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**FIRST-line support for Assistance in Breathing in Children (FIRST-ABC): A master protocol of two randomised trials to evaluate the non-inferiority of high flow nasal cannula (HFNC) versus continuous positive airway pressure (CPAP) for non-invasive respiratory support in paediatric critical care**

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3 **FIRST-line support for Assistance in Breathing in Children (FIRST-ABC):**  
4 **A master protocol of two randomised trials to evaluate the non-inferiority of**  
5 **high flow nasal cannula (HFNC) versus continuous positive airway pressure**  
6 **(CPAP) for non-invasive respiratory support in paediatric critical care**  
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## Abstract

### Introduction

Even though respiratory support is a common intervention in paediatric critical care, there is no randomised controlled trial (RCT) evidence regarding the effectiveness of two commonly used modes of non-invasive respiratory support (NRS), continuous positive airway pressure (CPAP) and high-flow nasal cannula therapy (HFNC). FIRST-ABC is a master protocol of two RCTs to evaluate the clinical and cost-effectiveness of HFNC (compared to CPAP) as the first-line mode of support in critically ill children.

### Methods and analysis

We will recruit participants over a 30-month period at 25 UK paediatric critical care units (PICU/HDUs). Patients will be eligible if they are admitted/accepted for admission, aged >36 weeks corrected gestational age and <16 years, and assessed by the treating clinician to require non-invasive respiratory support for an acute illness (step-up RCT) or within 72 hours of extubation following a period of invasive ventilation (step-down RCT). Due to the emergency nature of the treatment, written informed consent will be deferred to after randomisation. Randomisation will occur 1:1 to CPAP or HFNC, stratified by site and age (<12 months vs. ≥12 months). The primary outcome is time to liberation from respiratory support for a continuous period of 48 hours. A total sample size of 600 patients in each RCT will provide 90% power with a type I error rate of 2.5% (one-sided) to exclude the pre-specified noninferiority margin of hazard ratio (HR) of 0.75. Primary analyses will be undertaken separately in each RCT in both the intention-to-treat and per-protocol populations.

### Ethics and dissemination

This master protocol received favourable ethical opinion from NHS East of England - Cambridge South Research Ethics Committee (reference: 19/EE/0185) and approval from the Health Research Authority (reference: 260536). Results will be disseminated via publications in peer reviewed medical journals and presentations at national and international conferences.

### Trial registration

ISRCTN60048867; Pre-results.

## Article Summary

### Strengths and limitations of this study

1. FIRST-ABC is a master protocol of the two largest RCTs to date to study the clinical and cost-effectiveness of high flow nasal cannula as the first-line mode of non-invasive respiratory support in critically ill children.
2. The FIRST-ABC master protocol includes two separate RCTs, one in acutely ill children requiring respiratory support (step-up RCT) and one in children requiring respiratory support after extubation from invasive ventilation (step-down RCT), to address the research question in two distinct but common clinical scenarios.
3. The design and conduct of FIRST-ABC has been informed by a successful pilot RCT that confirmed the feasibility of delivering a large pragmatic trial in critically ill children.
4. The choice of the primary outcome, time to liberation from all forms of respiratory support for a continuous period of at least 48 hours, was informed by clinicians as well as through patient and public involvement.
5. Changes to clinical practice during the trial period, and a resultant shift in equipoise regarding the choice of first-line mode of respiratory support in critically ill children, may affect the ability to recruit successfully to the RCTs.



## Introduction

Nearly 75% of the 20,000 critically ill children admitted annually to United Kingdom (UK) paediatric intensive care units (PICUs) receive some form of respiratory support.<sup>1</sup> Increasing recognition of the risks of invasive ventilation has prompted greater use of non-invasive respiratory support (NRS) worldwide.<sup>1 2</sup> Two main modes of NRS are used, to support acutely ill children with respiratory failure or to provide post-extubation support after a spell of invasive ventilation.

Continuous positive airway pressure (CPAP) has been used by PICUs for over three decades.<sup>3-5</sup> Although observational data suggest that CPAP is effective, there have been few randomised clinical trials (RCTs) of CPAP in critically ill children.<sup>5-7</sup> CPAP can be uncomfortable and may be associated with complications such as air-leak and nasal trauma, often necessitating the use of sedation, close monitoring and a high level of nursing input. An alternate mode of NRS, high flow nasal cannula (HFNC), has gained popularity recently. It appears easy to use and is well-tolerated.<sup>8-11</sup> Between 16 and 35% of PICU admissions receive HFNC at some point during their stay.<sup>1 12 13</sup> The potential benefits of HFNC (improved patient comfort, safety profile and ease of nursing care), must be balanced against its potential risks (air leak, abdominal distension and nosocomial infection), and concerns regarding unnecessary prolongation of PICU/hospital stay and excess mortality from delayed escalation. There are few RCTs comparing HFNC with CPAP in the PICU setting. Previous RCTs do not include children with a range of ages and diagnoses needing either *step-up* or *step-down* (post-extubation) care, making it impossible to generalise their findings to contemporary practice.<sup>14-16</sup>

FIRST-ABC therefore addresses an important clinical dilemma faced daily by critical care clinicians: in a child requiring NRS, which modality, HFNC or CPAP, should they use as first-line therapy to achieve the best patient outcomes? Our research question was prioritised by clinicians as well as parents/patients. We previously successfully completed a pilot RCT, which supported the feasibility of performing a large pragmatic RCT comparing CPAP and HFNC in critically ill children, and informed its design and conduct.<sup>17</sup> This protocol has been written in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement.<sup>18</sup>

## Methods

### Aim

To evaluate the clinical and cost-effectiveness of the use of HFNC, as compared with CPAP, when used as the first-line mode in critically ill children requiring NRS:

- A. for an acute illness (*step-up RCT*);
- B. within 72 hours of extubation following a period of invasive ventilation (*step-down RCT*).

### Primary objective

To evaluate the non-inferiority of HFNC, as compared with CPAP, when used as the first-line mode of NRS, both as a step-up treatment (*step-up RCT*) and as a step-down treatment (*step-down RCT*), on the time to liberation from respiratory support.

### Design

FIRST-ABC is a master protocol comprising two pragmatic, multi-centre, parallel groups, non-inferiority RCTs (*step-up RCT* and *step-down RCT*) with shared infrastructure, including an internal pilot stage and integrated health economic evaluation. This design allows the research question to be addressed in each of the two important populations in an efficient way by minimising time and infrastructure costs as compared with conducting two sequential RCTs.<sup>19</sup>

A non-inferiority design was chosen based on previous RCTs in this area and feedback from clinicians indicating that the potential benefits of HFNC (in terms of patient comfort and ease of use) would mean that it would likely be preferred in usual practice even if not shown to be superior to CPAP.

### Setting

FIRST-ABC is set in NHS paediatric critical care units (PICU and/or high dependency units (HDUs)) across England, Wales and Scotland. Sites are eligible to take part if they confirm collective equipoise regarding the choice of first-line NRS in their unit and commit to following trial procedures, including randomisation and data collection. Sites can start recruitment only after a site initiation visit and all relevant regulatory approvals.

### Population

Critically ill children requiring NRS for (A) an acute illness (*step-up RCT*) or (B) within 72 hours of extubation following a period of invasive ventilation (*step-down RCT*).

### Screening

Potentially eligible patients admitted/accepted for admission to the participating critical care unit will be screened against the inclusion/exclusion criteria by the local clinical/research team. For the step-up RCT, all admissions to the unit will be screened. For the step-down RCT, all patients extubated during unit admission will be screened. From these, Screening and Enrolment Logs will record enrolled patients, reasons for exclusion and reasons eligible patients are not enrolled.

### Inclusion criteria

- 1) Admitted/Accepted for admission to PICU/HDU
- 2) Age >36 weeks corrected gestational age and <16 years
- 3) Assessed by the treating clinician to require non-invasive respiratory support, EITHER
  - A. for an acute illness (*step-up RCT*) OR
  - B. within 72 hours of extubation following a period of invasive ventilation (*step-down RCT*).

### Exclusion criteria

- 1) Assessed by the treating clinician to require immediate intubation and invasive ventilation due to severe hypoxia, acidosis and/or respiratory distress, upper airway obstruction, inability to manage airway secretions or recurrent apnoeas
- 2) Tracheostomy in place
- 3) Received HFNC/CPAP for >2 hours in the prior 24 hours
- 4) On home non-invasive ventilation prior to PICU/HDU admission
- 5) Presence of untreated air-leak (pneumothorax/pneumomediastinum)
- 6) Midfacial/craniofacial anomalies (unrepaired cleft palate, choanal atresia) or recent craniofacial surgery
- 7) Agreed 'not for intubation' or other limitation of critical care treatment plan in place.
- 8) Previously recruited to FIRST-ABC (step-up RCT or step-down RCT on this or a previous admission)
- 9) Clinician decision to start other form of non-invasive respiratory support (i.e. not HFNC or CPAP)

### *Randomisation*

Randomisation will be performed after confirming eligibility and as soon as possible to the anticipated start of the randomised treatment. In each RCT, eligible patients will be randomised in a 1:1 ratio to either CPAP or HFNC using a central telephone/web-based randomisation service available 24 hours/7 days a week. The randomisation sequence will be computer

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3 generated and variable block sizes will be used to strengthen allocation concealment.  
4 Randomisation will be stratified by site and age (<12 months versus ≥12 months).  
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8 The randomised treatment will be commenced as soon as practically possible. Following  
9 randomisation, each participant will be assigned a unique FIRST-ABC Trial Number and a Case  
10 Report Form (CRF) completed by the local research team.  
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### 13 *Delivery of HFNC*

