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## FIRST-line support for Assistance in Breathing in Children (FIRST-ABC)

Statistical Analysis Plan, Version 1.0

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## Roles and responsibilities

**Role, Name and Position**

**Signature**

**Date**

**Authors:**

Izabella Orzechowska, Statistician, ICNARC

.....

Karen Thomas, Senior Statistician, ICNARC

.....

**Chief Investigator:**

Dr Padmanabhan Ramnarayan, GOSH

.....

## Version history

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1.0			

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# 1 Introduction

## 1.1 Background and rationale

Increasing recognition of the risks of invasive ventilation for critically ill children, such as ventilator-induced lung injury and nosocomial infections, have prompted greater use of non-invasive respiratory support (NRS) techniques in paediatric intensive care units (PICUs) worldwide<sup>12</sup>. NRS is currently used in two distinct clinical scenarios: 1) in acutely ill children, aiming to prevent intubation and invasive mechanical ventilation (IMV) (step-up treatment), and 2) in children who have just come off IMV, aiming to prevent re-intubation and further IMV (step-down treatment). Continuous positive airway pressure (CPAP) is a mode of NRS which is commonly used and effective, but can be uncomfortable for some children, and is associated with a small but significant risk of complications such as air-leak and nasal trauma. More recently, an alternate mode of NRS, high-flow nasal cannula (HFNC), has gained popularity since it appears easy to use and well tolerated by patients<sup>3456</sup>.

FIRST-ABC (First-line support for Assistance in Breathing in Children feasibility study) therefore addresses an important clinical dilemma faced daily by paediatric critical care clinicians in the UK: in a child requiring non-invasive respiratory support as either a step-up or step-down treatment, which of the two commonly available modalities, HFNC or CPAP, should they use as first-line therapy to achieve the best patient outcomes?

The FIRST-ABC Trial is testing the hypothesis that in critically ill children who require non-invasive respiratory support (NRS), the first-line use of high flow nasal cannula (HFNC) is non-inferior to continuous positive airway pressure (CPAP) in terms of time to liberation from respiratory support.

This document describes the proposed Statistical Analyses Plan (SAP) for the trial. The SAP is agreed in advance of inspecting the outcome data for the trial, so that data-derived decisions in the analyses are avoided. This SAP has been prepared in accordance with published guidelines<sup>7</sup>.

## 1.2 Aim and Objectives

To evaluate the clinical and cost-effectiveness of the use of HFNC, as compared with CPAP, when used as the first-line mode of non-invasive respiratory support in two distinct clinical scenarios:

1. in critically ill children requiring non-invasive respiratory support for an acute illness (*step-up RCT*); and
2. in critically ill children requiring non-invasive respiratory support within 72 hours of extubation following a period of invasive ventilation (*step-down RCT*).

### 1.2.1 Primary Objectives

To evaluate the non-inferiority of HFNC, as compared with CPAP, when used as the first-line mode of non-invasive respiratory support, 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, defined as the start of a 48-hour period during which the child was free of all forms of respiratory support.

## 1.2.2 Secondary Objectives

To compare, between the groups:

- mortality at PICU/HDU discharge, day 60 and day 180;
- the rate of (re)intubation at 48 hours;
- the duration of PICU/HDU and hospital stay;
- patient comfort, during randomised treatment and during non-invasive respiratory support (i.e. HFNC and/or CPAP), measured using the validated COMFORT-B Score<sup>8</sup>;
- the proportion of patients receiving sedation during randomised treatment and during non-invasive respiratory support (i.e. HFNC and/or CPAP);
- parental stress, in hospital at the time of consent, measured using the Parental Stressor Scale: PICU (PSS:PICU)<sup>9</sup>
- Health-related Quality of Life (HrQoL) at six months measured using the age-appropriate Paediatric Quality of Life Inventory (Peds-QL)<sup>10</sup> and The Child Health Utility 9D (CHU 9D)<sup>11</sup>

## 2 Study Methods

### 2.1 Trial design

The FIRST-ABC trial comprises two pragmatic, multicentre, parallel groups, non-inferiority randomised clinical trials (step-up RCT and step-down RCT) with shared infrastructure. An internal pilot is incorporated into both trials.

The trials will be run in up to 25 NHS paediatric critical care units (PICU) and/or high dependency units (HDUs) in the UK. While most sites are expected to participate in both trials, it is permissible for a site to choose to recruit to only one of the two trials.

### 2.2 Randomisation

In each RCT, eligible patients will be randomised on a 1:1 basis to either CPAP or HFNC using a central telephone/web-based randomisation service. The randomisation sequence will be computer generated and variable block sizes will be used. Randomisation will be stratified by site and age (<12 months versus  $\geq$ 12 months).

