or re-intubation (Group B) within 72 hours of randomisation 2) Proportion of children randomised to the intervention or control who fail the assigned treatment and require either crossover or escalation to other forms of ventilation within 72 hours of randomisation 3) Number of children who experience pre-specified adverse events (pneumothorax, pneumomediastinum, nasal or facial trauma, abdominal distension, nosocomial infection) during the period they are receiving non-invasive respiratory support 4) Changes in oxygenation, pCO₂ levels, heart rate, respiratory rate, and work of breathing in the first 24 hours after the initiation of CPAP/HFNC 5) Length of PICU and hospital stay, length of invasive ventilation, length of non-invasive support, ventilator-free days at day 28, PICU mortality, hospital mortality

7 STUDY DESIGN AND SETTING

7.1 Study design

This is a feasibility study. It will be a randomised, controlled, open-label clinical trial comparing HFNC with CPAP as the first-line non-invasive respiratory support modality in critically ill children.

7.2 Study setting

Patients will be recruited at three, diverse PICUs in London (Great Ormond Street Hospital, St. Mary's Hospital, and Royal London Hospital). Together, the three PICUs admit around 2500 children annually. The use of NRS is variable on the units (between 15% and 43% of admissions) owing to differences in availability of beds for high dependency care. All units have access to both modes of NRS (CPAP and HFNC).

8 STUDY POPULATION

The study will be conducted in critically ill children at the three participating PICUs.

8.1 Inclusion Criteria

Pragmatic inclusion criteria will be used. In order to minimise variation in practice between and within centres, predefined, objective criteria are specified to provide clear directions to clinicians to guide the decision on when to start NRS.

Eligible patients will fall into one of two groups:

Group A (Step-up)

1. Age >36 weeks corrected gestational age and <16 years, AND
2. Deemed to require non-invasive respiratory support by the treating clinician for an acute illness, AND
3. Satisfies one or more of the following criteria:
 - a. Hypoxia (oxygen saturation <92% in $\text{FiO}_2 >0.40$, or equivalent). FiO_2 of 0.40 roughly equates to standard unhumidified nasal cannula oxygen delivered at 6 L/min or oxygen delivered via facemask without a rebreather bag at 6-10 L/min
 - b. Acute respiratory acidosis ($\text{pH} <7.3$ with a concomitant $\text{pCO}_2 >6.5$ kPa)
 - c. Moderate respiratory distress (use of accessory muscles, subcostal and intercostal recession, tachypnoea for age, grunting)

Group B (Step-down)

1. Age >36 weeks corrected for gestation and <16 years, AND
2. Deemed to require non-invasive respiratory support by the treating clinician after extubation, following a spell of invasive ventilation:
 - a. Either immediately after extubation as a 'planned' procedure, irrespective of clinical condition ('planned') OR
 - b. Prompted by deterioration in clinical condition within 72 hours after extubation ('rescue'). Clinical parameters to assess the need for NRS in this situation will be similar to point 3 in Group A

8.2 Exclusion Criteria

Children who:

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/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 non-invasive ventilation prior to PICU admission
7. Have been managed on either HFNC and/or CPAP (or other form of non-invasive ventilation such as BiPAP) in the preceding 24 hours
8. Have been previously recruited to this study during the same PICU admission
9. Cannot be treated with HFNC
 - a. Unavailability of appropriate sized nasal prongs
 - b. Unavailability of HFNC device
10. Cannot be treated with CPAP
 - a. Unavailability of right size of face mask, prong or other patient interface

- b. Unavailability of CPAP device

9 RECRUITMENT AND RANDOMISATION

A flow diagram according to the CONSORT statement is provided in Section 5.

9.1 Screening and Eligibility assessment

Patients admitted to study PICUs will be assessed by clinical and/or the research nurse teams to identify potentially eligible study participants. Screening procedures will be different for Groups A and B:

Group A: All new admissions to the PICU will be screened for study eligibility by the clinical/research team.

Group B: All invasively ventilated patients on the PICU will be screened on a daily basis by the clinical and/or research nurse teams to identify children who are planned for extubation. The treating clinician will be approached to ascertain 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 by the research nurse team.

9.2 Recruitment and Informed Consent

Patients in Group A and B will be recruited using different procedures. 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.