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15 Any approved medical device capable of delivering heated, humidified, high flow through nasal  
16 cannulae can be used to provide HFNC at the prescribed gas flow rates during the trial period.  
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18 To standardise treatment, clinical criteria and guidance for the initiation, maintenance and  
19 weaning of HFNC are provided in a trial algorithm (Figure 1). The trial recommends that patients  
20 are assessed for response to the treatment, readiness to wean and for stopping HFNC, as per  
21 the HFNC algorithm, at least twice per day (e.g. at ward rounds).  
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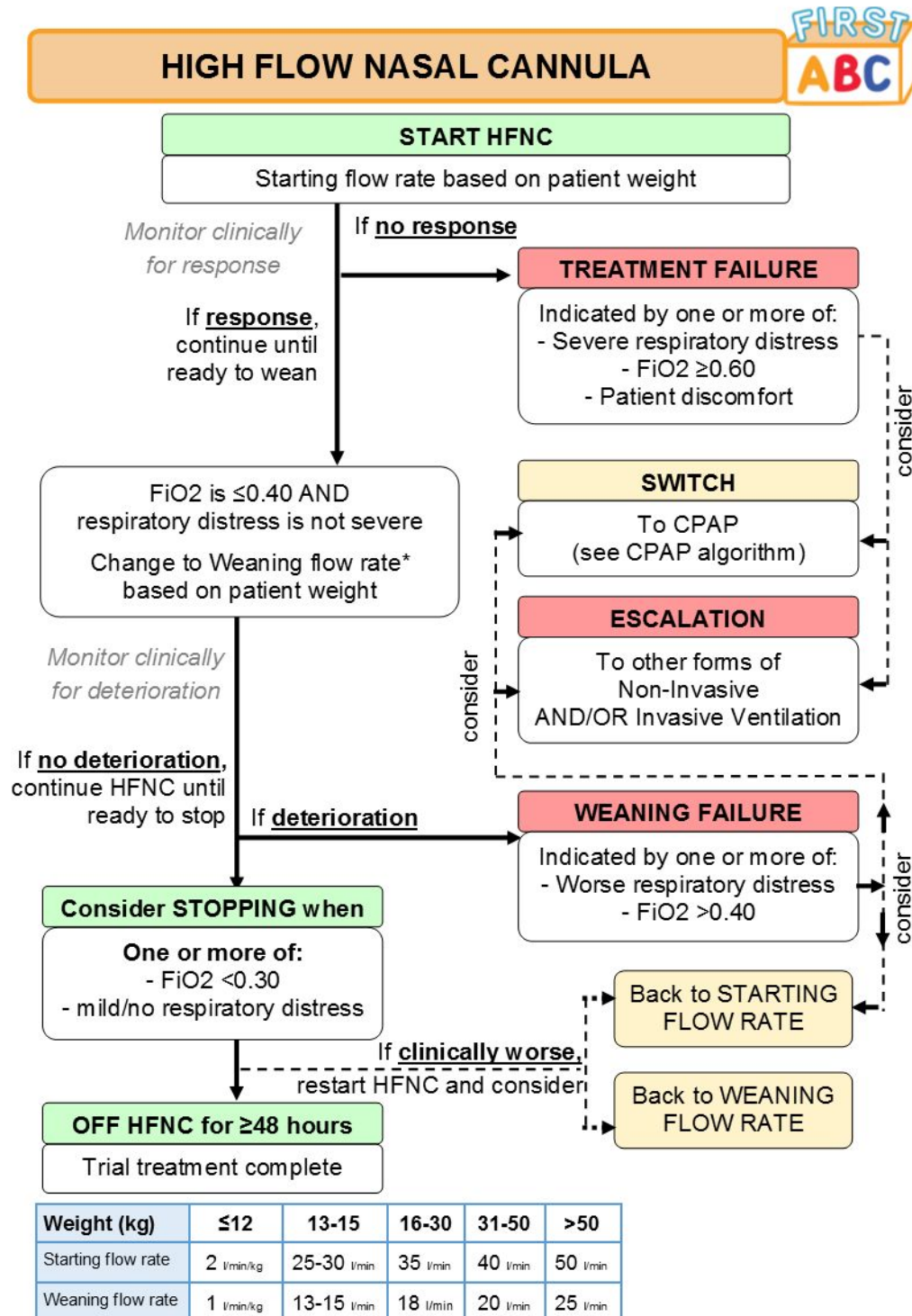


Figure 1. Algorithm for delivery of High Flow Nasal Cannula.

### *Delivery of CPAP*

CPAP will be started using an approved medical device at a set expiratory pressure of 7-8 cm H<sub>2</sub>O. The trial does not specify any particular device or patient interface for the provision of CPAP. To standardise treatment, clinical criteria and guidance for the initiation, maintenance and weaning of CPAP are provided in a trial algorithm (Figure 2). It is recommended that patients are assessed for response to the treatment, readiness to wean and for stopping CPAP, as per the CPAP algorithm, at least twice per day (e.g. at ward rounds).

### *Clinical practice during the trial*

Since staff in participating sites already use HFNC and CPAP, no additional training related to the use of HFNC or CPAP will be provided for the trial, but resources for training in the trial algorithms will be provided. As the medical devices and interfaces that deliver HFNC and CPAP are easily distinguishable from each other, it will not be possible to blind the patient, parents/guardians or clinical staff.

The trial algorithms will be followed until the patient has been liberated from all forms of respiratory support for at least 48 continuous hours. As per current practice, clinicians will be able to stop HFNC/CPAP and switch to the other treatment or escalate to other forms of respiratory support, if clinically deemed necessary. Pre-specified objective criteria to identify non-responders to HFNC/CPAP are provided in the algorithms as a guide for clinicians considering switching or escalating respiratory support. Reasons for switches or escalations will be recorded. Patients who switch or escalate treatments will remain in the trial and continue to be monitored until liberation from respiratory support. All other usual care will be at the discretion of the treating clinical team



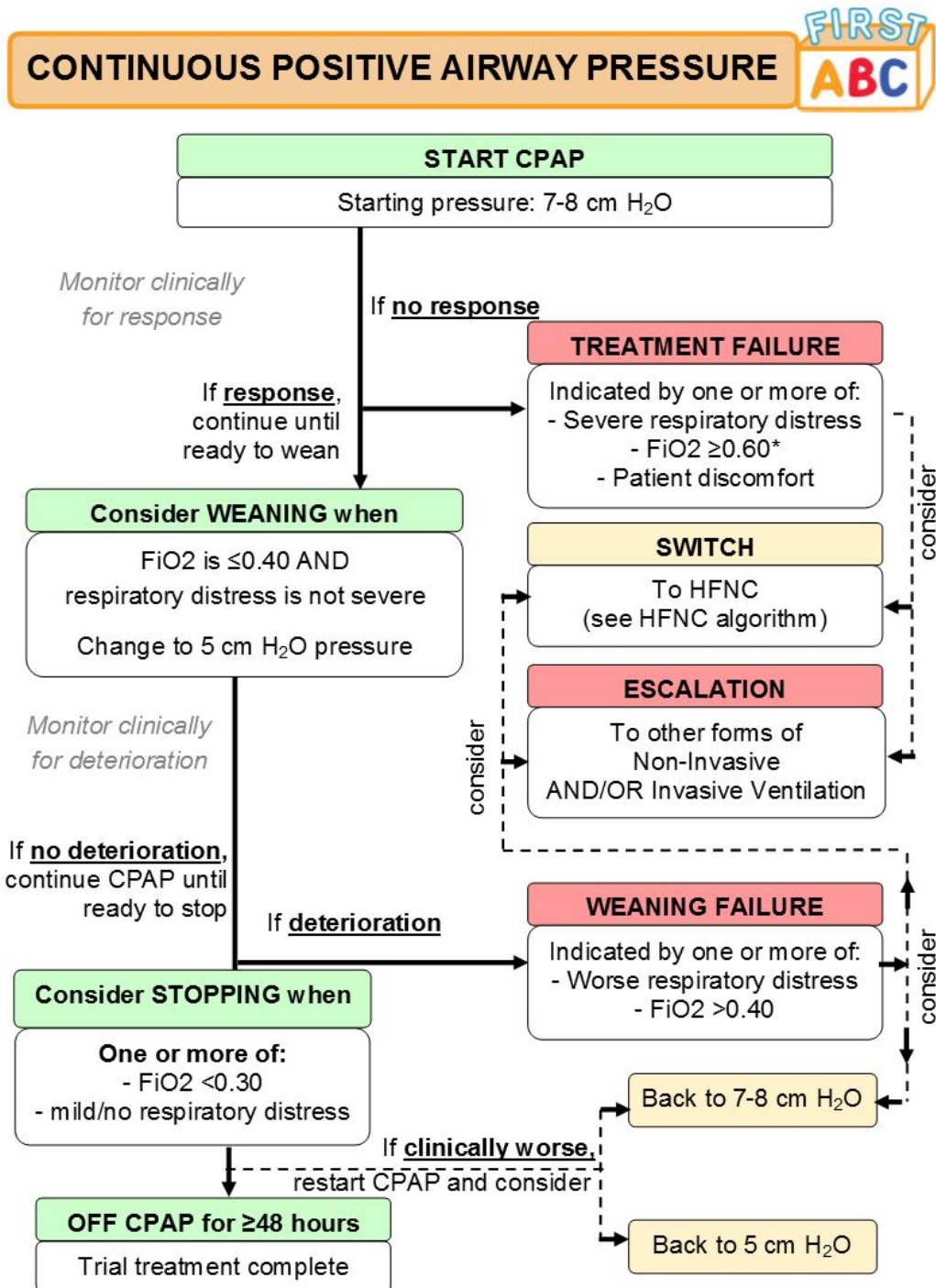


Figure 2. Algorithm for delivery of Continuous Positive Airway Pressure.

### *Consent procedures*

Consent will be sought for the child (patient) from their parent/legal guardian. Children become eligible for FIRST-ABC when critically ill, a profoundly stressful time for parents/guardians, during which there are ethical concerns both about the burden of trying to understand the trial and the ability to provide informed consent. Initiation of NRS typically occurs during a time-sensitive situation, where delays could be detrimental to the child and to the trial's scientific validity. Moreover, both CPAP and HFNC are already widely used in standard practice across the NHS. Considering these reasons, FIRST-ABC has been given ethical approval to use a deferred consent model ('research without prior consent'). Once a patient is confirmed eligible, they will be randomised and the allocated treatment (CPAP or HFNC) commenced as soon as possible. This model, developed in line with the CONseNt methods in paediatric Emergency and urgent Care Trials (CONNECT) guidance,<sup>20</sup> has been found acceptable to parents/guardians and clinicians in several recent RCTs in the PICU setting<sup>17 21-25</sup> and is informed by experience/feedback from the pilot RCT.<sup>17</sup>

Following randomisation, a trained, delegated member of the local research team will approach the child's parents/guardians as soon as appropriate and practically possible to discuss the trial (usually within 24-48 hours of randomisation). A Participant Information Sheet (PIS) will be provided, covering information about the purpose of the trial; the consequences of participating or not; confidentiality; use of personal data; data security; and the future availability of the trial results. A Consent Form will be provided, indicating that: the information given has been read and understood; participation is voluntary and consent can be withdrawn at any time without consequence; and that consent is given for access to medical records to continue data collection, to receive a follow-up questionnaire and for anonymised data to be shared in the future. Due to age and severity of illness, it will not be possible to involve the patient in the consenting process. Instead, assent will be obtained prior to hospital discharge if their condition allows (e.g. they regain mental capacity).