### 2.3 Sample size

The sample size was calculated as follows: to achieve 90% power with a one-sided type I error rate of 2.5% to exclude the prespecified noninferiority margin of HR=0.75 (corresponding to approximately a 16-hour increase in median time to liberation) requires 508 events to be observed. Based on data from the FIRST-ABC pilot RCT<sup>12</sup>, we anticipate 5% censoring due to death or transfer, leading to a required sample size of 268 patients per group in each of the two RCTs. To allow for withdrawal/refusal of deferred consent, and for exclusion due to non-adherence in the PP population, we will recruit a total sample size of 600 patients in each of the two RCTs.

## 2.4 Framework

The primary clinical outcomes will be tested for non-inferiority. Other secondary outcomes will be tested for superiority, where testing is specified, or analysed using descriptive statistics only if no testing is specified in this SAP. All analyses described in this SAP will be performed separately for each of the two trials, and any results will not be combined.

## 2.5 Analysis of internal pilot

The internal pilot phase was evaluated 6 months after the first site has opened to recruitment. At this point the following key progression criteria were assessed and classified as green, amber or red:

Criterion	Green light (go)	Amber light (amend)	Red light (stop)
Number of sites opened to recruitment	15 or more	8-14	7 or fewer
Overall recruitment rate in open sites (% of anticipated rate)	75% or more	50-74%	less than 50%
Proportion of patients who were started on the randomly allocated treatment	over 90%	75-90%	less than 75%
Changes to another form of NRS, escalation and weaning carried out as per protocol	At least two-thirds	Between one-third and two-thirds of cases	Less than one-third of cases

The proportion of patients started on the randomly allocated treatment was calculated using all randomised patients in the denominator.

For each patient, the first occurrence of one of the following events: treatment switch, escalation, start of weaning, or stopping treatment, had the reason for the event classified as either adherent (fulfils the criteria set out in the treatment algorithm) or not. Events occurring for other (free text) reasons were discussed by the TMG who decided whether the event was adherent or not. If a patient started the randomised treatment and was subsequently censored before occurrence of any of these events, they were classified as adherent. The proportion of patients with adherent (or censored) first events was calculated using all patients who started on the randomly allocated treatment as the denominator.

All progression criteria in both trial were classified as green, so the trials will proceed to the full sample size as planned.



## 2.6 Statistical interim analysis and stopping criteria

The internal pilot phase will be evaluated 6 months after the first site opened to recruitment against pre-specified progression criteria (Number of sites opened; recruitment rate; proportion of patients started on allocated treatment; Changes/escalation to other forms of respiratory support and weaning carried out as per protocol)

A single interim analysis will be carried out in each RCT, after recruitment and follow-up to day 60 of 300 patients. At this point, the following endpoints will be analysed in the intention to treat (mITT) population only:

- Time to liberation from respiratory support, which will be tested using an unadjusted log-rank test, with early termination of the trial recommended if any one arm is shown to be superior with  $p < 0.001$  (Peto-Haybittle stopping rule)
- Mortality to day 60, which will be tested using a log-rank test, with early termination of the trial recommended if any one arm is shown to be superior with  $p < 0.05$ .

For this interim analysis, patients discharged alive from hospital alive with no further death after discharge recorded are assumed to be alive on the day of data extract. Patients who have withdrawn or refused consent for access to medical records will be censored on the date of withdrawal or refusal of consent.

## 2.7 Timing of final analysis

The final analysis for each trial will be performed no earlier than 6 months after the last patient has been randomised to that trial.

## 2.8 Timing of outcome assessments

Following randomisation, details of respiratory support (type of support, flow rate/pressure), physiological parameters (respiratory rate, heart rate, SpO<sub>2</sub>, FiO<sub>2</sub>), and measures of patients comfort (respiratory distress scored as none/mild/moderate/severe, sedation delivered yes/no, and COMFORT-B scores) are recorded hourly for the first 6 hours, and six hourly thereafter until the end of respiratory support (or to at least 48 hours following randomisation, if patients are transferred to another unit or ward).

Survival status is recorded at unit discharge, at ultimate discharge from critical care (if the patient has been transferred to another critical care unit) and at discharge from acute hospital. Where consent is given for access to medical records, longer term survival is collected from linked NHS Digital records.

Parental stress is measured using the Parental Stressor Scale at the time of consent, which is expected to be within 24-48 hours of randomisation. Pediatric Quality of Life Inventory (Peds-QL) and The Child Health Utility 9D (CHU-9D)) and health services/resource use is assessed at six months post-randomisation.

## 3 Statistical Principles

### 3.1 Confidence intervals and p-values

The primary clinical outcome will be tested for non-inferiority. Other secondary outcomes will be tested for superiority, where testing is specified, or analysed using descriptive statistics. Statistical tests will be two-sided with significance set at  $P < 0.05$  unless otherwise specified. Effect estimates will be reported with 95% confidence intervals. There will be no adjustment for multiple testing. The results of subgroup analyses will be interpreted taking into account accepted criteria for credible subgroup effects<sup>13, 14</sup>. All analyses described in this SAP will be performed separately for each of the two RCTs, and any results will not be combined.