9.2.1 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. This will make 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, once a patient is identified as being eligible for the trial (i.e. satisfies inclusion and exclusion criteria), they will be randomised and the randomly assigned treatment (CPAP or HFNC) will be applied as soon as possible. Since both modes of NRS (CPAP and HFNC) are relatively safe, commonly used in clinical practice and only determined by individual clinician preferences, patients should not be disadvantaged in any way by this procedure.

Consent in this situation will be deferred. 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 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. It will usually not be possible to seek consent from the children themselves due to their critical illness. If written consent is provided, the patient will be followed up in the trial. If written consent is not provided, see section 9.3.

9.2.2 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, irrespective of the child's clinical condition, 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.

Consent will be obtained by clinical/research team members who have undergone GCP training. If new safety information results in significant changes in the risk/benefit assessment, the consent form will be reviewed and updated if necessary and subjects will be re-consented as appropriate.

9.3 Non-consent

If consent is not provided for patients in Group B, they will not be randomised to the trial. In order to monitor non-consent, a minimal dataset will be collected for each patient approached but not randomised: a) Study site; b) Date/time approached; c) Reason not randomised (if parents/guardians willing to provide reason for non-consent).

If consent is not provided for patients in Group A following randomisation, no further data will be collected from the child. The child will be recorded as not consented. Data collected up to the point of parental refusal of consent will be used. Following non-consent, the choice of whether to continue on the assigned mode of NRS or switch to an alternate mode of NRS will be made by the treating clinician (as per usual practice). In order to monitor non-consent, a minimal dataset will be collected for each patient approached but not consented: a) Study site; b) Date/time randomised; c) Randomised intervention (including whether started on assigned intervention or not); d) Reason not consented (if parents/guardians willing to provide reason for non-consent).

9.4 Death prior to consent being sought

In the situation where deferred consent is to be sought but a patient dies before the parents/guardians have been approached, 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.

9.5 Discharged prior to consent being sought

In the unlikely situation where deferred consent is to be sought but a patient is discharged from hospital before the parents/guardians have been approached, the parents/guardians will be sent a covering letter, personalised by the most appropriate clinical team member, and a copy of the participant information sheet and consent form (postal version) by post as soon as possible after discharge. Where possible, the clinical team member should already be known to the family. The letter will explain how to opt out of the study, direct them to the information sheet for detailed information on the study and provide telephone contact details if parents/guardians wish to discuss the study with a member of the site research team.

If there is no response after four weeks of sending the initial letter, a follow-up letter along with the information sheet and consent form (postal version) will be sent. This second letter will provide the same information as the first letter. In addition, this letter will also confirm that if no consent form is received within four 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.

9.6 Randomisation

Randomisation will be performed as soon as possible after identifying the child as being eligible for the study (no later than 24 hours). Pre-randomisation 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.

9.7 Blinding

The intervention in this study cannot be blinded, since both treatments (CPAP and HFNC) are already used in practice and recognisable by clinical staff.

9.8 Discontinuation/Withdrawal of Participants from Study

Participants may be withdrawn from the study at any time if parents/guardians choose not to continue their child's involvement in the research. Parents/guardians are free to withdraw their consent at any stage and will not need to provide a reason for withdrawal from the study. Study data collected on patients who withdraw from the study (up to the point of withdrawal) will be included for analysis unless parents/guardians do not consent to this.

Participants may also be withdrawn from the study by the investigators if a serious adverse event identified to be related to the study treatments occurs. In this case, patients will be followed up until discharge from the PICU and study data will be collected for analysis. Reason(s) for withdrawal from the study will be recorded on the CRF.

9.9 Definition of End of Study

The end of the study will be the PICU discharge date (or date of death) of the last participant.