A modification of the consent procedure will be utilised for two rare situations where either the patient: a) is discharged from hospital prior to obtaining consent, or b) dies prior to consent being sought. In the former, the local research team will follow up with the parent/guardian, initially by phone and then by post, for consent. Postal contact will be made again if there is no response after four weeks. If no Consent Form is received within four weeks of the second letter, the participant will be included in the trial unless they notify the research team otherwise. In the latter



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3 situation, the local research team will obtain information from colleagues and bereavement  
4 counsellors to establish the most appropriate clinical/research team member to notify the  
5 parents/guardians of involvement in the trial. If approach for consent is deemed not appropriate  
6 prior to the parent/guardian's departure from hospital, then they will be approached by post four  
7 weeks post-randomisation. The letter will explain how to opt out of the trial. Postal contact will be  
8 made again if there is no response after four weeks. If no Consent Form is received within four  
9 weeks of the second letter, the participant's data will be included in the trial.  
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16 If informed consent is refused or withdrawn, this decision will be respected and abided by, and  
17 no further contact made. All data occurring up to the point of this decision will be retained in the  
18 trial, unless parents/guardians request otherwise.  
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### 21 *Safety monitoring*

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23 Adverse Event (AE) reporting will follow the Health Research Authority guidelines on safety  
24 reporting in studies which do not use Investigational Medicinal Products (non-CTIMPs). The  
25 following events have been pre-specified as potential AEs that could be related to CPAP and/or  
26 HFNC and observed in participants from the date and time of randomisation until 48 hours of  
27 liberation from all forms of respiratory support:  
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- 32 1. Nasal trauma
- 33 2. Facial/neck trauma
- 34 3. Abdominal distension
- 35 4. Pneumothorax
- 36 5. Pneumomediastinum
- 37 6. Subcutaneous emphysema
- 38 7. Facial thermal injury
- 39 8. Respiratory arrest
- 40 9. Cardiac arrest
- 41 10. Aspiration
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50 Occurrences of the specified, expected adverse events will be recorded for all randomised  
51 patients. Considering that eligible patients are critically ill and at increased risk of experiencing  
52 AEs, occurrences of non-specified, adverse events will only be reported if considered to be  
53 related to either CPAP or HFNC (i.e. 'possibly', 'probably' or 'definitely' – see Supplement 1 for  
54 definitions). Any event classified as 'severe' or 'life-threatening' in severity is considered a  
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3 Serious Adverse Event (SAE) and must be reported to ICNARC CTU. If the SAE is evaluated by  
4 the Trial Management Group (TMG) as a related and unexpected SAE, the ICNARC CTU will  
5 submit a report to the REC within 15 calendar days.  
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### 8 *Questionnaire follow-up*

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10 At six months, after assessing the child's survival status, each consenting parent will be sent a  
11 questionnaire (via email or post) by the ICNARC CTU to assess Health-related Quality of Life  
12 (HrQoL) and health service/resource use. Non-responders will be followed-up by telephone  
13 three weeks later.  
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## 18 **Outcome measures**

### 19 **Primary outcome**

- 20 • Time to liberation from respiratory support, defined as the start of a 48-hour period during  
21 which the child was free of all forms of respiratory support (not including supplemental  
22 oxygen alone).  
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### 28 **Secondary outcomes**

- 29 • Mortality at PICU/HDU discharge, day 60 and day 180
- 30 • Rate of (re)intubation at 48 hours
- 31 • Duration of PICU/HDU and hospital stay
- 32 • Patient comfort, during randomised treatment and during non-invasive respiratory  
33 support (i.e. HFNC and/or CPAP), assessed using the COMFORT-B score<sup>26</sup>
- 34 • Proportion of patients in whom sedation is used during non-invasive respiratory support
- 35 • Parental stress, in hospital at/around the time of consent at 24-48 hours, measured using  
36 the Parental Stressor Scale: PICU<sup>27</sup>
- 37 • HrQoL at six months using age-appropriate Pediatric Quality of Life Inventory (Peds-  
38 QL)<sup>32</sup> and Child Health Utility (CHU-9D) questionnaire<sup>28</sup>  
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### 47 **Cost effectiveness analysis (CEA) outcomes**

- 48 • Total costs at six months
- 49 • Quality-Adjusted Life-Years (QALYs) at six months
- 50 • Incremental net monetary benefit gained at a willingness-to-pay of £20,000 per QALY at  
51 six months associated with HFNC versus CPAP<sup>29</sup>  
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### Data collection

To maximise efficiency, FIRST-ABC collaborates with the Paediatric Intensive Care Audit Network (PICANet) to make best use of established PICU data collection infrastructure. Where possible, recruited patients will be consented for data linkage with routine sources (e.g. national death registration data via NHS Digital or equivalent). Additional trial-specific data collection items are limited to the minimum required to deliver trial objectives (**Error! Reference source not found.**).

**Table 1 Patient data collection schedule**

	Baseline	At time of consent	During non-invasive respiratory support	End of PICU/HDU stay	End of hospital stay	At six months
<b>In-hospital</b>						
Clinical/baseline data	✓					
Patient/parent details		✓				
Types of respiratory support received*	✓		✓			
Patient comfort and sedation use			✓			
Parental stress		✓				
Discharge data				✓	✓	
Safety monitoring data			✓			
<b>At follow-up</b>						
PedsQL						✓
CHU-9D						✓
Health services/ resource use						✓

*PICU: paediatric intensive care unit, HDU: high dependency unit, PedsQL: Pediatric Quality of Life Inventory (Peds-QL), CHU-9D: Child Health Utility questionnaire.*

*\*including weaning, switches and escalations from High Flow Nasal Cannula (HFNC)/Continuous Positive Airway Pressure (CPAP)*

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3 All participant data will be entered onto the secure electronic case report form and undergo  
4 validation checks for completeness, accuracy and consistency. The site Principal Investigator  
5 will oversee and be responsible for data collection, quality and recording.  
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## 10 **Statistical Methods**

### 11 **Sample size**

12 To achieve 90% power with a type I error rate of 2.5% (one-sided) to exclude the pre-specified  
13 noninferiority margin of HR=0.75 requires 508 events to be observed. Based on pilot RCT  
14 data,<sup>17</sup> we anticipate 5% censoring due to death or transfer, leading to a required sample size of  
15 268 patients per group in each of the two RCTs. To allow for withdrawal/refusal of consent, and  
16 for exclusion due to non-adherence in the per-protocol (PP) population, we will recruit a total  
17 sample size of 600 patients in each RCT.  
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### 24 **Internal pilot**

25 Data will be analysed at the end of the internal pilot stage (months 7-12 of the grant timeline) on  
26 patients recruited during the first six months in each RCT. The RCTs will progress from pilot to  
27 full trial based on pre-specified progression criteria related to successful site set-up, screening  
28 and recruitment, and adherence. The final decision on progression will be made by the funder  
29 after recommendation, or not, by the Trial Steering Committee (TSC).  
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### 35 **Clinical effectiveness analysis**

36 All analyses will be publicly lodged in a statistical analysis plan, a priori, before the investigators  
37 are unblinded to any trial outcomes. Following best practice for non-inferiority trials, the primary  
38 analyses will be undertaken in both intention-to-treat (ITT) and PP populations, with robust  
39 conclusions possible in the situation where both populations provide concordant results. Results  
40 will be reported in accordance with the CONSORT statement extension for non-inferiority and  
41 equivalence trials.<sup>30</sup>  
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47 Analyses will be undertaken independently for each RCT. In each RCT, baseline patient  
48 characteristics will be compared between the two groups to observe balance and the success of  
49 randomisation. These comparisons will not be subjected to statistical testing. The delivery of the  
50 intervention will be described for each group in detail, including number and percentage of  
51 patients who commence the randomised treatment, remain on the randomised treatment until  
52 liberation from ventilation, who are changed to a different mode of respiratory support.  
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5 HFNC will be considered non-inferior to CPAP if the lower bounds of the 95% confidence  
6 intervals for the hazard ratio (HR) from Cox regression models on time to liberation from  
7 respiratory support fitted in both the ITT and PP populations exclude the pre-specified non-  
8 inferiority margin of 0.75 (corresponding to approximately a 16-hour increase in median time to  
9 liberation, based on pilot RCT data). This margin was considered adequate such that the other  
10 potential benefits of HFNC in terms of comfort and tolerability would mean that it would be likely  
11 to be preferred in usual practice. The Cox regression models will be adjusted for important  
12 baseline characteristics. The covariates for inclusion in the regression models will be selected a  
13 priori based on an established relationship with outcome for critically ill children, and not  
14 because of observed imbalance, significance in univariable analyses or by a stepwise selection  
15 method.  
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24 Subgroup analyses for the primary outcome will be performed to test for interactions between  
25 the effect of allocated treatment group and the following baseline covariates:

- 26 • age (<12 months versus ≥12 months)
  - 27 • severity of respiratory distress at randomisation (severe versus mild/moderate)
  - 28 • Co-morbidities (None versus Neurological/neuromuscular versus Other)
  - 29 • SpO<sub>2</sub>/FiO<sub>2</sub> (SF) ratio at randomisation
  - 30 • for step-up RCT only:
    - 31 ○ clinical indication (bronchiolitis versus other respiratory (airway problem,  
32 asthma/wheeze or any other respiratory) versus cardiac versus other  
33 (neurological, sepsis/infection, any other))
    - 34 ○ whether child was on NRS at randomisation (Yes/No)
  - 35 • for step-down RCT only:
    - 36 ○ length of prior invasive mechanical ventilation (<5 days versus ≥5 days)
    - 37 ○ reason for invasive mechanical ventilation (cardiac versus other)
    - 38 ○ planned (randomisation followed by extubation) vs rescue (extubation followed by  
39 randomisation) non-invasive respiratory support
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51 As a sensitivity analysis, the primary analysis will be repeated using time to start weaning of  
52 NRS (i.e. duration of 'acute' respiratory support) and time to meeting objective 'readiness to  
53 wean NRS' criteria.  
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3 Secondary analyses of binary outcomes (mortality, reintubation) will be performed by Fisher's  
4 exact test and adjusted logistic regression. Duration of survival to day 180 will be plotted as  
5 Kaplan-Meier survival curves, compared unadjusted with the log rank test and adjusted using  
6 Cox regression models. Analyses of duration of PICU/HDU and hospital stay will be performed  
7 by Wilcoxon rank-sum tests, stratified by survival status. Analyses of COMFORT-B score,  
8 sedation use, PSS:PICU and HrQoL will be performed by t-tests and adjusted linear regression.  
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14 In the step-up RCT, a single interim analysis will be carried out after the recruitment and follow-  
15 up to day 60 of 300 patients. The interim analysis will use a Peto-Haybittle stopping rule to  
16 recommend early termination due to superiority of either intervention ( $P < 0.001$ ) in time to  
17 liberation from respiratory support or evidence of harm from either intervention ( $P < 0.05$ ) in  
18 mortality at day 60. Both tests will be performed using a log-rank test on all available data within  
19 the ITT population. Further interim analyses will be performed only if requested by the Data  
20 Monitoring and Ethics Committee (DMEC).  
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26 In the step-down RCT, due to faster than anticipated recruitment, no formal interim analysis will  
27 be performed. Safety data (counts and percentages of adverse events by arm, and a line listing  
28 of SAEs) will be available for scrutiny by the DMEC, by the end of the internal pilot stage.  
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### 32 **Integrated health economic evaluation**

33 The CEA will take an NHS and Personal Social Services perspective.<sup>29</sup> Patient-level resource  
34 use data will be obtained from CRFs, PICANet, and a health services questionnaire (HSQ).  
35 Resource use data from the PICU/HDU stay will be taken from the CRF and linked routine data  
36 from PICANet. Information on subsequent PICU/HDU and hospital admissions will be obtained  
37 via data linkage with PICANet and through completion of the HSQ. Data on the level of care for  
38 PICU bed-days will be gathered through routine collection of the Paediatric Critical Care  
39 Minimum Dataset (PCCMDS) in the participating sites via the PICANet database. Use of primary  
40 care and community health services will be assessed by HSQ at six months. Patient-level  
41 resource use data will be combined with appropriate unit costs from the NHS payment by results  
42 and Personal Social Services Research Unit databases to report total costs per patient for up to  
43 six months post-randomisation. Data from PedsQL and CHU-9D at six months will be combined  
44 with survival data to report QALYs at six months. The CEA will follow the intention-to-treat  
45 principle and report the mean (95% confidence interval) incremental costs, QALYs and net  
46 monetary benefit at six months. The CEA will use multilevel linear regression models that allow  
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3 for clustering of patients at site. The analysis will adjust for key baseline covariates at both  
4 patient and site level.  
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## 8 **Governance and oversight**

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### 10 **Research ethics**

11 The trial received favourable ethical opinion from NHS East of England - Cambridge South  
12 Research Ethics Committee (reference number: 19/EE/0185) and approval from the Health  
13 Research Authority (Integrated Research Application System (IRAS) number: 260536).  
14 Evidence of local confirmation of capacity and capability at each site must be provided to the  
15 ICNARC CTU prior to site activation.  
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### 21 **Confidentiality**

22 ICNARC CTU will act to preserve participant confidentiality and will not disclose or reproduce  
23 any information by which participants could be identified. All data will be stored securely.  
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### 27 **Oversight**

28 The TMG, led by the Chief Investigator, is responsible for the management of FIRST-ABC. It  
29 meets regularly and includes the Investigators and ICNARC CTU trial team. FIRST-ABC is  
30 managed by the ICNARC CTU in accordance with the Medical Research Council's Good  
31 Research Practice: Principles and Guidelines<sup>31</sup> which is based on the International Conference  
32 on Harmonisation guidelines on Good Clinical Practice<sup>32</sup> principles and the UK Department of  
33 Health's Policy Framework for Health and Social Care Research.<sup>33</sup> The on-site monitoring plan  
34 will follow a risk-based strategy.  
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41 A majority independent TSC has been established to monitor trial progress and includes PPI  
42 representatives, experienced clinicians and researchers, in addition to the Chief Investigator and  
43 Head of Research at ICNARC. An independent DMEC has been established to monitor patient  
44 recruitment and retention, adherence and safety.  
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49 The Great Ormond Street Hospital for Children NHS Foundation Trust are the trial sponsor  
50 (reference: 17IA05). As the sponsor is an NHS organisation, NHS indemnity will apply for legal  
51 liability arising from the design, management and conduct of the research.  
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### *Patient and Public Involvement (PPI)*

We had considerable PPI input into the pilot RCT<sup>17</sup> as well as the main trial described here. The parent of a child who received respiratory support is a co-investigator and has actively contributed to the trial design and procedures, including the use of deferred consent.

