Great Ormond Street Hospital Charity

UCL INSTITUTE OF CHILD HEALTH

Great Ormond Street Hospital for Children NHS Foundation Trust

Joint Research and Development Office
Division of Research and Innovation

Feasibility study for a randomised trial of high flow nasal cannula (HFNC) versus continuous positive airway pressure (CPAP) for non-invasive respiratory support in critically ill children (FIRST-ABC Feasibility Study)

Statistical Analysis Plan

Version 1.0, 31/05/2017

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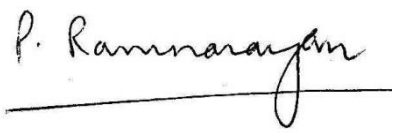
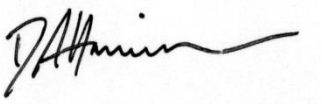
Author:	Dr Jerome Wulff, Trial Statistician

Role, Name and Position	Signature	Date
Chief investigator: Dr Padmanabhan Ramnarayan (Consultant in Paediatric Intensive Care & Retrieval Children's Acute Transport Service (CATS) Critical Care Division, GOSH)		31/05/2017
Senior Statistician: Dr David Harrison (Senior Statistician, ICNARC)		31/05/2017

Version history

Version number	Date	Summary of main changes from previous versions
1.0	31/05/2017	N/A

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Abbreviations

CI	Chief Investigator
CPAP	Continuous Positive Airway Pressure
GOSH	Great Ormond Street Hospital
HFNC	High Flow Nasal Cannula
NHS	National Health Service
NRS	Non-invasive Respiratory Support
PICU	Paediatric Intensive Care Unit
PSS:PICU	Parental stressor scale: PICU
REC	Research Ethics Committee
RLH	Royal London Hospital
SAE	Serious Adverse Event
SMH	St Mary's Hospital, London
SOP	Standard Operating Procedure
UCL	University College London