10 DETAILS OF INTERVENTION

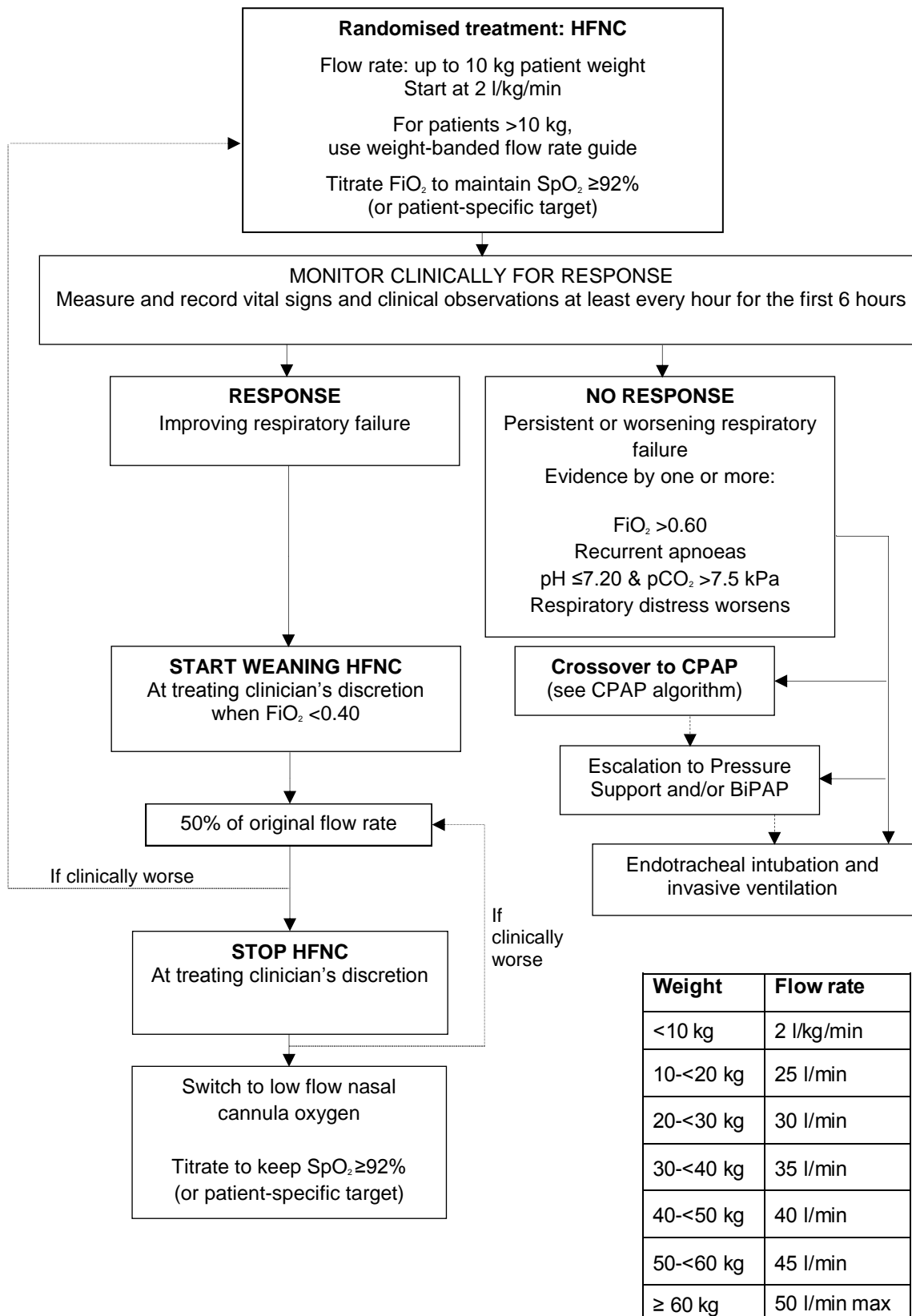
10.1 High Flow Nasal Cannula

A heated, humidified, HFNC device will be used to deliver a prescribed gas flow rate for the duration that the patient needs non-invasive respiratory support. The study protocol specifies clinical criteria and procedures for the initiation, maintenance and weaning of HFNC (see algorithm below).

Staff in all participating units already use HFNC – therefore, no additional training will be provided for the study. Since the medical device and the nasal interface that delivers HFNC is easily distinguishable from the CPAP device and its interface, it will not be possible to blind the subject or the clinical staff; however, study investigators, including those performing the final analysis, will be blinded to the allocation.

As per current practice, clinicians in the study will be able to stop HFNC and crossover to CPAP if clinically deemed necessary. Pre-specified objective criteria to identify non-responders to HFNC will be provided in the study protocol as a guide for clinicians considering crossover from HFNC to CPAP. Reasons for crossover will be recorded. Crossover patients will remain in the study and continue to be monitored until they are off respiratory support.