### **Trial status**

This paper presents the master protocol (v1.2, dated 23 January 2020)<sup>34</sup> for the two largest RCTs studying the clinical and cost effectiveness of HFNC therapy as the first-line mode of NRS in critically ill children. It will provide robust evidence for the two distinct but common clinical scenarios in which NRS is primarily used. The first participant was recruited in August 2019. At the time of submission, patient recruitment was ongoing – with recruitment planned to complete in November 2020 and January 2022 for the step-down RCT and step-up RCT, respectively. Each RCT will be disseminated independently, including through publication in peer-reviewed medical journals and at national and international conferences.



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## Footnotes

### Acknowledgements

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### Contributors

PR is Chief Investigator. ARB is Trial Manager. PR and ARB drafted the manuscript. PD, RF, RG, DH, JL, KM, PM, RP, MP, KR, SZ, and LT are trial co-applicants and members of the Trial Management Group. LD supported management of the trial. All authors read and approved the final version.

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### Competing interests

None declared.

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3 **Patient consent**

4 Not required.  
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8 **Ethics approval**

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10 The trial has received a favourable ethical opinion from the NHS East of England - Cambridge  
11 South Research Ethics Committee (reference number: 19/EE/0185) and approval from the  
12 Health Research Authority (Integrated Research Application System (IRAS) number: 260536).  
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## Supplement 1 – Safety monitoring definitions

### Severity

- **None:** indicates no event or complication.
- **Mild:** complication results in only temporary harm and does not require clinical treatment.
- **Moderate:** complication requires clinical treatment but does not result in significant prolongation of hospital stay. Does not usually result in permanent harm and where this does occur the harm does not cause functional limitation to the participant.
- **Severe:** complication requires clinical treatment and results in significant prolongation of hospital stay, permanent functional limitation.
- **Life-threatening:** complication that may lead to death or where the participant died as a direct result of the complication/adverse event.

### Relatedness

- **None:** there is no evidence of any relationship to the study treatment.
- **Unlikely:** There is little evidence to suggest a causal relationship (e.g. because the event did not occur within a reasonable time after administration of the trial treatment). There is another reasonable explanation of the event (e.g. the participant's clinical condition, other concomitant medications).
- **Possibly:** There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial procedure). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant medications).

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3 • **Probably:** There is evidence to suggest a causal relationship and the influence of other  
4 factors is unlikely.  
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8 • **Definitely:** There is clear evidence to suggest a causal relationship and other possible  
9 contributing factors can be ruled out.  
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### 11 **Expectedness**

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15 • **Expected:** the event is listed as an expected AE (see *Error! Reference source not*  
16 *found.*).  
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20 • **Unexpected:** the event is not listed as an expected AE (see *Error! Reference source*  
21 *not found.*).  
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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents\*

Section/item	Item No	Description	Page No.
<b>Administrative information</b>			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial	P1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	P3
	2b	All items from the World Health Organization Trial Registration Data Set	Throughout
Protocol version	3	Date and version identifier	P20
Funding	4	Sources and types of financial, material, and other support	P24
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	P24
	5b	Name and contact information for the trial sponsor	P19
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of ..	P24
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	P19
<b>Introduction</b>			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	P4
	6b	Explanation for choice of comparators	P4
Objectives	7	Specific objectives or hypotheses	P5

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Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority,	P5
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For peer review only



**Methods: Participants, interventions, and outcomes**

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4	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
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9	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
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15	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
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20		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
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26		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
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30		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
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33	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
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43	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
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49	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
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55	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size
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**Methods: Assignment of interventions (for controlled trials)**

Allocation:

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3	Sequence	16a	P6-7
4	generation	Method of generating the allocation sequence (eg,	
5		computer-generated random numbers), and list of any	
6		factors for stratification. To reduce predictability of a random	
7		sequence, details of any planned restriction (eg, blocking)	
8		should be provided in a separate document that is	
9		unavailable to those who enrol participants or assign	
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For peer review only

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2	Allocation	16b	Mechanism of implementing the allocation sequence
3	concealment		(eg, central telephone; sequentially numbered,
4	mechanism		opaque, sealed envelopes), describing any steps to
5			conceal the sequence until interventions are assigned
6			
7	Implementation	16c	Who will generate the allocation sequence, who will enrol
8			participants, and who will assign participants to
9			interventions
10			
11			
12	Blinding	17a	Who will be blinded after assignment to interventions
13	(masking)		(eg, trial participants, care providers, outcome
14			assessors, data analysts), and how
15			
16		17b	If blinded, circumstances under which unblinding is
17			permissible, and procedure for revealing a
18			participant's allocated intervention during the trial
19			
20			
21	<b>Methods: Data collection, management, and analysis</b>		
22			
23	Data collection	18a	Plans for assessment and collection of outcome,
24	methods		baseline, and other trial data, including any related
25			processes to promote data quality (eg, duplicate
26			measurements, training of assessors) and a description
27			of study instruments (eg, questionnaires, laboratory
28			tests) along with their reliability and validity, if known.
29			Reference to where data collection forms can be found,
30			if not in the protocol
31			
32			
33		18b	Plans to promote participant retention and complete
34			follow-up, including list of any outcome data to be
35			collected for participants who discontinue or deviate
36			from intervention protocols
37			
38			
39	Data	19	Plans for data entry, coding, security, and storage,
40	management		including any related processes to promote data
41			quality (eg, double data entry; range checks for data
42			values). Reference to where details of data
43			management procedures can be found, if not in the
44			protocol
45			
46			
47	Statistical	20a	Statistical methods for analysing primary and
48	methods		secondary outcomes. Reference to where other details
49			of the statistical analysis plan can be found, if not in the
50			protocol
51			
52			
53		20b	Methods for any additional analyses (eg,
54			subgroup and adjusted analyses)
55			
56			
57		20c	Definition of analysis population relating to protocol
58			non-adherence (eg, as randomised analysis), and any
59			statistical methods to handle missing data (eg,
60			multiple imputation)

**Methods: Monitoring**

1				
2				
3				
4	Data monitoring	21a	Composition of data monitoring committee (DMC);	P19
5			summary of its role and reporting structure; statement	
6			of whether it is independent from the sponsor and	
7			competing interests; and reference to where further	
8			details about its charter can be found, if not in the	
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2		21b	Description of any interim analyses and stopping	P17-18
3			guidelines, including who will have access to these interim	
4			results and make the final decision to terminate the trial	
5				
6	Harms	22	Plans for collecting, assessing, reporting, and managing	P12-13
7			solicited and spontaneously reported adverse events and	
8			other unintended effects of trial interventions or trial	
9			conduct	
10				
11	Auditing	23	Frequency and procedures for auditing trial conduct, if	P19
12			any, and whether the process will be independent from	
13			investigators and the sponsor	
14				
15				
16	<b>Ethics and dissemination</b>			
17				
18	Research ethics	24	Plans for seeking research ethics committee/institutional	P19,25
19	approval		review board (REC/IRB) approval	
20				
21	Protocol	25	Plans for communicating important protocol modifications	Not provided
22	amendments		(eg, changes to eligibility criteria, outcomes, analyses) to	
23			relevant parties (eg, investigators, REC/IRBs, trial	
24			participants, trial registries, journals, regulators)	
25				
26				
27	Consent or assent	26a	Who will obtain informed consent or assent from	P11-12
28			potential trial participants or authorised	
29			surrogates, and how (see Item 32)	
30				
31		26b	Additional consent provisions for collection and use of	NA
32			participant data and biological specimens in ancillary	
33			studies, if applicable	
34				
35				
36	Confidentiality	27	How personal information about potential and enrolled	P19
37			participants will be collected, shared, and maintained in	
38			order to protect confidentiality before, during, and after the	
39			trial	
40				
41				
42	Declaration of	28	Financial and other competing interests for principal	P24
43	interests		investigators for the overall trial and each study site	
44				
45	Access to data	29	Statement of who will have access to the final trial	P19
46			dataset, and disclosure of contractual agreements	
47			that limit such access for investigators	
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50	Ancillary and	30	Provisions, if any, for ancillary and post-trial care,	NA
51	post-trial care		and for compensation to those who suffer harm	
52			from trial participation	
53				
54	Dissemination	31a	Plans for investigators and sponsor to communicate trial	P20
55	policy		results to participants, healthcare professionals, the	
56			public, and other relevant groups (eg, via publication,	
57			reporting in results databases, or other data sharing	
58			arrangements), including any publication restrictions	
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|-----|--|--------------|
| 31b | Authorship eligibility guidelines and any intended use of professional writers                                   | Not provided |
| 31c | Plans, if any, for granting public access to the full protocol, participant- level dataset, and statistical code |              |

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2 **Appendices**  
3

4 5 6 7	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Not provided
8 9 10 11 12	Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future	NA

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13 \*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013  
14 Explanation & Elaboration for important clarification on the items. Amendments to the  
15 protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT  
16 Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](#)"  
17 license.  
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# BMJ Open

**FIRST-line support for Assistance in Breathing in Children (FIRST-ABC): A master protocol of two randomised trials to evaluate the non-inferiority of high flow nasal cannula (HFNC) versus continuous positive airway pressure (CPAP) for non-invasive respiratory support in paediatric critical care**

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	STATISTICS & RESEARCH METHODS

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3 **+FIRST-line support for Assistance in Breathing in Children (FIRST-ABC):**  
4 **A master protocol of two randomised trials to evaluate the non-inferiority of**  
5 **high flow nasal cannula (HFNC) versus continuous positive airway pressure**  
6 **(CPAP) for non-invasive respiratory support in paediatric critical care**  
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**Keywords**

non-invasive respiratory support, high flow nasal cannula, continuous positive airway pressure, randomised clinical trial

*Word count:* Abstract (298), Main manuscript (4483)

## Abstract

### Introduction

Even though respiratory support is a common intervention in paediatric critical care, there is no randomised controlled trial (RCT) evidence regarding the effectiveness of two commonly used modes of non-invasive respiratory support (NRS), continuous positive airway pressure (CPAP) and high-flow nasal cannula therapy (HFNC). FIRST-ABC is a master protocol of two pragmatic non-inferiority RCTs to evaluate the clinical and cost-effectiveness of HFNC (compared to CPAP) as the first-line mode of support in critically ill children.