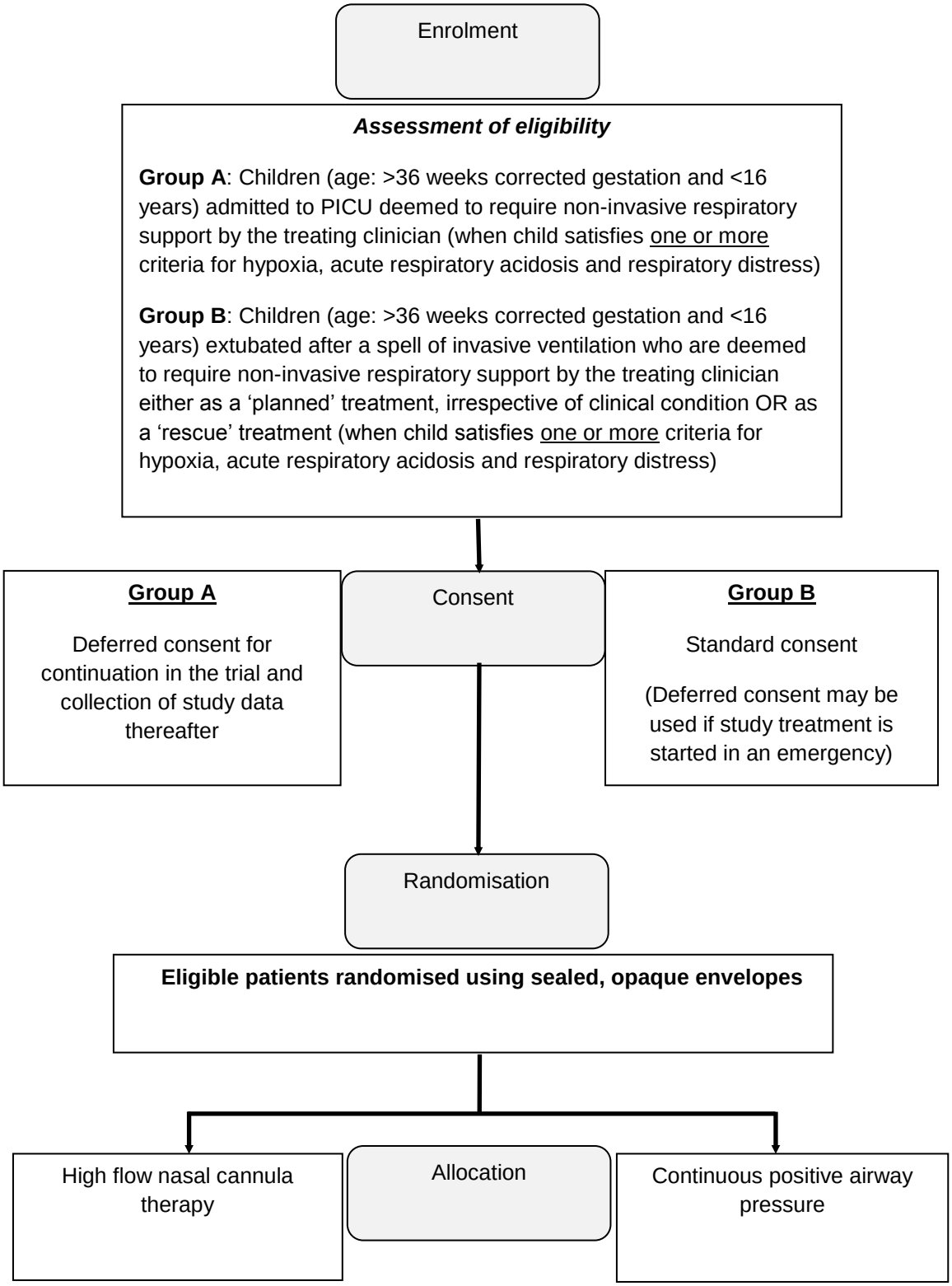
1. Background and rationale

The FIRST-ABC (First-line support for Assistance in Breathing in Children feasibility study) trial is a randomised open label feasibility trial comparing high flow nasal cannula (HFNC) with continuous positive airway pressure (CPAP) to demonstrate feasibility for a full randomised controlled trial (RCT) for non-invasive respiratory support in critically ill children. The study design included the recruitment of 120 sick children from three NHS hospitals over six months where consent will be sought from the parents/guardians of the children, usually before CPAP or HFNC is started, unless emergency life-saving treatment is required, in which case consent will be deferred until there is more time to discuss the study with the parents/guardians of the children. The flow chart of the study is illustrated in Figure 1 below.

The purpose of this Statistical Analysis Plan (SAP) is to outline the planned analyses to be carried out to support the completion of the Final Report to the study funder and for inclusion in manuscripts for publication in the scientific literature. Additional exploratory analyses, which may not have been identified in this SAP, may also be performed. Any unplanned analyses not identified in this SAP will be clearly outlined as such in the respective Report/manuscript.

This SAP would be agreed in advance of inspecting the outcome data for the Trial, so that data-derived decisions in the analyses are avoided.

Figure 1: Study flow chart



2. Study objectives

2.1 Primary objectives

The primary objective of this study is to determine the feasibility of an RCT of HFNC versus CPAP in critically ill children. This objective was measured based on the following endpoints:

i. Assess the number of eligible patients in Group A (step-up) and Group B (step-down)
ii. Assess the acceptability of using a mixed model of consent (prospective and deferred)
iii. Assess the feasibility of randomising at least 50% of eligible patients
iv. Test the practical aspects of implementing the study protocol in terms of initiation, maintenance and weaning of the study intervention
v. Assess whether a modified COMFORT score (COMFORT score minus the respiratory component) can be used to measure patient tolerance to CPAP/HFNC
vi. Assess the feasibility of using the Parental Stressor Scale: PICU (PSS:PPICU) to measure parental stress 24 hours after the initiation of CPAP/HFNC

2.2 Secondary objectives

The secondary objectives are:

i. To determine the rate of intubation within 72 hours of randomisation
ii. To determine the rate of treatment failure (i.e. require either crossover or escalation to other forms of ventilation within 72 hours of randomisation)
iii. To assess safety of the study treatments during the period the children were receiving non-invasive respiratory support
iv. To assess physiological effects in the first 24 hours after the initiation of CPAP/HFNC
v. To assess effects on patient outcome (i.e. Length of PICU and hospital stay, length of invasive ventilation, length of non-invasive

support, ventilator-free days at day 28, PICU mortality, hospital mortality)

3. Methods

3.1 Trial design

A randomised, controlled, open-label clinical trial for first-line non-invasive respiratory support modality in critically ill children.