STUDY ALGORITHM (HFNC)

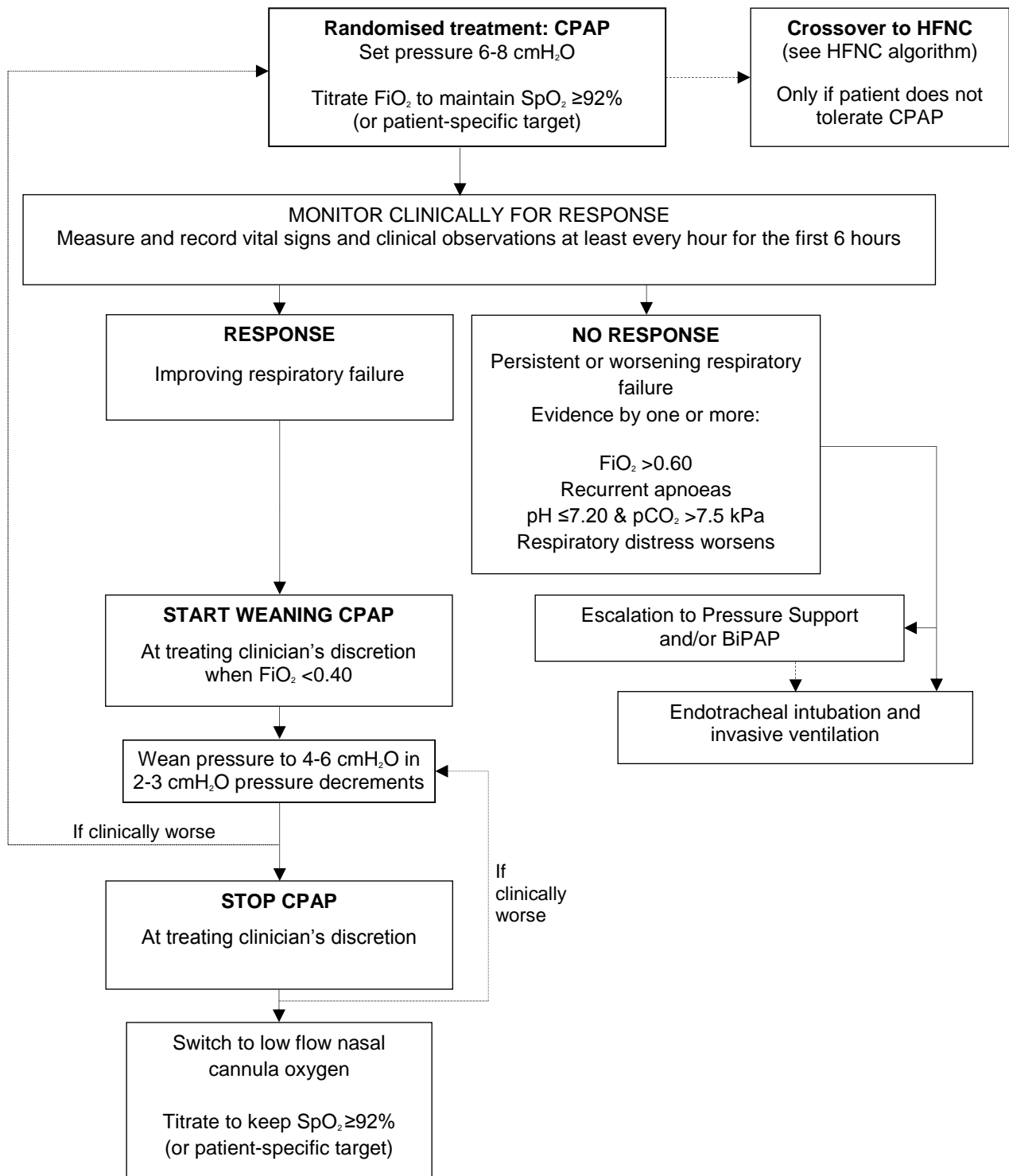


10.2 Continuous positive airway pressure

Conventional nasal CPAP will be provided using a set expiratory pressure of 6-8 cm H₂O for the duration that the infant needs non-invasive respiratory support. In order to standardise treatment, the study protocol specifies clinical criteria and procedures for the initiation, maintenance and weaning of CPAP (see algorithm below). Staff in all participating units already use CPAP – therefore, no additional training will be provided for the study.