### Methods and analysis

We will recruit participants over a 30-month period at 25 UK paediatric critical care units (paediatric intensive care units/high dependency units). Patients are eligible if admitted/accepted for admission, aged >36 weeks corrected gestational age and <16 years, and assessed by the treating clinician to require non-invasive respiratory support for an acute illness (step-up RCT) or within 72 hours of extubation following a period of invasive ventilation (step-down RCT). Due to the emergency nature of the treatment, written informed consent will be deferred to after randomisation. Randomisation will occur 1:1 to CPAP or HFNC, stratified by site and age (<12 vs. ≥12 months). The primary outcome is time to liberation from respiratory support for a continuous period of 48 hours. A total sample size of 600 patients in each RCT will provide 90% power with a type I error rate of 2.5% (one-sided) to exclude the pre-specified noninferiority margin of hazard ratio of 0.75. Primary analyses will be undertaken separately in each RCT in both the intention-to-treat and per-protocol populations.

### Ethics and dissemination

This master protocol received favourable ethical opinion from NHS East of England - Cambridge South Research Ethics Committee (reference: 19/EE/0185) and approval from the Health Research Authority (reference: 260536). Results will be disseminated via publications in peer reviewed medical journals and presentations at national and international conferences.

### Trial registration

ISRCTN60048867; Pre-results.

## Article Summary

### Strengths and limitations of this study

1. FIRST-ABC is a master protocol of the two largest RCTs to date to study the clinical and cost-effectiveness of high flow nasal cannula as the first-line mode of non-invasive respiratory support in critically ill children.
2. The FIRST-ABC master protocol includes two separate RCTs, one in acutely ill children requiring respiratory support (step-up RCT) and one in children requiring respiratory support after extubation from invasive ventilation (step-down RCT), to address the research question in two distinct but common clinical scenarios.
3. The design and conduct of FIRST-ABC has been informed by a successful pilot RCT that confirmed the feasibility of delivering a large pragmatic trial in critically ill children.
4. The choice of the primary outcome, time to liberation from all forms of respiratory support for a continuous period of at least 48 hours, was informed by clinicians as well as through patient and public involvement.
5. Changes to clinical practice during the trial period, and a resultant shift in equipoise regarding the choice of first-line mode of respiratory support in critically ill children, may affect the ability to recruit successfully to the RCTs.

## Introduction

Nearly 75% of the 20,000 critically ill children admitted annually to United Kingdom (UK) paediatric intensive care units (PICUs) receive some form of respiratory support.<sup>1</sup> Increasing recognition of the risks of invasive ventilation has prompted greater use of non-invasive respiratory support (NRS) worldwide.<sup>1 2</sup> Two main modes of NRS are used, to support acutely ill children with respiratory failure or to provide post-extubation support after a spell of invasive ventilation.

Continuous positive airway pressure (CPAP) has been used by PICUs for over three decades.<sup>3-5</sup> Although observational data suggest that CPAP is effective, there have been few randomised clinical trials (RCTs) of CPAP in critically ill children.<sup>5-7</sup> CPAP can be uncomfortable and may be associated with complications such as air-leak and nasal trauma, often necessitating the use of sedation, close monitoring and a high level of nursing input. An alternate mode of NRS, high flow nasal cannula (HFNC), has gained popularity more recently. It appears easy to use and is well-tolerated.<sup>8-11</sup> Between 16 and 35% of PICU admissions receive HFNC at some point during their stay.<sup>1 12 13</sup> The potential benefits of HFNC (improved patient comfort, safety profile and ease of nursing care), must be balanced against its potential risks (air leak, abdominal distension and nosocomial infection), and concerns regarding unnecessary prolongation of PICU/hospital stay and excess mortality from delayed escalation. There are few RCTs comparing HFNC with CPAP in the PICU setting. Previous RCTs do not include children with a range of ages and diagnoses needing either *step-up* or *step-down* (post-extubation) care, making it impossible to generalise their findings to contemporary practice.<sup>14-16</sup>

FIRST-ABC therefore addresses an important clinical dilemma faced daily by critical care clinicians: in a child requiring NRS, which modality, HFNC or CPAP, should they use as first-line therapy to achieve the best patient outcomes? Our research question was prioritised by clinicians as well as parents/patients. We previously successfully completed a pilot RCT, which supported the feasibility of performing a large pragmatic RCT comparing CPAP and HFNC in critically ill children, and informed its design and conduct.<sup>17</sup> This protocol has been written in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement.<sup>18</sup>

## Methods

### Hypothesis

In critically ill children assessed by the treating clinician to require non-invasive respiratory support (NRS), first-line use of high flow nasal cannula (HFNC) is non-inferior to continuous positive airway pressure (CPAP) in time to liberation from respiratory support.

### Aim

To evaluate the clinical and cost-effectiveness of the use of HFNC, as compared with CPAP, when used as the first-line mode in critically ill children requiring NRS:

- A. for an acute illness (*step-up RCT*);
- B. within 72 hours of extubation following a period of invasive ventilation (*step-down RCT*).

### Primary objective

To evaluate the non-inferiority of HFNC, as compared with CPAP, when used as the first-line mode of NRS, both as a step-up treatment (*step-up RCT*) and as a step-down treatment (*step-down RCT*), on the time to liberation from respiratory support.

### Design

FIRST-ABC is a master protocol comprising two pragmatic, multi-centre, parallel groups, non-inferiority RCTs (*step-up RCT* and *step-down RCT*) with shared infrastructure, including an internal pilot stage and integrated health economic evaluation. This design allows the research question to be addressed in each of the two important populations in an efficient way by minimising time and infrastructure costs as compared with conducting two sequential RCTs.<sup>19</sup> The pragmatic study design ensures that research findings can be more easily generalised to real-world practice.

A non-inferiority design was chosen based on previous RCTs in this area and feedback from clinicians from the UK Paediatric Intensive Care Society – Study Group in July 2017 which indicated that the potential benefits of HFNC (in terms of patient comfort and ease of use) would mean that it would likely be preferred in usual practice even if not shown to be superior to CPAP.

### Setting

FIRST-ABC is set in NHS paediatric critical care units (PICU and/or high dependency units (HDUs)) across England, Wales and Scotland. General medical-surgical, cardiac and mixed units were considered for participation. Sites are eligible to take part if they confirm collective



equipoise regarding the choice of first-line NRS in their unit and commit to following trial procedures, including randomisation and data collection. Sites can start recruitment only after a site initiation visit and all relevant regulatory approvals.

### Population

Critically ill children assessed by the treating clinician to require NRS for (A) an acute illness (*step-up RCT*) or (B) within 72 hours of extubation following a period of invasive ventilation (*step-down RCT*).

### Screening

Potentially eligible patients admitted/accepted for admission to the participating critical care unit will be screened against the inclusion/exclusion criteria by the local clinical/research team. For the step-up RCT, all admissions to the unit will be screened. For the step-down RCT, all patients extubated during unit admission will be screened. From these, Screening and Enrolment Logs will record enrolled patients, reasons for exclusion and reasons eligible patients are not enrolled.

### Inclusion criteria

- 1) Admitted/Accepted for admission to PICU/HDU
- 2) Age >36 weeks corrected gestational age and <16 years
- 3) Assessed by the treating clinician to require non-invasive respiratory support, EITHER
  - A. for an acute illness (*step-up RCT*) OR
  - B. within 72 hours of extubation following a period of invasive ventilation (*step-down RCT*).

### Exclusion criteria

- 1) Assessed by the treating clinician to require immediate intubation and invasive ventilation due to severe hypoxia, acidosis and/or respiratory distress, upper airway obstruction, inability to manage airway secretions or recurrent apnoeas
- 2) Tracheostomy in place
- 3) Received HFNC/CPAP for >2 hours in the prior 24 hours
- 4) On home non-invasive ventilation prior to PICU/HDU admission
- 5) Presence of untreated air-leak (pneumothorax/pneumomediastinum)
- 6) Midfacial/craniofacial anomalies (unrepaired cleft palate, choanal atresia) or recent craniofacial surgery
- 7) Agreed 'not for intubation' or other limitation of critical care treatment plan in place.

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- 3 8) Previously recruited to FIRST-ABC (step-up RCT or step-down RCT on this or a previous
- 4 admission)
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- 6 9) Clinician decision to start other form of non-invasive respiratory support (i.e. not HFNC or
- 7 CPAP - e.g. bilevel positive pressure and negative pressure ventilation)
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### 10 *Randomisation*

11 Randomisation will be performed after confirming eligibility and as close as possible to the  
12 anticipated start of the randomised treatment. In each RCT, eligible patients will be randomised  
13 in a 1:1 ratio to either CPAP or HFNC using a central telephone/web-based randomisation  
14 service available 24 hours/7 days a week. The randomisation sequence will be computer  
15 generated and variable block sizes will be used to strengthen allocation concealment.  
16 Randomisation will be stratified by site and age (<12 months versus  $\geq$ 12 months) to minimise  
17 imbalance arising from unit practices and interface selection.  
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24 The randomised treatment will be commenced as soon as practically possible. Following  
25 randomisation, each participant will be assigned a unique FIRST-ABC Trial Number and a Case  
26 Report Form (CRF) completed by the local research team.  
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### 30 *Delivery of HFNC*

31 Any approved medical device capable of delivering heated, humidified, high flow through nasal  
32 cannulae can be used to provide HFNC at the prescribed gas flow rates during the trial period.  
33 To standardise treatment, clinical criteria and guidance for the initiation, maintenance and  
34 weaning of HFNC are provided in a trial algorithm (**Error! Reference source not found.**). The  
35 trial algorithms were developed iteratively in consultation with paediatric critical care clinicians  
36 across the UK (both via email and in person at a Collaborators' Meeting held prior to the start of  
37 the trial).  
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44 The trial recommends that patients are assessed for response to the treatment, readiness to  
45 wean and for stopping HFNC, as per the HFNC algorithm, at least twice per day (e.g. at ward  
46 rounds).  
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### 52 *Delivery of CPAP*

53 CPAP will be started using an approved medical device at a set expiratory pressure of 7-8 cm  
54 H<sub>2</sub>O. The trial does not specify any particular device or patient interface for the provision of  
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3 CPAP. To standardise treatment, clinical criteria and guidance for the initiation, maintenance  
4 and weaning of CPAP are provided in a trial algorithm (**Error! Reference source not found.**). It  
5 is recommended that patients are assessed for response to the treatment, readiness to wean  
6 and for stopping CPAP, as per the CPAP algorithm, at least twice per day (e.g. at ward rounds).  
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### 10 *Clinical practice during the trial*