3.2 Setting

Three diverse NHS PICUs in London in England

4. Inclusion and exclusion criteria

The inclusion and exclusion criteria of this study are as described below.

4.1 Inclusion criterial of patients

In order to minimise variation in practice between and within centres predefined, objective criteria were specified to provide clear directions to clinicians to guide the decision on when to start NRS. Eligible patients fell into one of two groups:

Group A (Step-up)

i. Age >36 weeks corrected gestational age and <16 years, and
ii. Deemed to require non-invasive respiratory support by the treating clinician for an acute illness, and
iii. Satisfies <u>one or more</u> of the following criteria:
    a. Hypoxia (oxygen saturation <92% in FiO_2 >0.40, or equivalent). FiO_2 of 0.40 roughly equates to standard unhumidified nasal cannula oxygen delivered at 6 L/min or oxygen delivered via facemask without a rebreather bag at 6-10 L/min
    b. Acute respiratory acidosis (pH <7.3 with a concomitant pCO_2 >6.5 kPa)
    c. Moderate respiratory distress (use of accessory muscles, subcostal and intercostal recession, tachypnoea for age, grunting)

Group B (Step-down)

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

4.2 Exclusion criteria of patients

The exclusion criteria are children who:

i. Are deemed by the treating clinician to require immediate intubation/invasive ventilation due to severe hypoxia, acidosis and/or respiratory distress, upper airway obstruction or recurrent apnoeas
ii. Have a tracheostomy in place
iii. Have a pre-existing air-leak syndrome (pneumothorax /pneumomediastinum)
iv. Have mid-facial/craniofacial anomalies (unrepaired cleft palate, choanal atresia) or had recent craniofacial surgery
v. Have an agreed limitation of intensive care treatment plan in place ('not for intubation')
vi. Have been on domiciliary non-invasive ventilation prior to PICU admission
vii. Have been managed on either HFNC and/or CPAP (or other form of non-invasive ventilation such as BiPAP) in the preceding 24 hours
viii. Have been previously recruited to this study during the same PICU admission
ix. Cannot be treated with HFNC
    a. Unavailability of appropriate sized nasal prongs
    b. Unavailability of HFNC device
i. Cannot be treated with CPAP
    a. Unavailability of right size of face mask, prong or other patient interface
    b. Unavailability of CPAP device

5. Outcomes

5.1 Primary outcomes

The primary outcomes of this study measure the respective primary objectives stated in section 2.1.

i. Estimate the number of eligible patients in Group A (step-up) and Group B (step-down)

ii. Examine the acceptability of using a mixed model of consent (prospective and deferred), i.e. estimate the number of prospective and deferred consent among the treatment groups

iii. Assess the feasibility of randomising at least 50% of eligible patients, i.e. examine if 50% of the eligible patients were randomised into the trial

iv. Test the practical aspects of implementing the study protocol in terms of initiation, maintenance and weaning of the study intervention, i.e. estimate:

   a. Initiation
      – Proportion receiving allocated treatment
      – Time from randomisation to initiation
   b. Maintenance (excluding patients who did not continue treatment for the full six hours)
      – Proportion at correct pressure/flow rate by Hour 2
      – Proportion with >50% of time at correct pressure/flow rate in first 6 hours
   c. Weaning
      – Proportion started weaning when should (by next time point)
      – Proportion weaned by prescribed flow rate (HFNC) or pressure (CPAP) according to protocol

v. Assess whether a modified COMFORT score (COMFORT score minus the respiratory component) can be used to measure patient tolerance to CPAP/HFNC, i.e. estimate:

   a. Number of completed COMFORT scores
   b. Number of lower COMFORT scores when not tolerating (within/between patients)

vi. Assess the feasibility of using the Parental Stressor Scale: PICU (PSS:PPICU) to measure parental stress 24 hours after the initiation of CPAP/HFNC, i.e. estimate:
    b. Number of questionnaires returned
    c. Number/quality of questionnaires completed

5.2 Secondary outcomes

The secondary outcomes of this study measure the respective secondary objectives stated in section 2.2.