In current practice, it is not usual for clinicians to switch from CPAP to HFNC other than for reasons of patient intolerance to CPAP. Therefore, in this study, 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.

STUDY ALGORITHM (CPAP)



10.3 Clinical management

Recruited patients will be treated according to the study protocol with respect to the provision of non-invasive respiratory support. Due to the pragmatic nature of the trial, all other treatment in both groups will be as per standard practice at the study sites (e.g. use of medications such as bronchodilators or hypertonic saline, physiotherapy schedule, feeding route/regime, and level of nursing care assigned to the patient). Infants who fail to improve on CPAP or HFNC may be switched to other non-invasive modes of ventilation such as BiPAP or pressure support (before intubation and ventilation) according to the treating clinician's discretion.

11 ASSESSMENTS AND PROCEDURES

A full schedule of assessments is provided in a table below. In summary:

11.1 Baseline assessments

Patient demographics will be assessed at the time of establishing eligibility for the study (e.g. age, gender, primary reason for PICU admission, co-morbidities). In addition, routinely performed clinical observations related to oxygenation status (SpO_2 , FiO_2), ventilation status (pH, pCO_2), heart rate, respiratory rate, and clinical signs of respiratory distress (subcostal and intercostal recessions, grunting, use of accessory muscles) will be assessed.

Physiological parameters (as described above) will also be assessed at the time of randomisation. If the assigned mode of NRS is not commenced soon after randomisation, these parameters will also be assessed immediately prior to starting NRS.

11.2 Assessments to determine clinical response

Clinical assessment to determine whether a patient has responded to NRS or not is usually performed at least on an hourly basis in the PICU. For the study, clinical observations related to oxygenation status (SpO_2 , FiO_2), ventilation status (pH, pCO_2 , serum bicarbonate, base excess), heart rate, respiratory rate, and clinical signs of respiratory distress (subcostal and intercostal recessions, grunting, use of accessory muscles) will be assessed on an hourly basis for the first 6 hours, at 12 hours, and 12 hourly thereafter until the end of treatment (or crossover, escalation, or intubation/ventilation).

11.3 Assessment of patient comfort

The COMFORT score (excluding the respiratory component) will be assessed hourly for the first 6 hours, then at 12 hours, and 12-hourly thereafter until the end of treatment (or crossover, escalation or intubation/ventilation).

11.4 Assessment of consent process

A consent questionnaire [37] will be administered to parents/guardians who both do and do not consent to FIRST-ABC (see Appendix A). This questionnaire was developed for and used in similar paediatric RCTs (e.g. the CATCH trial (ISRCTN34884569) and the EcLiPSE trial (ISRCTN22567894)).

11.5 Assessment of parental stress

The validated instrument PSS:PICU will be administered to parents/guardians at 24 hours following initiation of NRS.[38]

11.6 Assessment of safety

Adverse events whose causal relationship to the trial intervention (CPAP or HFNC) will be assessed and judged by the investigator to be possibly, probably, or almost certainly related to the intervention, occurring anytime from the initiation to the end of the intervention, will be reported as they arise (see Section 15).

SCHEDULE OF PROCEDURES

	PICU admission OR Prior to extubation	Study entry	Hourly for the first 6 hours	At 12 hours, then 12 hourly until end of treatment	Hospital discharge (or death)	At day 28
Screening for eligibility	•					
Informed consent		•				
Randomisation		•				
Treatment (HFNC or CPAP)			•	•		
Physiology			•	•		
COMFORT score			•	•		
PSS:PICU & consent questionnaire (at 24 hours only)				•		
Hospital stay data					•	
Safety monitoring						•

12 STATISTICAL CONSIDERATIONS

12.1 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.

12.2 Sample size

Since this is 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 (i.e. we expect to see eight intubation events), and a 10% rate of re-intubation for Group B (i.e. we expect to see eight re-intubation events).