11 Since staff in participating sites already use HFNC and CPAP, no additional central training  
12 related to the use of HFNC or CPAP will be provided for the trial, but resources for training in the  
13 trial algorithms will be provided. As the medical devices and interfaces that deliver HFNC and  
14 CPAP are easily distinguishable from each other, it will not be possible to blind the patient,  
15 parents/guardians or clinical staff.  
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22 The trial algorithms will be followed until the patient has been liberated from all forms of  
23 respiratory support for at least 48 continuous hours. As per current practice, clinicians will be  
24 able to stop HFNC/CPAP and switch to the other treatment or escalate to other forms of  
25 respiratory support, if clinically deemed necessary. Pre-specified objective criteria to identify  
26 non-responders to HFNC/CPAP are provided in the algorithms as a guide for clinicians  
27 considering switching or escalating respiratory support. Reasons for switches or escalations will  
28 be recorded. Patients who switch or escalate treatments will remain in the trial and continue to  
29 be monitored until liberation from respiratory support. All other usual care (e.g. sedation,  
30 feeding) will be at the discretion of the treating clinical team.  
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### 40 *Consent procedures*

41 Consent will be sought for the child (patient) from their parent/legal guardian. Children become  
42 eligible for FIRST-ABC when critically ill, a profoundly stressful time for parents/guardians,  
43 during which there are ethical concerns both about the burden of trying to understand the trial  
44 and the ability to provide informed consent. Initiation of NRS typically occurs during a time-  
45 sensitive situation, where delays could be detrimental to the child and to the trial's scientific  
46 validity. Moreover, both CPAP and HFNC are already widely used in standard practice across  
47 the NHS. Considering these reasons, FIRST-ABC has been given ethical approval to use a  
48 deferred consent model ('research without prior consent'). Once a patient is confirmed eligible,  
49 they will be randomised and the allocated treatment (CPAP or HFNC) commenced as soon as  
50 possible. This model, developed in line with the CONseNt methods in paediatric Emergency and  
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3 urgent Care Trials (CONNECT) guidance,<sup>20</sup> has been found acceptable to parents/guardians  
4 and clinicians in several recent RCTs in the PICU setting<sup>17 21-25</sup> and is informed by  
5 experience/feedback from the pilot RCT.<sup>17</sup>  
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9 Following randomisation, a trained, delegated member of the local research team will approach  
10 the child's parents/guardians as soon as appropriate and practically possible to discuss the trial  
11 (usually within 24-48 hours of randomisation). A Participant Information Sheet (PIS) will be  
12 provided, covering information about the purpose of the trial; the consequences of participating  
13 or not; confidentiality; use of personal data; data security; and the future availability of the trial  
14 results. A Consent Form (see supplementary file 1) will be provided, indicating that: the  
15 information given has been read and understood; participation is voluntary and consent can be  
16 withdrawn at any time without consequence; and that consent is given for access to medical  
17 records to continue data collection, to receive a follow-up questionnaire and for anonymised data  
18 to be shared in the future. Due to age and severity of illness, it will not be possible to involve the  
19 patient in the consenting process. Instead, assent will be obtained prior to hospital discharge if  
20 their condition allows (e.g. they regain mental capacity).  
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30 A modification of the consent procedure will be utilised for two rare situations where either the  
31 patient: a) is discharged from hospital prior to obtaining consent, or b) dies prior to consent being  
32 sought.<sup>24 26</sup> In the former, the local research team will follow up with the parent/guardian, initially  
33 by phone and then by post, for consent. Postal contact will be made again if there is no  
34 response after four weeks. If no Consent Form is received within four weeks of the second letter,  
35 the participant will be included in the trial unless they notify the research team otherwise. In the  
36 latter situation, the local research team will obtain information from colleagues and bereavement  
37 counsellors to establish the most appropriate clinical/research team member to notify the  
38 parents/guardians of involvement in the trial. If approach for consent is deemed not appropriate  
39 prior to the parent/guardian's departure from hospital, then they will be approached by post four  
40 weeks post-randomisation. The letter will explain how to opt out of the trial. Postal contact will be  
41 made again if there is no response after four weeks. If no Consent Form is received within four  
42 weeks of the second letter, the participant's data will be included in the trial.  
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52 If informed consent is refused or withdrawn, this decision will be respected and abided by, and  
53 no further contact made. All data occurring up to the point of this decision will be retained in the  
54 trial, unless parents/guardians request otherwise.  
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### *Safety monitoring*

Adverse Event (AE) reporting will follow the Health Research Authority (HRA) guidelines on safety reporting in studies which do not use Investigational Medicinal Products (non-CTIMPs). The following events have been pre-specified as potential AEs that could be related to CPAP and/or HFNC and observed in participants from the date and time of randomisation until 48 hours of liberation from all forms of respiratory support:

1. Nasal trauma
2. Facial/neck trauma
3. Abdominal distension
4. Pneumothorax
5. Pneumomediastinum
6. Subcutaneous emphysema
7. Facial thermal injury
8. Respiratory arrest
9. Cardiac arrest
10. Aspiration

Occurrences of the specified, expected adverse events will be recorded for all randomised patients. Considering that eligible patients are critically ill and at increased risk of experiencing AEs, occurrences of non-specified, adverse events will only be reported if considered to be related to either CPAP or HFNC (i.e. 'possibly', 'probably' or 'definitely' related). Any event classified as 'severe' or 'life-threatening' in severity is considered a Serious Adverse Event (SAE) and must be reported to ICNARC CTU. If the SAE is evaluated by the Trial Management Group (TMG) as a related and unexpected SAE, the ICNARC CTU will submit a report to the REC within 15 calendar days.

### *Questionnaire follow-up*

At six months, after assessing the child's survival status, each consenting parent will be sent a questionnaire (via email or post) by the ICNARC CTU to assess Health-related Quality of Life (HrQoL) and health service/resource use. Non-responders will be followed-up by telephone three weeks later.

## Outcome measures

### Primary outcome

Time to liberation from respiratory support, defined as the start of a 48-hour period during which the child was free of all forms of respiratory support.

The primary outcome definition of respiratory support does not include administration of supplementary oxygen alone. In addition, the primary outcome will to be monitored/recorded after discharge from critical care, as necessary. We chose time to liberation from respiratory support, instead of rate of (re)intubation, as the primary outcome for several reasons, including: 1) through our patient and public involvement (PPI) work, parents/families reported that even though intubation was clearly an undesirable outcome, the fact that the child needed a 'breathing machine' of any description would be more important for them, in terms of assessing the success or failure of the intervention. Normalisation of 'breathing' was an important outcome prioritised over intubation; 2) since the rate of intubation on average was around 20% in the pilot RCT, nearly 80% of patients may not fulfil the intubation outcome. In these patients, several non-invasive support modes may be used, which prolong the time the patient is on 'breathing support' with resource implications for critical care. Clinicians felt that it was important that the effect of the intervention was assessed on patients who did not need intubation as well as on those who did. 3) unpublished data from the pilot RCT showed that the length of respiratory support is longer in patients who need intubation compared to those who do not. Therefore, the adverse impact of intubation is likely reflected in longer duration of respiratory support.

### Secondary outcomes

- Mortality at PICU/HDU discharge, day 60 and day 180
- Rate of (re)intubation at 48 hours
- Duration of PICU/HDU and hospital stay
- Patient comfort, during randomised treatment and during non-invasive respiratory support (i.e. HFNC and/or CPAP), assessed using the COMFORT-B score<sup>27</sup>
- Proportion of patients in whom sedation is used during non-invasive respiratory support
- Parental stress, in hospital at/around the time of consent at 24-48 hours, measured using the Parental Stressor Scale: PICU<sup>28</sup>
- HrQoL at six months using age-appropriate Pediatric Quality of Life Inventory (Peds-QL)<sup>29</sup> and Child Health Utility (CHU-9D) questionnaire<sup>30</sup>

### Cost effectiveness analysis (CEA) outcomes

- Total costs at six months
- Quality-Adjusted Life-Years (QALYs) at six months
- Incremental net monetary benefit gained at a willingness-to-pay of £20,000 per QALY at six months associated with HFNC versus CPAP<sup>31</sup>

### Data collection

To maximise efficiency, FIRST-ABC collaborates with the Paediatric Intensive Care Audit Network (PICANet) to make best use of established PICU data collection infrastructure. Where possible, recruited patients will be consented for data linkage with routine sources (e.g. national death registration data via NHS Digital or equivalent). Additional trial-specific data collection items are limited to the minimum required to deliver trial objectives (**Error! Reference source not found.**).

**Table 1 Patient data collection schedule**

	Baseline	At time of consent	During non-invasive respiratory support	End of PICU/HDU stay	End of hospital stay	At six months
<b>In-hospital</b>						
Clinical/baseline data	✓					
Patient/parent details		✓				
Types of respiratory support received*	✓		✓			
Patient comfort and sedation use			✓			
Parental stress		✓				
Discharge data				✓	✓	
Safety monitoring data			✓			
<b>At follow-up</b>						
PedsQL						✓
CHU-9D						✓
Health services/ resource use						✓

PICU: paediatric intensive care unit, HDU: high dependency unit, PedsQL: Pediatric Quality of Life Inventory (Peds-QL), CHU-9D: Child Health Utility questionnaire.

\* including weaning, switches and escalations from High Flow Nasal Cannula (HFNC)/Continuous Positive Airway Pressure (CPAP)

All participant data will be entered onto the secure electronic case report form and undergo validation checks for completeness, accuracy and consistency. The site Principal Investigator will oversee and be responsible for data collection, quality and recording.

## Statistical Methods

### Sample size

To achieve 90% power with a type I error rate of 2.5% (one-sided) to exclude the pre-specified noninferiority margin of HR=0.75 requires 508 events to be observed. Based on pilot RCT



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3 data,<sup>17</sup> we anticipate 5% censoring due to death or transfer, leading to a required sample size of  
4 268 patients per group in each of the two RCTs. To allow for withdrawal/refusal of consent, and  
5 for exclusion due to non-adherence in the per-protocol (PP) population, we will recruit a total  
6 sample size of 600 patients in each RCT.  
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### 9 10 **Internal pilot**

11 Data will be analysed at the end of the internal pilot stage (months 7-12 of the grant timeline) on  
12 patients recruited during the first six months in each RCT. The RCTs will progress from pilot to  
13 full trial based on pre-specified progression criteria related to successful site set-up, screening  
14 and recruitment, and adherence. The final decision on progression will be made by the funder  
15 after recommendation, or not, by the Trial Steering Committee (TSC).  
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### 19 20 **Clinical effectiveness analysis**