### 3.2 Adherence and protocol deviations

#### 3.2.1 Exposure

Exposure to the intervention will be assessed by the following parameters, which will be calculated for each treatment group and summarised using descriptive statistics (mean, standard deviation, median and interquartile range (IQR), or counts and percentages for binary and categorical variables) unless otherwise specified:

- In patients randomised to CPAP, pressure (in cm H<sub>2</sub>O as a continuous variable, and grouped as <7cm, 7-8cm, >8cm), by hour during the first 6 hours from randomisation.
- In patients randomised to HNFC, flow rate (as % of recommended starting rate, and grouped as ≤50%, 51-75%, 76-85%, 86-95%, ≥95% of recommended starting rate), by hour during the first 6 hours from randomisation.
- Time from first recorded observation meeting weaning/failure/stopping criteria to time of weaning/switch or escalation/treatment stop

Further treatment patterns across each group and time from first meeting weaning criteria to start of weaning attempt will be explored using summary statistics and graphic methods only, no formal statistical testing will be performed.

#### 3.2.2 Protocol adherence

The number and % of patients affected will be reported for each of the following potential protocol deviations:

- Did not start randomised treatment (i.e. first recorded respiratory support post-randomisation is not the randomised treatment)
- Switched or escalated from randomised treatment without meeting treatment failure criteria
- Weaning attempt made, when weaning criteria is not met in last recorded observation prior to weaning
- Respiratory support is discontinued while  $FiO_2 \geq 0.3$  and moderate or severe respiratory distress is present

### 3.3 Analysis Population

All randomised patients will be included in the intention to treat (ITT) population. A modified ITT (mITT) population will be used for analysis of the primary endpoint, consisting of the ITT populations excluding those with no recorded respiratory support post-randomisation.

The per protocol (PP) population will consist of all randomised patients who met the eligibility criteria and were started on the randomised respiratory support, as the first respiratory support post-randomisation.

## 4 Trial population

### 4.1 Screening data

Screening logs will be used to record all patients who are admitted or accepted for admittance to critical care (step-up RCT), and all patients extubated during critical care unit stay (step-down RCT). The following summaries will be presented:

- Number and % of patients who did not meet inclusion criteria, overall and by criteria
- Of the patients who met the inclusion criteria, number and % who met exclusion criteria, overall and by criteria.
- Of the eligible patients (i.e. met inclusion criteria and did not meet exclusion criteria), number and % not randomised, overall and by reason (if known)

### 4.2 Eligibility

#### 4.2.1 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).

#### 4.2.2 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 the FIRST-ABC trial\*
9. Clinician decision to start other form of non-invasive respiratory support (i.e. not HFNC or CPAP)

\*i.e. patients randomised to the step-up RCT will not be eligible for randomisation to the step-down RCT. Similarly, patients once enrolled to the step-up or step-down RCTs and satisfied the primary outcome of being liberated from respiratory support will not be eligible for re-randomisation to the trial even if they require further episode(s) of NRS during the same or on subsequent hospital admissions.

#### 4.3 Recruitment

The following CONSORT<sup>15</sup> flow diagrams for the ITT and PP populations will be completed for each trial:

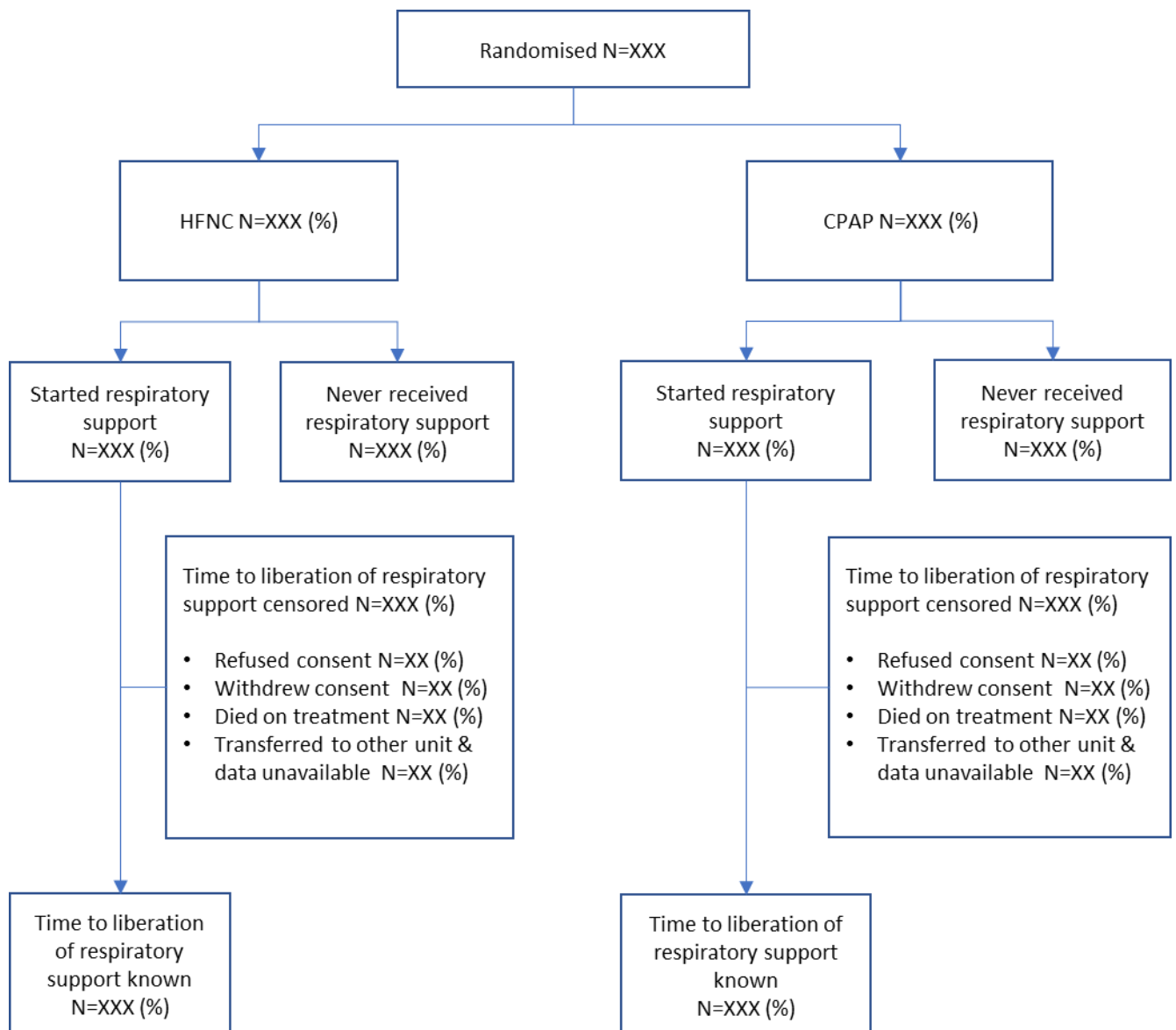


Figure 1: CONSORT diagram for ITT population

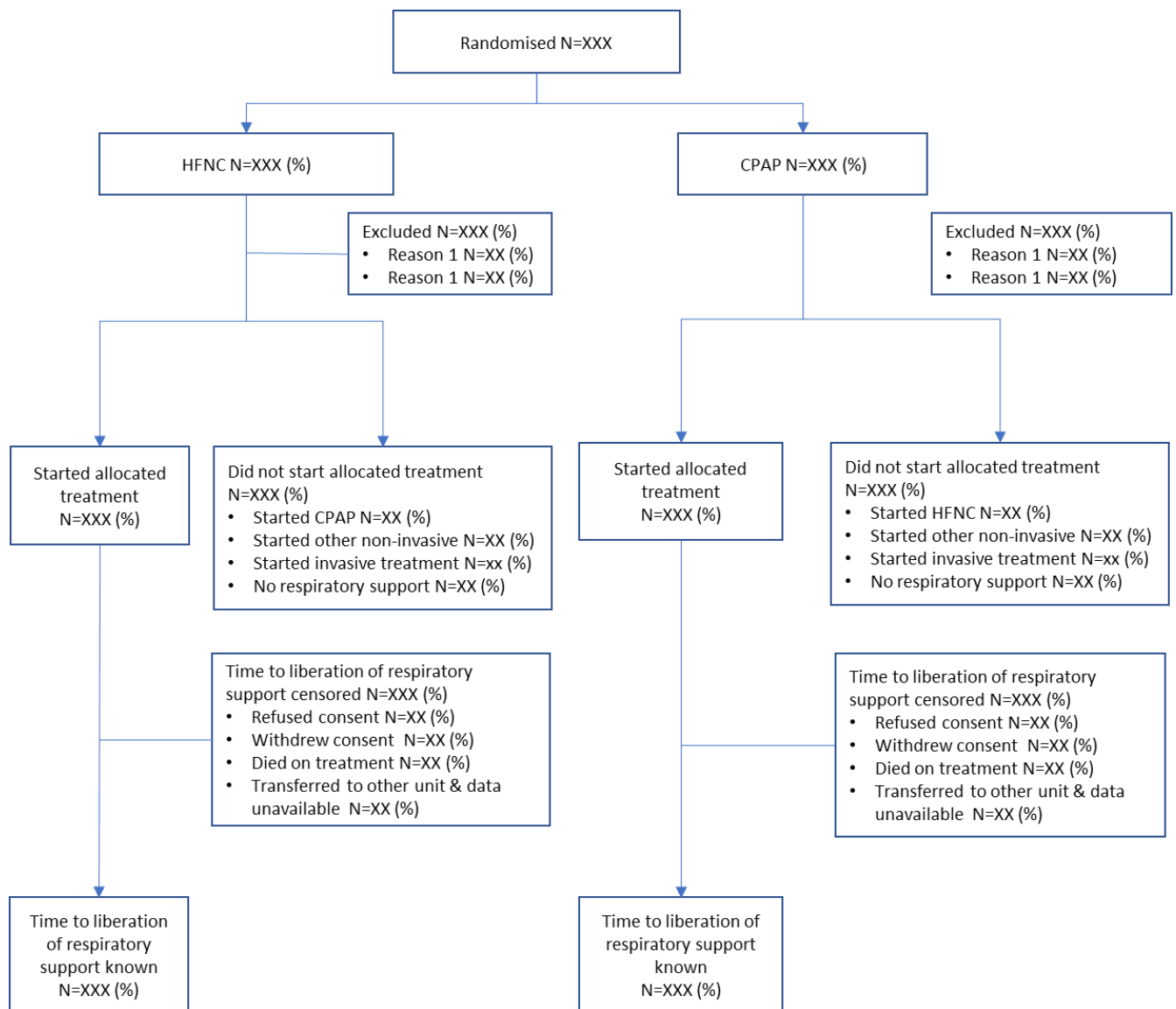


Figure 2: CONSORT diagram for PP population

#### 4.4 Consent

The parent/legal guardian of trial participants will be asked to consent to the study as soon appropriate and practical after randomisation (usually within 24-48 hrs of randomisation but the timing will vary according to the child’s clinical situation). They may consent to any one or more of the following aspects: Trial continuation (i.e. treatment); access to medical records for ongoing data collection; completion of the parental stress questionnaire (at/around the time of consent); to receive a follow-up questionnaire at 6 months post-randomisation; sharing of anonymised data to support future research; to be contacted regarding future research participation. When consent is refused for access to medical records (regardless of whether or not consent has been given for trial continuation), all trial data collection should cease and no data linkage to PICANET or NHSDigital should be performed. Data collected by site staff directly to the trial CRF up to the point of consent refusal will be retained and used for analysis, but no events after this point will be recorded or reported on. If any data has already been obtained via linkage from PICANET or NHSDigital, this data will be deleted.

Where consent has been refused for trial continuation, but granted for access to medical records, data collection and linkage may continue and the patient may be included in the analysis as appropriate for each endpoint.

If consent is refused for access to medical records and/or trial continuation, the parental stress questionnaire may still be completed and reported on if this has been consented to.

#### 4.5 Withdrawal/follow-up

Once given, consent can be withdrawn at any time up to the end of the study. Data collected up to the point of non-consent or withdrawal of consent to data collection will be retained.