13 ETHICAL CONSIDERATIONS

The trial will abide by the principles of the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP), World Medical Association Declaration of Helsinki (1964) and Tokyo (1975), Venice (1983), Hong Kong (1989) and South Africa (1996). The relevant approvals will be obtained. The specific ethical issues are:

13.1 Clinical equipoise

Although HFNC is being used in critically ill children, there is no RCT evidence to support its clinical effectiveness, especially in comparison to CPAP. There are significant potential benefits associated with the use of HFNC: it appears to be much more comfortable and appears to be associated with a low risk of complications. Concerns regarding its safety (risk of air-leak syndromes, nosocomial infections, and abdominal distension) and inadvertent adverse effects on patient outcomes (delaying invasive ventilation and prolonging length of ICU or hospital stay) have also been reported.

In the absence of evidence supporting one treatment over the other, clinicians are currently using CPAP and HFNC interchangeably based on personal preference and anecdotal practice. Therefore, before an expensive health technology such as HFNC is adopted more widely across the NHS, it is crucial that evidence from a well-conducted RCT is available to clarify its effectiveness compared to established practice (CPAP). It is also important that evidence is generated in a timely fashion, since loss of clinical equipoise regarding the risks and benefits of HFNC is already occurring among clinicians.[36]

Our feasibility study will compare the two most commonly used modes of non-invasive respiratory support (CPAP and HFNC) in the PICU setting, and inform the design and conduct of a future national RCT.

13.2 Consent in an emergency situation

Many of the children participating in the study will be very ill and require treatment urgently. Therefore, we will employ a mixed model of consent in this study as described in Section 9.2. In summary:

13.2.1 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. This will make 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, once a patient is identified as being eligible for the trial (i.e. satisfies inclusion and exclusion criteria), they will be randomised and the randomly assigned treatment (CPAP or HFNC) applied as soon as possible. Since both modes of NRS (CPAP and HFNC) are relatively safe, commonly used in clinical practice and only determined by individual clinician preferences, patients should not be disadvantaged in any way by this procedure.

Consent in this situation will be deferred – once notified of the recruitment of a patient to the study, the clinical/research team will approach the parents/guardians as soon as practically possible after randomisation (usually within 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. It will usually not be possible to seek consent from the children themselves due to their critical illness. If written consent is

provided, the patient will be followed up in the trial. If written consent is not provided, see section 9.3.

13.2.2 *Group B*

Patients requiring NRS as a 'step-down' treatment will be receiving invasive ventilation on the PICU prior to extubation. 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 considered as a 'planned' intervention by the treating clinician following extubation, 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.

Consent will be obtained by clinical/research team members who have undergone GCP training. If new safety information results in significant changes in the risk/benefit assessment, the consent form will be reviewed and updated if necessary and subjects will be re-consented as appropriate.

14 REGULATORY CONSIDERATIONS

The trial involves the use of CE-marked medical devices employed for their intended purpose, therefore this trial 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.

15 ASSESSMENT OF SAFETY

15.1 Definitions

15.1.1 *Adverse Event*

An Adverse Event (AE) is any untoward medical occurrence in a patient or clinical study subject, including occurrences that are not necessarily caused by or related to that procedure.

15.1.2 *Serious Adverse Event*

A Serious Adverse Event (SAE) is any untoward medical occurrence that:

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- consists of a congenital anomaly or birth defect.

Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. All deaths that occur during the study will be reviewed for AEs/SAEs that fulfil the definitions as above.

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event, which hypothetically might have caused death if it were more severe.

The National Research Ethics Service defines related and unexpected SAEs as follows:

- Related – that is, it resulted from administration of any of the research procedures, and
- Unexpected – that is, the type of event is not listed in the protocol as an expected occurrence.

15.2 Severity / Grading of Adverse Events

The assignment of the severity/grading should be made by the investigator responsible for the care of the participant using the definitions below. Regardless of the classification of an AE as serious or not, its severity must be assessed according to medical criteria alone using the following categories:

- Mild: does not interfere with routine activities
- Moderate: interferes with routine activities
- Severe: impossible to perform routine activities

A distinction is drawn between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined using the criteria in Section 12.1; hence, a severe AE need not necessarily be a Serious AE.

15.3 Relationship to trial interventions

The assignment of the causality should be made by the investigator responsible for the care of the participant using the definitions in the Table below.

If any doubt about the causality exists, the local investigator should inform the ICNARC CTU who will notify the Chief Investigator. In the case of discrepant views on causality between the investigator and others, the Research Ethics Committee (REC) will be informed of both points of view.