21 All analyses will be publicly lodged<sup>32</sup> in a statistical analysis plan, a priori, before the  
22 investigators are unblinded to any trial outcomes. Following best practice for non-inferiority trials,  
23 the primary analyses will be undertaken in both intention-to-treat (ITT) and PP populations, with  
24 robust conclusions possible in the situation where both populations provide concordant results.  
25 Results will be reported in accordance with the CONSORT statement extensions for non-  
26 inferiority and pragmatic trials.<sup>33 34</sup>  
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33 Analyses will be undertaken independently for each RCT. In each RCT, baseline patient  
34 characteristics will be compared between the two groups to observe balance and the success of  
35 randomisation. These comparisons will not be subjected to statistical testing. The delivery of the  
36 intervention will be described for each group in detail, including (but not limited to) number and  
37 percentage of patients who commence the randomised treatment, remain on the randomised  
38 treatment until liberation from ventilation, who are changed to a different mode of respiratory  
39 support.  
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46 HFNC will be considered non-inferior to CPAP if the lower bounds of the 95% confidence  
47 intervals for the hazard ratio (HR) from Cox regression models on time to liberation from  
48 respiratory support fitted in both the ITT and PP populations exclude the pre-specified non-  
49 inferiority margin of 0.75 (corresponding to approximately a 16-hour increase in median time to  
50 liberation, based on pilot RCT data). This margin was considered adequate such that the other  
51 potential benefits of HFNC in terms of comfort and tolerability would mean that it would be likely  
52 to be preferred in usual practice. The Cox regression models will be adjusted for important  
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3 baseline characteristics. The covariates for inclusion in the regression models will be selected a  
4 priori based on an established relationship with outcome for critically ill children, and not  
5 because of observed imbalance, significance in univariable analyses or by a stepwise selection  
6 method.  
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11 Subgroup analyses for the primary outcome will be performed to test for interactions between  
12 the effect of allocated treatment group and the following baseline covariates:  
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- 14 • age (<12 months versus  $\geq$ 12 months)
- 15 • severity of respiratory distress at randomisation (severe versus mild/moderate)
- 16 • Co-morbidities (None versus Neurological/neuromuscular versus Other)
- 17 • SpO<sub>2</sub>/FiO<sub>2</sub> (SF) ratio at randomisation
- 18 • for step-up RCT only:
  - 19 ○ clinical indication (bronchiolitis versus other respiratory (airway problem,  
20 asthma/wheeze or any other respiratory) versus cardiac versus other  
21 (neurological, sepsis/infection, any other))
  - 22 ○ whether child was on NRS at randomisation (Yes/No)
- 23 • for step-down RCT only:
  - 24 ○ length of prior invasive mechanical ventilation (<5 days versus  $\geq$ 5 days)
  - 25 ○ reason for invasive mechanical ventilation (cardiac versus other)
  - 26 ○ planned (randomisation followed by extubation) vs rescue (extubation followed by  
27 randomisation) non-invasive respiratory support

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38 We will treat age as a continuous variable and determine whether the model goodness-of-fit is  
39 better versus treating age as a categorical term for any analyses focusing on those over the age  
40 of 12 months. We anticipate a high proportion of patients will be aged <12 months and therefore  
41 exploration of age effects in the older ages will only be conducted if there are sufficient patient  
42 numbers.  
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48 As a sensitivity analysis, the primary analysis will be repeated using time to start weaning of  
49 NRS (i.e. duration of 'acute' respiratory support) and time to meeting objective 'readiness to  
50 wean NRS' criteria.  
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55 Secondary analyses of binary outcomes (mortality, reintubation) will be performed by Fisher's  
56 exact test and adjusted logistic regression. Duration of survival to day 180 will be plotted as  
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3 Kaplan-Meier survival curves, compared unadjusted with the log rank test and adjusted using  
4 Cox regression models. Analyses of duration of PICU/HDU and hospital stay will be performed  
5 by Wilcoxon rank-sum tests, stratified by survival status. Analyses of COMFORT-B score,  
6 sedation use, PSS:PICU and HrQoL will be performed by t-tests and adjusted linear regression.  
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11 In the step-up RCT, a single interim analysis will be carried out after the recruitment and follow-  
12 up to day 60 of 300 patients. The interim analysis will use a Peto-Haybittle stopping rule to  
13 recommend early termination due to superiority of either intervention ( $P < 0.001$ ) in time to  
14 liberation from respiratory support or evidence of harm from either intervention ( $P < 0.05$ ) in  
15 mortality at day 60. Both tests will be performed using a log-rank test on all available data within  
16 the ITT population. Further interim analyses will be performed only if requested by the Data  
17 Monitoring and Ethics Committee (DMEC).  
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24 In the step-down RCT, due to faster than anticipated recruitment, no formal interim analysis will  
25 be performed. Safety data (counts and percentages of adverse events by arm, and a line listing  
26 of SAEs) will be available for scrutiny by the DMEC, by the end of the internal pilot stage.  
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### 29 **Integrated health economic evaluation**

30 The CEA will take an NHS and Personal Social Services perspective.<sup>31</sup> Patient-level resource  
31 use data will be obtained from CRFs, PICANet, and a parent-completed health services  
32 questionnaire (HSQ). Resource use data from the PICU/HDU stay will be taken from the CRF  
33 and linked routine data from PICANet. Information on subsequent PICU/HDU and hospital  
34 admissions will be obtained via data linkage with PICANet and NHS Digital and also through  
35 completion of the HSQ. Data on the level of care for PICU bed-days will be gathered through  
36 routine collection of the Paediatric Critical Care Minimum Dataset (PCCMDS) in the participating  
37 sites via the PICANet database. Use of primary care and community health services will be  
38 assessed by HSQ at six months. Patient-level resource use data will be combined with  
39 appropriate unit costs from the NHS payment by results and Personal Social Services Research  
40 Unit databases to report total costs per patient for up to six months post-randomisation. Data  
41 from PedsQL and CHU-9D at six months will be combined with survival data to report QALYs at  
42 six months. The CEA will follow the intention-to-treat principle and report the mean (95%  
43 confidence interval) incremental costs, QALYs and net monetary benefit at six months. The CEA  
44 will use multilevel linear regression models that allow for clustering of patients at site. The  
45 analysis will adjust for key baseline covariates at both patient and site level.  
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## Ethics and dissemination

### Research ethics

The trial received favourable ethical opinion from NHS East of England - Cambridge South Research Ethics Committee (reference number: 19/EE/0185) and approval from the HRA (Integrated Research Application System (IRAS) number: 260536). Evidence of local confirmation of capacity and capability at each site must be provided to the ICNARC CTU prior to site activation.

### Confidentiality

ICNARC CTU will act to preserve participant confidentiality and will not disclose or reproduce any information by which participants could be identified. All data will be stored securely.

### Oversight

The TMG, led by the Chief Investigator, is responsible for the management of FIRST-ABC. It meets regularly and includes the Investigators and ICNARC CTU trial team. FIRST-ABC is managed by the ICNARC CTU in accordance with the Medical Research Council's Good Research Practice: Principles and Guidelines<sup>35</sup> which is based on the International Conference on Harmonisation guidelines on Good Clinical Practice<sup>36</sup> principles and the UK Department of Health's Policy Framework for Health and Social Care Research.<sup>37</sup> The on-site monitoring plan will follow a risk-based strategy.

A majority independent TSC has been established to monitor trial progress and includes PPI representatives, experienced clinicians and researchers/statisticians, in addition to the Chief Investigator and Head of Research at ICNARC. An independent DMEC, comprising experienced clinicians and statisticians, has been established to monitor patient recruitment and retention, adherence and safety.

The Great Ormond Street Hospital for Children NHS Foundation Trust are the trial sponsor (reference: 17IA05). As the sponsor is an NHS organisation, NHS indemnity will apply for legal liability arising from the design, management and conduct of the research.

### *Patient and Public Involvement (PPI)*

We had considerable PPI input into the pilot RCT<sup>17</sup> as well as the main trial described here. Following the pilot RCT, the PPI Group for Research at Great Ormond Street Hospital was consulted on the choice of the primary outcome for the main RCTs (see *Outcome measures*

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3 section). The parent of a child who received respiratory support is a co-investigator and has  
4 actively contributed to the trial design and procedures, including the use of deferred consent and  
5 patient/parent information sheets and other materials.  
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### 8 **Trial status** 9

10 This paper presents the master protocol (v1.2, dated 23 January 2020)<sup>38</sup> for the two largest  
11 RCTs studying the clinical and cost effectiveness of HFNC therapy as the first-line mode of NRS  
12 in critically ill children. It will provide robust evidence for the two distinct but common clinical  
13 scenarios in which NRS is primarily used. The first participant was recruited in August 2019. At  
14 the time of submission, patient recruitment was ongoing – with recruitment planned to complete  
15 in November 2020 and January 2022 for the step-down RCT and step-up RCT, respectively.  
16 Each RCT will be disseminated independently, including through publication in peer-reviewed  
17 medical journals and at national and international conferences.  
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## Footnotes

### Acknowledgements

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### Contributors

PR is Chief Investigator. ARB is Trial Manager. PR and ARB drafted the manuscript. PD, RF, RG, DH, JL, KM, PM, MP, KR, ZS, and LT are trial co-applicants and members of the Trial Management Group. LD supported management of the trial. All authors read and approved the final version.

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### Competing interests

None declared.

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2  
3 **Patient consent**

4 Not required.  
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8 **Ethics approval**

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10 The trial has received a favourable ethical opinion from the NHS East of England - Cambridge  
11 South Research Ethics Committee (reference number: 19/EE/0185) and approval from the  
12 Health Research Authority (Integrated Research Application System (IRAS) number: 260536).  
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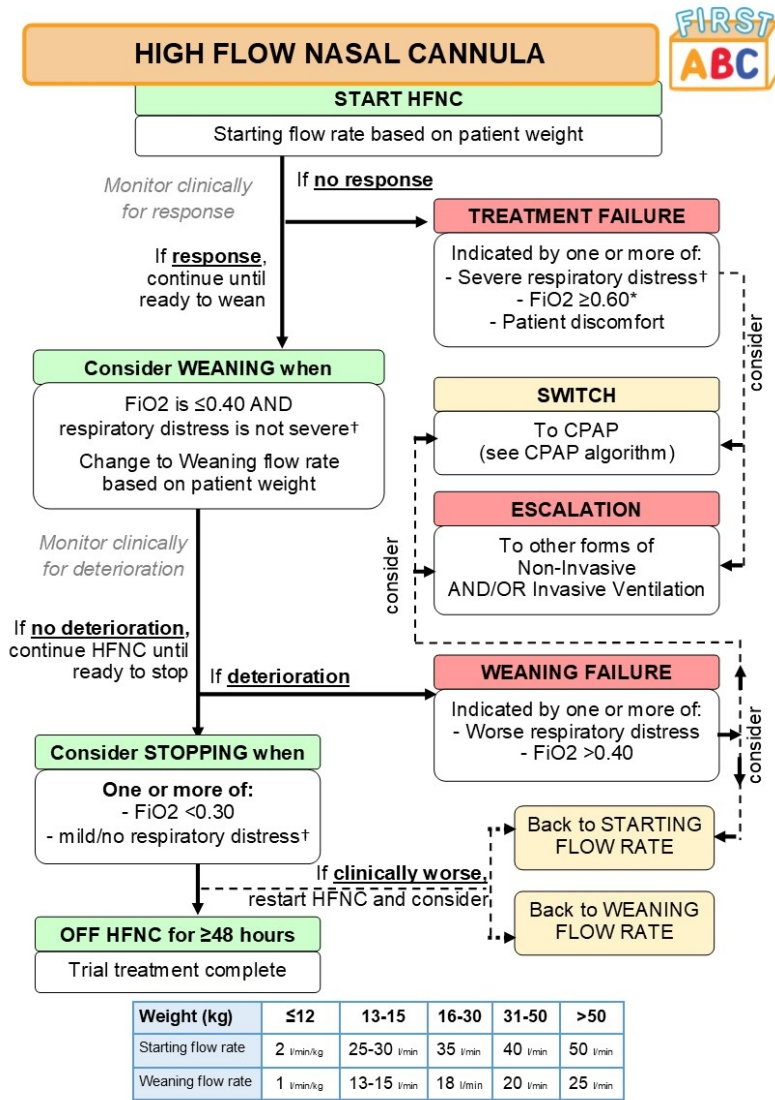
## Figure legends