#### 4.6 Baseline patient characteristics

Baseline data is collected at critical care admission via data linkage to PICANET, and directly via trial CRF for physiology at randomisation. The following baseline demographic and clinical data will be summarised in the mITT and PP populations, by allocated treatment group, (using mean, standard deviation, median and interquartile range (IQR), or counts and percentages for binary and categorical variables:), but not subjected to statistical testing:

In both trials:

Age (years)– median and IQR, and number and % by age group (<=28 days, 29-180 days, 181-364 days, 1 year, 2 years, 3 years, 4 years, 5-10 years, 11-15 years)

Sex (male, female) – number and %

Respiratory distress at randomisation – number and % by category

Heart rate at randomisation (both as absolute values, and converted to centile for age) – median and IQR, mean and SD

SpO2 at randomisation – median and IQR, mean and SD

FiO2 at randomisation – median and IQR, mean and SD

Ratio of SpO2:FiO2 at randomisation – median and IQR, mean and SD

Comfort-B score at randomisation (last available) – mean and IQR, number and % with COMFORT-B score  $\geq 23$  (representing possible distress<sup>16</sup>)

Comorbidities – number and % by type of comorbidities (as specified on the CRF)

Step-up only:

Main reason for admission to critical care – number and %

Any respiratory support received in 24hrs prior to randomisation (overall, and by type and duration of support) – number and %

Whether on respiratory support at time of randomisation – number and %

Received general anaesthesia for surgery/procedure in the 6 hours preceding randomisation – number and %

Step-down only:

Main reason for invasive ventilation

Duration of invasive ventilation - median and IQR , and number and % with duration <5 days, number and % with duration >=5 days

## 5 Analysis

### 5.1 Outcome definitions

#### 5.1.1 Primary outcome

The primary clinical outcome is time to liberation from respiratory support, defined as the time from randomisation to the start of a 48-hour period during which the child was free of all forms of respiratory support.

#### 5.1.2 Secondary outcomes

##### 5.1.2.1 Mortality at discharge from PICU (day 60 and day 180)

Mortality at discharge from the critical care unit will be defined as death due to any cause before discharge to any location providing a level of care less than Level 2 (high dependency care).