Definitions of Causality

Relationship	Description
Unrelated	There is no evidence of any causal relationship. There is an alternative cause for the AE.
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur during HFNC treatment). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
Possibly*	There is some evidence to suggest a causal relationship (e.g. because the event occurs during HFNC treatment). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant interventions).
Probably*	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Almost certainly*	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

*Possibly, probably, or almost certainly related will be referred to throughout the protocol as 'related'.

15.4 Reporting

AEs and SAEs will only be reported for patients where the causal relationship to the trial intervention has been assessed and judged by the investigator to be related to HFNC or CPAP.

All the events listed in Table below are expected within the trial population and can be related to the trial interventions.

Expected adverse events

Expected event	AE/SAE
Nasal trauma	AE
Facial trauma	AE
Abdominal distension	AE
Endotracheal intubation	AE/SAE
Pneumothorax	AE/SAE
Pneumomediastinum	AE/SAE
Subcutaneous emphysema	AE/SAE
Facial thermal injury	AE/SAE
Respiratory/cardiac arrest	AE/SAE
Aspiration	AE/SAE

15.5 Recording of Adverse Events

All the adverse events will be recorded in the medical notes of the patients.

15.6 Reporting Procedures for Serious Adverse Events

All SAEs (other than those defined in the protocol as not requiring reporting) will be reported to the ICNARC CTU within 24 hours of the Site Study Team becoming aware of the event using the following email address: firstabc@icnarc.org.

For SAEs defined as unexpected, the ICNARC CTU will inform the Sponsor using the following email address: CTIMP.safety@gosh.nhs.uk.

SAEs will be documented from the time of randomisation to the time of discharge from the PICU.

The minimum requirements for SAE reporting to the sponsor includes:

- Event details with the date of event onset
- The relatedness to the study intervention or to other protocol related procedure or disease
- The expectedness of the event
- The outcome of the event
- The date of initial notification by the site

All on-going Serious Adverse Events will be followed-up until the end of study period.

15.7 SAE Reporting to the Ethics Committee

An SAE occurring to a research participant will be reported to the main REC, where in the opinion of the Chief Investigator the event is:

- Related – that is, it resulted from administration of any of the research procedures; and
- Unexpected – that is, the type of event is not listed in the protocol as an expected occurrence.

16 DATA MANAGEMENT

16.1 Source Documents

Source documents are original documents, data, and records from which participants' CRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the CRF), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

All documents will be stored safely in confidential conditions. On all study-specific documents, other than the signed consent, the participant will be referred to by the study participant number/code, not by name.

16.2 Direct Access to source data / documents

Only members of the study research team and authorised representatives from the ICNARC CTU and the sponsor will have direct access to the source data and study documentation. All source data and study documentation will also be available to external auditors if and when required. Access to the final data set will remain with the chief investigator.

16.3 Data Recording and Record Keeping

Study data, including serious adverse events, will be collected and managed using REDCap electronic data capture tools hosted at University College London.[39] REDCap (Research Electronic Data Capture) 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 in REDCap. The name and any other identifying detail will NOT be included in any study data electronic file.

16.4 Trial monitoring

The ICNARC CTU will conduct at least one monitoring visit to participating sites during the course of the trial. In addition, the REC may request access to source data/documents for audit and review.

Following a routine monitoring visit, a report will be sent, which will summarise the visit and the documents reviewed, along with any findings. The Site PI will be responsible for ensuring that all findings are addressed appropriately. Additional site monitoring visits may be scheduled where there is evidence or suspicion of non-compliance with the trial protocol.

16.5 Archiving

Archiving will be authorised by the Sponsor following submission of the end of study report. Essential documents will be retained for a **minimum** of 10 years after completion of the study. These documents will be retained for longer if required by the applicable regulatory requirements.

16.6 Research ethics approval

This protocol, patient information sheets, informed consent forms and other study-related documents will be reviewed and approved by the Sponsor and Research Ethics Committee with respect to scientific content and compliance with applicable research regulations involving human subjects.

17 PATIENT CONFIDENTIALITY AND DATA PROTECTION

Patient identifiable data, including initials, date of birth and NHS/hospital number will be required for the registration process. The study staff will ensure that the participants' anonymity is maintained. The participants will be identified only by a participant ID number on the CRF and any other electronic database. All documents will be stored securely and only accessible by study staff and authorised personnel. The study will comply with the Data Protection Act, which requires data to be anonymised as soon as it is practical to do so. Data will be stored in a secure manner and in accordance with the Data Protection Act 1998.