i. To determine the rate of intubation - i.e. estimate the proportion of children randomised to the intervention or control who need intubation (Group A) or re-intubation (Group B) within 72 hours of randomisation

ii. To determine the rate of treatment failure - i.e. estimate the proportion of children randomised to the intervention or control who fail the assigned treatment and require either crossover or escalation to other forms of ventilation within 72 hours of randomisation

iii. To assess safety – i.e. estimate the number of children who experience pre-specified adverse events i.e.
    a. Pneumothorax
    b. Pneumomediastinum
    c. Subcutaneous emphysema
    d. Abdominal distension
    e. Nasal or facial trauma
    f. Facial trauma
    g. Facial thermal injury
    h. Respiratory/Cardiac arrest
    i. Aspiration

    during the period they were receiving non-invasive respiratory support

iv. To assess physiological effects – i.e. estimate changes in:
    a. oxygenation
    b. pCO_2 levels

c. heart rate
d. respiratory rate
e. and work of breathing
in the first 24 hours after the initiation of CPAP/HFNC

v. To assess effects on patient outcome – i.e. estimate:
a. length of PICU stay
b. hospital stay
c. length of invasive ventilation
d. length of non-invasive support
e. ventilator-free days at day 28
f. PICU mortality
g. hospital mortality

6. Power calculation

Since this is a feasibility study, no formal sample size calculations was performed. Based on analysis of audit data, we expect around 250 eligible patients over the 6-month period at the three sites. Assuming a 50% recruitment rate, we will have recruited 120 study patients (around 40 patients in Group A). Data from the literature suggests a 20% rate of intubation for Group A (i.e. we expect to see eight intubation events), and a 10% rate of re-intubation for Group B (i.e. we expect to see eight re-intubation events).

7. Statistical methods

7.1 General analysis issues

7.1.1 Analysis population

All analyses will be based on the intention to treat (ITT) principle. The patients will be analysed according to the group they were randomised to, irrespective of whether the treatment allocated was received.

7.1.2 Analysis software

Analyses will be performed using Stata/SE Version 14.2 for Windows 64-bit x86-64

8. Statistical analysis

Numbers of patients screened, eligible, randomised, consented and withdrawn from the study will be reported by site. Numbers will be reported for Group A and Group B, with Group B split into 'planned' and 'rescue' subgroups. The information will be summarised as a CONSORT flow diagram. Reasons for exclusion and for withdrawal will be summarised, where reported.

Baseline demographic and clinical data will be summarised for the ITT population, for each of the two treatment groups overall and for Group A and Group B. Continuous variables will be summarized as mean (standard deviation) and median (interquartile range) whilst categorical variables will be summarized as number (percent). There will be no statistical testing for any of the summary measures whilst comparing the baseline variables between the treatment groups. The following baseline variables will be compared between the two treatment groups.

i. Demographics
ii. Diagnosis
iii. Prior treatment
iv. Physiological parameters related to oxygenation
v. Ventilation, and
vi. Work of breathing

For full details of included variables see Appendices.

Adherence will be reported as:

i. Number and percentage of patients receiving the allocated treatment
ii. Time from randomisation to initiation (separately for groups A and B)
iii. Number and percentage of patients at correct pressure/flow rate by Hour 2
iv. Number and percentage of patients with >50% of time at the correct pressure/flow rate in the first 6 hours
v. Number and percentage of patients who started weaning in whom the fraction of inspired oxygen (FiO_2) was <0.40
vi. Number and percentage of patients weaned by the correct amount
    a. HFNC flow rate is reduced by 50%
    b. CPAP pressure is reduced by 2 cm H_2O

Flow rate (HFNC group) and pressure (CPAP group) over time will be displayed graphically at the timepoints recorded (Hours 0, 1, 2, 3, 4, 5, 6, 12, 24, 36, 48 and 72).