##### 5.1.2.2 Rate of (re)intubation at 48 hours

Intubation at 48 hours is defined as present if the child has started any invasive ventilation at any time up to and including 48 hours and zero minutes after time of randomisation. Patients are included in the denominator if they have received invasive ventilation by 48 hours, or are known not to have received any invasive ventilation from randomisation to critical care discharge (or at 48hrs following randomisation if this is before critical care discharge).

##### 5.1.2.3 Duration of PICU/HDU and acute hospital stay

Duration of PICU/HDU will be calculated as the sum of the duration (in days and fractions of days) from the date and time of randomisation to the date and time of first discharge from the critical care unit (or ultimate discharge from critical care if transferred to another critical care unit) or to death in the critical care unit, plus the duration of any subsequent admissions to the critical care unit within the same acute hospital stay (these are measured in whole days only).

Duration of acute hospital stay will be calculated as the duration in days from the date of randomisation to the date of ultimate acute hospital discharge or death in acute hospital.

##### 5.1.2.4 Patient comfort, during randomised treatment and during non-invasive respiratory support (i.e. HFNC and/or CPAP), measured using the COMFORT-B score.

Patient comfort is measured during respiratory support using the validated modified COMFORT-B score which will be summarised at patient level using the median of all recorded scores. To be measured in all patients with at least one recorded COMFORT-B score in the first six hours of support following randomisation, AND, while respiratory support continues, at least one COMFORT-B score per day during at least the first 48 hours of respiratory support.

##### 5.1.2.5 Need for Sedation

Need for sedation will be defined as the proportion of patients in whom sedation is used during non-invasive respiratory support at any point until liberation from respiratory support. Patients will be included in the denominator if they have a minimum of three non-missing observations in the first



six hours of respiratory support, AND, while respiratory support continues, at least two non-missing observations per day during the first 48 hours of respiratory support.

#### *5.1.2.6 Parental stress at 24-48h*

Parental stress will be measured using the validated Parental Stressor Scale: PICU (PSS: PICU) in hospital at/around the time of consent (anticipated to be within 24-48 hours post-randomisation). This consists of 37 items each scored in whole numbers from 1 (not stressful) to 5 (extremely stressful). A total score is calculated as the mean of all completed items.

#### *5.1.2.7 Health-related quality of life at 6 months*

Health-related quality of life at 6 months will be measured using the Paediatric Quality of Life Inventory (Peds-QL)<sup>32</sup> and the Child Health Utility 9D (CHU-9D), completed by parents at six month post-randomisation.

The PEDS-QL instrument uses a different set of question of each age group of 1-12 months; 13-24 months; 2-4 years; 5-7 years; 8-12 years; 13+years. For each age group an overall score is calculated on a scale of 0-100 with higher scores indicating better quality of life. In infants under 2 years five subscales are defined, relating to physical functioning, physical symptoms, emotional functioning, social functioning, and cognitive functioning , and in children of 2 years and over four subscales are defined, relating to physical functioning, emotional functioning, social functioning and school functioning.

CHU-9D was developed with children aged 7-17 and is designed to produce utility values for use in calculating quality adjusted life years (QALYs)

#### *5.1.2.8 Total costs at 6 months*

Cost will be calculated from patient-level resource use data on resources required to deliver the intervention, length of stay in PICU/HDU and acute hospital, for the index admission and any readmission before 6 months, and use of personal health services after acute hospital discharge within 6 months post-randomisation. Patient level resource use data will be valued using appropriate unit costs data from the NHS Payment by Results database, unit costs of health and social care (PSSRU) and from local Trust Finance Departments, to calculate total costs at 6 months.

#### *5.1.2.9 Quality-Adjusted Life Years (QALYs) at 6 months*

The health outcome for the economic evaluation will be summarised using QALYs, which unites quantity (survival) and quality of life into a single metric. To do this, HRQoL, which is measured on an index scale of 1 (equals full health) and 0 (equals death), at 6 months will be assessed using the CHU-9D instrument, with valuation using the validated UK tariffs (Stevens, 2012). HRQoL data will be combined with the survival data to calculate QALYs at 6 months. QALYs will be calculated by valuing each patient's survival time by their HRQoL at 6 months according to the "area under the curve" approach. For 6-month survivors, QALYs will be calculated using the CHU-9D scores at 6 months, assuming an CHU-9D score of zero at randomisation, and a linear interpolation between randomisation and 6 months. For decedents between randomisation and 6 months, we will assume zero QALYs.

5.1.2.10 *Incremental net monetary benefit gained at a willingness-to-pay of £20,000 per QALY at six months associated with HFNC vs. CPAP*

Net monetary benefits will be calculated by valuing QALY gains at £20,000 per QALY and subtracting incremental costs.