18 FINANCIAL INFORMATION AND INSURANCE

The trial is funded by the Great Ormond Street Children's Charity clinical research starter grant (ref: V0316).

Cover for negligent harm will be provided by the Great Ormond Street Hospital for Children NHS Foundation Trust through the Clinical Negligent Scheme for Trusts (CNST).

19 PUBLICATIONS POLICY

All individuals who have made substantial intellectual, scientific and practical contributions to the study and the manuscript will, where possible, be credited as authors; all individuals credited as authors will deserve that designation. It is the responsibility of the Chief Investigator and co-investigators and, ultimately, the Sponsor to ensure that these principles are upheld. The status of manuscripts in preparation will be reviewed by the chief Investigator and sponsor if required. In all cases where journal policies permit, all investigators who contribute patients to the study will be acknowledged.

The results of the study will be reported and disseminated as follows:

- Peer reviewed scientific journals;
- Internal report, plus possible article on Institute web pages (publicly accessible);
- Conference presentation(s);
- Written feedback to patient support groups.

20 APPENDIX A – CONSENT QUESTIONNAIRE



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FIRST-ABC Feasibility Study

Parent/Guardian Consent Questionnaire

Directions

- The following questions are about the FIRST-ABC Feasibility Study consent process that you took part in
- We refer to people agreeing to take part in research as 'consenting'
- If your child received treatment as an emergency, consent for your child to take part in the FIRST-ABC Feasibility Study would have been sought after the emergency situation
- This is known as research without prior consent, or deferred consent

Completing this questionnaire

Today's date

 / /

Did you complete this questionnaire

Alone

☐

With help

☐

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1. Please indicate how strongly you agree or disagree with the following statements by placing a circle around the answer that best fits your opinion or decision

Statements	Agree	Neither agree nor disagree	Disagree	
a. The doctor or nurse checked that it was a convenient time to discuss research before discussing FIRST-ABC	1	2	3	
b. I was initially surprised to find out that my child had already been entered into FIRST-ABC	1	2	3	N/A
c. The information I received about FIRST-ABC was clear and straightforward to understand	1	2	3	
d. I understood why consent for my child's participation in FIRST-ABC was sought after the treatment had been given	1	2	3	N/A
e. I had enough opportunity to ask questions about FIRST-ABC	1	2	3	
f. I was satisfied with the deferred consent process for FIRST-ABC	1	2	3	N/A
g. It was difficult to take in the information I was given about FIRST-ABC	1	2	3	
h. It was difficult to make a decision about FIRST-ABC	1	2	3	
i. I made this decision	1	2	3	
j. Someone took this decision away from me	1	2	3	
k. I was not in control of this decision	1	2	3	
l. The decision about the research was inappropriately influenced by others	1	2	3	
<p>If the answer to this question is 'Agree', please state who you think influenced the decision about the research:</p> <p>_____</p>				



2. Did you consent for your child to participate in FIRST-ABC?

☐

Yes (Go to Question 3)

☐

No (Go to Question 4)

3. What were your reasons for providing consent for your child to participate in FIRST-ABC?

Please tick all that apply and then circle your main reason (e.g. ☒)

- | | |
|---|--------------------------|
| a. To help my child | <input type="checkbox"/> |
| b. To help other children in the future | <input type="checkbox"/> |
| c. I felt that medical studies like FIRST-ABC are important | <input type="checkbox"/> |
| d. Because I trusted the doctor or nurse who explained FIRST-ABC | <input type="checkbox"/> |
| e. The treatment had already been given to my child | <input type="checkbox"/> |
| f. My child recovered | <input type="checkbox"/> |
| g. I didn't feel comfortable saying no to the nurse or doctor who explained the study | <input type="checkbox"/> |
| h. Other (Please state): | <input type="checkbox"/> |

4. If you did not provide consent, please provide your reasons for deciding that your child would not take part in FIRST-ABC
(If you do not wish to do so, please leave this space blank)

5. We would value any comments or suggestions you have to improve the recruitment and consent process for FIRST-ABC

We would like to thank you for taking the time to complete this questionnaire.

Please place the questionnaire in the envelope provided, seal it and give it back to the doctor or research nurse.

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