Assessment of the suitability of the modified COMFORT score will be evaluated by:

i. Number of completed measurements, reported as a percentage of all possible measurements (i.e. all time points when the patient was on HFNC or CPAP in PICU)
ii. Number and percentage of patients with at least one measurement recorded
iii. Mean (SD) modified COMFORT score at individual time points by tolerating allocated treatment (Yes or No) at that time point
iv. Mean (SD) across patients of the mean within-patient modified COMFORT score for patients with a highest level of respiratory distress of moderate or severe compared with those with a highest level of none or mild

Assessment of the suitability of the PSS:PICU will be evaluated by:

i. Number and percentage of parents returning a completed questionnaire
ii. Number and percentage of returned questionnaires with:
    a. All questions completed
    b. >90% of questions completed

The number and percentage of patients experiencing treatment failures, defined as crossover or escalation to other forms of ventilation within 72 hours of randomisation, will be reported for each group. Breakdowns of the numbers of crossovers and escalation (by level of respiratory support) will be reported.

The number and percentage of patients experiencing each pre-specified adverse event (plus any other adverse events as reported) will be summarised for each treatment group. Numbers of severe adverse events and their reported relatedness to treatment will be reported in text.

The physiological effects of treatment will be presented graphically by plotting the mean±SD of each physiological parameter at the time points recorded (Hours 0, 1, 2, 3, 4, 5, 6, 12, 24, 36, 48 and 72).

A comparison of outcomes by treatment group will be reported for the following outcome measures:

i. Intubation within 72 hours
ii. Treatment failure within 72 hours (separately for crossover and escalation patients)
iii. Length of PICU stay
iv. Length of hospital stay
v. Length of invasive ventilation
vi. Length of non-invasive support
vii. Ventilator-free days at day 28
viii. PICU mortality
ix. Hospital mortality

Binary outcomes will be reported as the number and percentage in each group, the risk ratio and absolute risk reduction with 95% confidence intervals. Continuous outcomes will be reported as the mean (SD) and median (IQR) in each group and the difference in means with 95% confidence interval.

Differences in treatment effect between Group A and Group B for all outcome measures will be tested as interaction tests (Mantel-Haenszel tests for binary outcomes, interaction terms in linear regression models for continuous outcomes) and presented as forest plots.

9. Reporting conventions

The following reporting conventions will be used for the SAP. These conventions will enhance the review of the study report and help to standardize presentation with common notations.

i. Sample sizes will be presented for each treatment group as totals in the column header as “(N = xxx)”, where appropriate.
ii. Sample sizes shown with summary statistics are the samples sizes (n) of patients with non-missing values.
iii. All summaries for categorical variables will include all categories that were available and will not be restricted to those with at least one response.

iv. Summaries for continuous variables that are approximately normally distributed will be reported as n, mean and standard deviation (SD).

v. Summaries for continuous variables that are not normally distributed will be reported as n, median and quartiles.

vi. All percentages will be rounded and reported to a single decimal place (xx.x%). A percentage of 0% will be reported as “0%”; a percentage of 100% will be reported as “100%”.

vii. Summaries that include P-values will report the P-value to three decimal places with a leading zero (0.xxx). P-values of less than 0.0005 will be reported as “<0.001” not “0.000”.

viii. Missing values for both numeric and string variables will be presented as dashes (“---”) or as “Not available” / “Not applicable” / “Not reported” (as appropriate) in tables or data listings.

10. Appendix – proposed tables and figures

Table 1a: Number of patients screened, eligible, consented and randomised by site

Variables	Site A	Site B	Site C	Total
Number screened, N				
Group A	XX	XX	XX	XXX
Group B:	XX	XX	XX	XXX
Planned	XX	XX	XX	XXX
Rescued	XX	XX	XX	XXX
Total	XX	XX	XX	XXX
Number of eligible patients, n (% of screened)				
Group A	XX	XX	XX	XXX
Group B:	XX	XX	XX	XXX
Planned	XX	XX	XX	XXX
Rescued	XX	XX	XX	XXX
Total	XX	XX	XX	XXX
Number of patients randomised, n (% of eligible)				
Group A	XX	XX	XX	XXX
Group B:	XX	XX	XX	XXX
Planned	XX	XX	XX	XXX
Rescued	XX	XX	XX	XXX
Total	XX	XX	XX	XXX
Consent obtained, n (% of randomised)				
Group A	XX	XX	XX	XXX
Group B:	XX	XX	XX	XXX
Planned	XX	XX	XX	XXX
Rescued	XX	XX	XX	XXX
Refused consent, n (% of randomised)				
Group A	XX	XX	XX	XXX
Group B:	XX	XX	XX	XXX
Planned	XX	XX	XX	XXX
Rescued	XX	XX	XX	XXX
Total	XX	XX	XX	XXX
Death prior to consent, n (% of randomised)				
Group A	XX	XX	XX	XXX
Group B:	XX	XX	XX	XXX
Planned	XX	XX	XX	XXX
Rescued	XX	XX	XX	XXX
Total	XX	XX	XX	XXX
Discharged prior to consent, n (% of randomised)				
Group A	XX	XX	XX	XXX
Group B:	XX	XX	XX	XXX
Planned	XX	XX	XX	XXX
Rescued	XX	XX	XX	XXX
Total	XX	XX	XX	XXX
Discontinuation/Withdrawal, n (% of consented)				
Group A	XX	XX	XX	XXX
Group B:	XX	XX	XX	XXX
Planned	XX	XX	XX	XXX
Rescued	XX	XX	XX	XXX
Total	XX	XX	XX	XXX
Number of patients analysed, n (% of randomised)				
Group A	XX	XX	XX	XXX
Group B:	XX	XX	XX	XXX