## 5.2 Clinical effectiveness analysis methods

### 5.2.1 Primary outcome

The median (with 95% CI) time to liberation from respiratory support will be reported for each arm using Kaplan-Meier estimates, and compared between groups using Cox regression, unadjusted and adjusted for important baseline characteristics (including shared frailty at the site level). The covariates for inclusion in the regression models are the following, which have been selected a priori based on an established relationship with outcome for critically ill children:

In both trials

- age (<12 months versus ≥12 months)
- severity of respiratory distress at randomisation (severe versus mild/moderate)
- SpO<sub>2</sub>:FiO<sub>2</sub> ratio at randomisation (linear)
- Co-morbidities (None versus Neurological/neuromuscular versus Other)

Step-up only

- reason for admission (bronchiolitis versus other respiratory (airway problem, asthma/wheeze or any other respiratory) versus cardiac versus other (neurological, sepsis/infection, any other)
- whether the patient was on NRS at randomisation (yes/no)

Step-down only

- length of prior IMV (<5 days versus ≥5 days).
- Reason for IMV (cardiac versus other).

The primary effect estimate will be the adjusted hazard ratio, reported with a 95% confidence interval. HFNC will be considered non-inferior to CPAP if the lower bound of the 95% confidence interval is above 0.75 in both the mITT and PP populations. Patients without a recorded time of liberation will be censored at date & time of death (for patients who died while on treatment) or at date & time of last recorded respiratory support. The assumption of proportional hazards will be explored by fitting a Cox model with time dependent covariates.

Subgroup analyses will be performed to test for interactions between the effect of allocated treatment group and the following baseline covariates, with groupings defined as for the adjusted model specification above:

(both trials)

- age
- severity of respiratory distress at randomisation
- SF ratio at randomisation
- Co-morbidities

(step-up only)

- reason for admission
- whether the patient was on NRS at randomisation

(step-down only)

- length of prior IMV
- Reason for respiratory support post-extubation, categorised as planned (randomisation followed by extubation), indeterminate (extubation followed by randomisation within 60 minutes of extubation) vs rescue (extubation followed by randomisation more than 60 minutes post extubation) breathing support
- Reason for IMV

The interaction effect for linear covariates (SF ratio) will be illustrated by calculating the adjusted hazard ratio within five categories at quintiles of the continuous variable.

As a sensitivity analysis, the primary analysis will be repeated using time to start weaning of NRS (i.e. duration of 'acute' respiratory support), time to meeting objective 'readiness to wean NRS' criteria, and time from start of support to liberation from support

#### 5.2.2 Secondary outcomes

Binary outcomes (mortality at discharge from critical care, at 60 and 90 days post-randomisation, (re-)intubation at 48 hours, sedation use during randomised treatment, sedation use during HFNC or CPAP) will be reported in each treatment group, in the PP and mITT populations. Absolute risk reduction and unadjusted odds ratios will be reported with 95% confidence intervals. Multilevel logistic regression (adjusted for the same baseline variables as the adjusted analysis of the primary outcome) will be used to calculate adjusted odds ratios with 95% confidence intervals.

Continuous outcomes (duration of PICU and hospital stays) will be summarised by treatment groups, stratified by survival status, in the PP and mITT populations. Mean difference between groups will be calculated, with 95% confidence interval using bootstrapping to account for anticipated non-normality in the distribution.

Duration of survival to d180 will be plotted as Kaplan-Meier survival curves, in the PP and mITT populations, and unadjusted and adjusted hazard ratios with 95% confidence intervals will be calculated using Cox regression models.

Parent/patient reported outcomes (PSS:PICU score, PEDS-QL score) will be summarised by treatment groups, in the PP and mITT populations. Mean difference between groups will be calculated, with 95% confidence interval using bootstrapping to account for anticipated non-normality in the distribution. Linear regression will be used to calculate adjusted mean differences.

For each patient, their median Comfort-B score while on randomised treatment, and their median Comfort-B score while on either HFNC or CPAP will be calculated. These median scores will be summarised by treatment groups, using median (IQR) and mean (sd). The number and % of patients with any recorded COMFORT-B score  $\geq 23$  while on randomised treatment, and the number and % of patients with any recorded COMFORT-B score  $\geq 23$  while on either HFNC or CPAP will be reported. Mean difference between groups will be calculated, with 95% confidence interval using

bootstrapping to account for anticipated non-normality in the distribution. Linear regression will be used to calculate adjusted mean differences.

### 5.3 Cost effectiveness analysis methods

A full cost-effectiveness analysis (CEA) will be undertaken to assess the relative cost-effectiveness of HFNC versus CPAP according to the intention-to-treat principle. Resource use and outcome data collected as a part of the FRIST-ABC trial will be used to report cost-effectiveness at 6 months by randomised treatment group.