### Figure 1. Algorithm for delivery of High Flow Nasal Cannula.

- † Respiratory distress defined as: Mild (one accessory muscle used, mild indrawing of subcostal and intercostal muscles, mild tachypnea, no grunting), Moderate (two accessory muscles used, moderate indrawing of subcostal and intercostal muscles, moderate tachypnea, occasional grunting); or Severe (use of all accessory muscles, severe indrawing of subcostal and intercostal muscles, severe tachypnea, regular grunting).
- \* Titrate FiO<sub>2</sub> while on HFNC to maintain SpO<sub>2</sub> ≥92% (or patient-specific target)

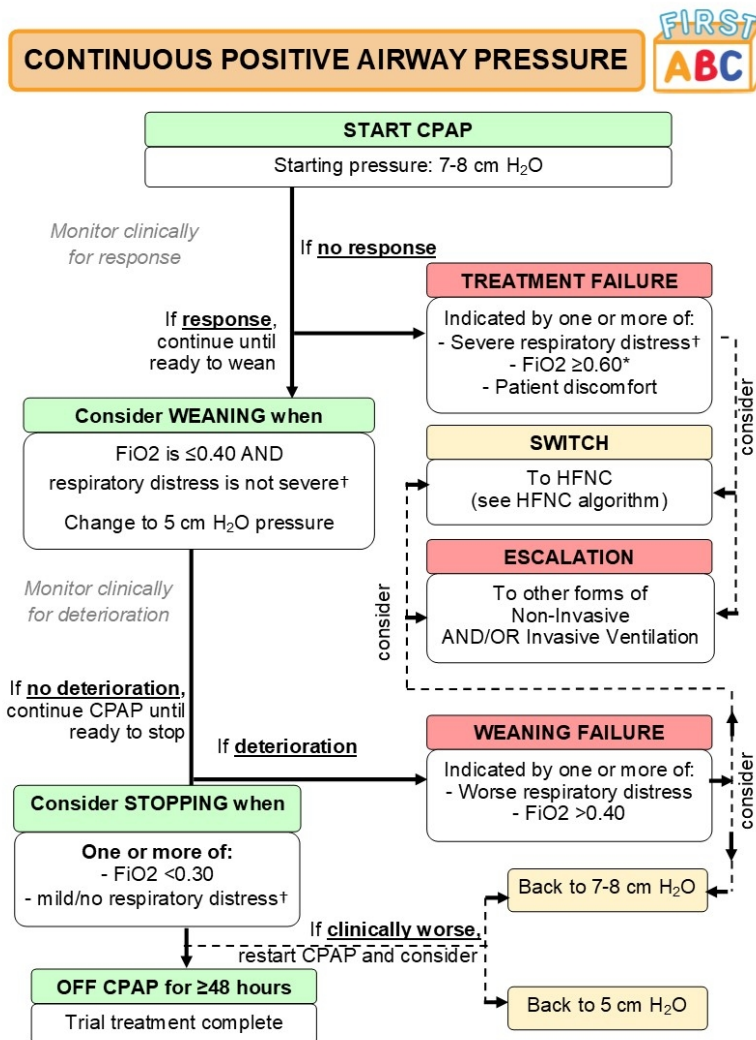
### Figure 2. Algorithm for delivery of Continuous Positive Airway Pressure.

- † Respiratory distress defined as: Mild (one accessory muscle used, mild indrawing of subcostal and intercostal muscles, mild tachypnea, no grunting), Moderate (two accessory muscles used, moderate indrawing of subcostal and intercostal muscles, moderate tachypnea, occasional grunting); or Severe (use of all accessory muscles, severe indrawing of subcostal and intercostal muscles, severe tachypnea, regular grunting).
- \* Titrate FiO<sub>2</sub> while on HFNC to maintain SpO<sub>2</sub> ≥92% (or patient-specific target)



Algorithm for delivery of High Flow Nasal Cannula.

147x209mm (150 x 150 DPI)



Algorithm for delivery of Continuous Positive Airway Pressure.

147x209mm (150 x 150 DPI)

To be printed on local hospital headed paper



FIRST-line support for Assistance in Breathing in Children

Consent Form - Parent or Legal Guardian

Version 1.2, 17 January 2020

To be completed by the Researcher:

Hospital name:	
Trial Number:	
Child's full name:	

To be completed by the Parent or Legal Guardian:

Once you have read and understood each statement – **if you agree, please write your initials in each box**

1. I confirm that I have read and understood the Participant Information Sheet (version 1.2, dated 27/11/2019) for the above research study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.
2. I understand that participation is voluntary, and that I am free to withdraw consent at any time, without giving any reason and without my child's medical care or legal rights being affected.
3. I agree to for my child to continue to take part in this study.
4. I understand that relevant sections of my child's medical records and data collected during the study (including name, date of birth, postcode and NHS number), held by the NHS or by NHS Digital, may be looked at by individuals from the NHS Trust, the Intensive Care National Audit & Research Centre (ICNARC), NHS Digital or regulatory authorities where it is relevant to my participation in this research. I give permission for these individuals to have access to my child's records.
5. I agree to complete a questionnaire about my experiences and reactions to being in the intensive care or high dependency unit.
6. I understand that ICNARC will send me a questionnaire to find out how my child is doing in six months time.
7. I understand that the information collected in the study will be used to support other research in the future, and may be shared anonymously with other researchers.
8. I would like to be contacted about any future related studies.

Your signature:		Date:	
Your full name (PRINT):			
Researcher signature:		Date:	
Researcher full name (PRINT):			

Once signed please turn over and complete

## FIRST-line support for Assistance in Breathing in Children

### Parent or Legal Guardian contact information

*To be completed by the Parent or Legal Guardian:*

If you would prefer to receive the questionnaire (as detailed on point 6 of the Consent Form) by **email**, please provide your details below:

<b>Email address:</b>	
<b>Telephone number(s):</b>	

OR

if you would prefer to receive the questionnaire in the **post**, please provide your details below:

<b>Postal address:</b>											
<b>Postcode:</b>	<table border="1"> <tr> <td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td> </tr> </table>										
<b>Telephone number(s):</b>											

*1 copy for patient and parent/guardian; 1 copy for Investigator Site File; 1 copy to be kept with hospital notes*



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

Section/item	Item No	Description	Page No.
<b>Administrative information</b>			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial	P1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	P3
	2b	All items from the World Health Organization Trial Registration Data Set	Throughout
Protocol version	3	Date and version identifier	P20
Funding	4	Sources and types of financial, material, and other support	P24
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	P24
	5b	Name and contact information for the trial sponsor	P19
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of .. . . .	P24
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	P19
<b>Introduction</b>			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	P4
	6b	Explanation for choice of comparators	P4
Objectives	7	Specific objectives or hypotheses	P5



Trial design

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Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority,

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For peer review only

**Methods: Participants, interventions, and outcomes**

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4	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
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9	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
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15	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
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20		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
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26		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
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30		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
31			
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33	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
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44	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
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50	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
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56	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size
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**Methods: Assignment of interventions (for controlled trials)**

Allocation:

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Sequence generation

16a Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign

P6-7

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2	Allocation	16b	Mechanism of implementing the allocation sequence
3	concealment		(eg, central telephone; sequentially numbered,
4	mechanism		opaque, sealed envelopes), describing any steps to
5			conceal the sequence until interventions are assigned
6			
7	Implementation	16c	Who will generate the allocation sequence, who will enrol
8			participants, and who will assign participants to
9			interventions
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12	Blinding	17a	Who will be blinded after assignment to interventions
13	(masking)		(eg, trial participants, care providers, outcome
14			assessors, data analysts), and how
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16		17b	If blinded, circumstances under which unblinding is
17			permissible, and procedure for revealing a
18			participant's allocated intervention during the trial
19			
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21	<b>Methods: Data collection, management, and analysis</b>		
22			
23	Data collection	18a	Plans for assessment and collection of outcome,
24	methods		baseline, and other trial data, including any related
25			processes to promote data quality (eg, duplicate
26			measurements, training of assessors) and a description
27			of study instruments (eg, questionnaires, laboratory
28			tests) along with their reliability and validity, if known.
29			Reference to where data collection forms can be found,
30			if not in the protocol
31			
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33		18b	Plans to promote participant retention and complete
34			follow-up, including list of any outcome data to be
35			collected for participants who discontinue or deviate
36			from intervention protocols
37			
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39	Data	19	Plans for data entry, coding, security, and storage,
40	management		including any related processes to promote data
41			quality (eg, double data entry; range checks for data
42			values). Reference to where details of data
43			management procedures can be found, if not in the
44			protocol
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47	Statistical	20a	Statistical methods for analysing primary and
48	methods		secondary outcomes. Reference to where other details
49			of the statistical analysis plan can be found, if not in the
50			protocol
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53		20b	Methods for any additional analyses (eg,
54			subgroup and adjusted analyses)
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57		20c	Definition of analysis population relating to protocol
58			non-adherence (eg, as randomised analysis), and any
59			statistical methods to handle missing data (eg,
60			multiple imputation)

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2 **Methods: Monitoring**  
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4 Data monitoring 21a Composition of data monitoring committee (DMC); P19  
5 summary of its role and reporting structure; statement  
6 of whether it is independent from the sponsor and  
7 competing interests; and reference to where further  
8 details about its charter can be found, if not in the  
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1		21b	Description of any interim analyses and stopping	P17-18
2			guidelines, including who will have access to these interim	
3			results and make the final decision to terminate the trial	
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6	Harms	22	Plans for collecting, assessing, reporting, and managing	P12-13
7			solicited and spontaneously reported adverse events and	
8			other unintended effects of trial interventions or trial	
9			conduct	
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11	Auditing	23	Frequency and procedures for auditing trial conduct, if	P19
12			any, and whether the process will be independent from	
13			investigators and the sponsor	
14				
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16	<b>Ethics and dissemination</b>			
17				
18	Research ethics	24	Plans for seeking research ethics committee/institutional	P19,25
19	approval		review board (REC/IRB) approval	
20				
21	Protocol	25	Plans for communicating important protocol modifications	Not provided
22	amendments		(eg, changes to eligibility criteria, outcomes, analyses) to	
23			relevant parties (eg, investigators, REC/IRBs, trial	
24			participants, trial registries, journals, regulators)	
25				
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27	Consent or assent	26a	Who will obtain informed consent or assent from	P11-12
28			potential trial participants or authorised	
29			surrogates, and how (see Item 32)	
30				
31		26b	Additional consent provisions for collection and use of	NA
32			participant data and biological specimens in ancillary	
33			studies, if applicable	
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36	Confidentiality	27	How personal information about potential and enrolled	P19
37			participants will be collected, shared, and maintained in	
38			order to protect confidentiality before, during, and after the	
39			trial	
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42	Declaration of	28	Financial and other competing interests for principal	P24
43	interests		investigators for the overall trial and each study site	
44				
45	Access to data	29	Statement of who will have access to the final trial	P19
46			dataset, and disclosure of contractual agreements	
47			that limit such access for investigators	
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50	Ancillary and	30	Provisions, if any, for ancillary and post-trial care,	NA
51	post-trial care		and for compensation to those who suffer harm	
52			from trial participation	
53				
54	Dissemination	31a	Plans for investigators and sponsor to communicate trial	P20
55	policy		results to participants, healthcare professionals, the	
56			public, and other relevant groups (eg, via publication,	
57			reporting in results databases, or other data sharing	
58			arrangements), including any publication restrictions	
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31b	Authorship eligibility guidelines and any intended use of professional writers	Not provided
31c	Plans, if any, for granting public access to the full protocol, participant- level dataset, and statistical code	Full protocol is referenced

For peer review only

## Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary file
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for	NA

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\*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.