The cost analysis will take a health and personal health services perspective. The primary sources of the resource use data will be the FIRST-ABC trial case report forms (CRFs), PICANET data, hospital episode statistics (HES) database and individual health service questionnaires (HSQ) on the use of personal health services which are posted to surviving patients at 6 months following randomisation. Resource use data from the PICU/HDU stay will be taken from the CRF and linked to routine data from PICANet. Data on the level of care for PICU/HDU bed-days will be gathered through routine collection of the Paediatric Critical Care Minimum Dataset (PCCMDS) in the participating centres via the PICANet database. Information on subsequent PICU/HDU and hospital admissions will be obtained via data linkage with PICANet and HES database. Use of primary care and community health services will be assessed by HSQ at six months. Resource use data from the trial datasets, PICANet data, HES database and 6 months follow-up questionnaires will be combined with unit costs from the NHS Payment by Results database, unit costs of health and social care (PSSRU) and from local Trust Finance Departments, to report the total costs per patient at six months for both randomised groups.

Missing data in costs and HRQoL will be handled with multiple imputation, assuming the data are missing at random (MAR) conditional on the observed data (see below for details on methods used to handle missing data). On the imputed datasets the cost-effectiveness analysis will use a Bivariate Seemingly Unrelated Regression model to allow for correlation between costs and QALYs and multilevel structure of the data. We will calculate the interclass correlation coefficient (ICC) which measures the proportion of the overall variation that occurs at the cluster level<sup>17</sup>. If ICC > 10% we will use multilevel models (MLM) to handle clustering and avoid potential biases and incorrect inferences. The incremental results from multiply-imputed datasets will be summarised using Rubin's rule {Rubin, 1987 #54}.

The CEA will follow the intention-to-treat principle and report the mean (95% confidence interval) incremental costs, QALYs and net monetary benefit at 6 months. The base case analysis will report the incremental effects of randomisation to a HFNC strategy versus CPAP. We will report incremental effects as mean differences (95% CI) at a willingness to pay (WTP) of £20,000 per QALY and the probability that the intervention is cost-effective compared to usual care at different levels of WTP for a QALY gain.

#### 5.3.1 Sensitivity analysis for cost-effectiveness

The following sensitivity analyses will be performed to check the robustness of primary CEA results at 6 months.

##### *a. HRQoL data*

A mapping technique will be used to predict the CHU-9D scores from the PedsQL responses. (Lambe et al., 2018). We will also explore alternative distributional assumptions for QALYs.

#### *b. Cost data*

Because of the likely skewed distribution of costs, we will consider several distributions that can give a better fit of cost data. We will assess the implications of potential double-counting of inpatient costs (e.g. costs for vasopressors) across the three sources of resource data.

### 5.4 Handling of missing data

As the primary endpoint will be analysed using time-to-event methods, patients with missing data will be included in the analysis as censored at the point of last recorded non-invasive respiratory support. Time to censoring will be compared between arms using Kaplan-Meier curves to explore the assumption of censoring at random.

Multiple imputation will be used to complete missing data in secondary outcomes, costs and HRQoL, under the assumption that the responses are missing at random (MAR) conditional on the observed data. Multiple imputation will be undertaken using the Multivariate Imputation using Chained Equations algorithm, with the model including all baseline variables included in the adjusted models and all outcome variables. The number of imputations will be determined according to level of missingness in the outcome variables. Models will be fitted in each imputed dataset and results combined using Rubin's rules.

### 5.5 Additional analyses

The primary analysis will be repeated adjusting for adherence to allocated intervention using a structural mean model with an instrumental variable of allocated treatment to estimate the complier average causal effect of treatment. Adherence will be measured for each patient as the proportion of all events (weaning, escalation, switch or withdrawal of support) which were classified as non-adherent, where for each observation non-adherence is as previously defined in section 2.5. Children who did not start on the randomised treatment will be recorded as having 100% non-adherence. A descriptive analysis of baseline characteristics and some secondary outcomes (mortality and length of stay outcomes, where available) will be performed for patients who did not start any respiratory support post randomisation (i.e. those excluded from the mITT analysis)

### 5.6 Safety

Adverse events (nasal trauma, facial/neck trauma, abdominal distention, pneumothorax, pneumomediastinum, subcutaneous emphysema, facial thermal injury, respiratory arrest, cardiac arrest) and any other possibly related adverse event, are recorded only in patients who commenced respiratory support post-randomisation, and are recorded from randomisation up to 48 hours after date/time of liberation of respiratory support.

The percentage of patients experiencing one or more adverse event in patients who commenced respiratory support post randomisation, will be compared between groups using Fisher's exact test. Counts and percentages of adverse events, and serious adverse events, overall and by type, will be presented by allocated treatment group.

### 5.7 Statistical software

All analyses will be conducted in Stata/SE Version 14.2 64-bit x86-64 (StatCorp LLC, College Station, TX). Some additional cost-effectiveness analysis may be carried out in R if required.



## 6 References

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