Planned	XX	XX	XX	XXX
Rescued	XX	XX	XX	XXX
Number of patients analysed but not started treatment, n (% of randomised)				
Group A	XX	XX	XX	XXX
Group B:	XX	XX	XX	XXX
Planned	XX	XX	XX	XXX
Rescued	XX	XX	XX	XXX
Total	XX	XX	XX	XXX

n: Number of patients; %: Percentage of patients; N: Total number of patients

Table 1b: Number of patients consented and randomised by treatment group

Variables	HFNC	CPAP	Total
Number of patients randomised, n (% of eligible)			
Group A	XX (XX.X)	XX (XX.X)	XX (XX.X)
Group B:			
Planned	XX (XX.X)	XX (XX.X)	XX (XX.X)
Rescued	XX (XX.X)	XX (XX.X)	XX (XX.X)
Total	XX (XX.X)	XX (XX.X)	XX (XX.X)
Consent obtained, n (% of randomised)			
Group A	XX (XX.X)	XX (XX.X)	XX (XX.X)
Group B:			
Planned	XX (XX.X)	XX (XX.X)	XX (XX.X)
Rescued	XX (XX.X)	XX (XX.X)	XX (XX.X)
Total	XX (XX.X)	XX (XX.X)	XX (XX.X)
Refused consent, n (% of randomised)			
Group A	XX (XX.X)	XX (XX.X)	XX (XX.X)
Group B:			
Planned	XX (XX.X)	XX (XX.X)	XX (XX.X)
Rescued	XX (XX.X)	XX (XX.X)	XX (XX.X)
Total	XX (XX.X)	XX (XX.X)	XX (XX.X)
Death prior to consent, n (% of randomised)			
Group A	XX (XX.X)	XX (XX.X)	XX (XX.X)
Group B:			
Planned	XX (XX.X)	XX (XX.X)	XX (XX.X)
Rescued	XX (XX.X)	XX (XX.X)	XX (XX.X)
Total	XX (XX.X)	XX (XX.X)	XX (XX.X)
Discharged prior to consent, n (% of randomised)			
Group A	XX (XX.X)	XX (XX.X)	XX (XX.X)
Group B:			
Planned	XX (XX.X)	XX (XX.X)	XX (XX.X)
Rescued	XX (XX.X)	XX (XX.X)	XX (XX.X)
Total	XX (XX.X)	XX (XX.X)	XX (XX.X)
Discontinuation/Withdrawal, n (% of consented)			
Group A	XX (XX.X)	XX (XX.X)	XX (XX.X)
Group B:			
Planned	XX (XX.X)	XX (XX.X)	XX (XX.X)
Rescued	XX (XX.X)	XX (XX.X)	XX (XX.X)
Total	XX (XX.X)	XX (XX.X)	XX (XX.X)
Number of patients analysed, n (% of randomised)			
Group A	XX (XX.X)	XX (XX.X)	XX (XX.X)
Group B:			
Planned	XX (XX.X)	XX (XX.X)	XX (XX.X)
Rescued	XX (XX.X)	XX (XX.X)	XX (XX.X)
Total	XX (XX.X)	XX (XX.X)	XX (XX.X)
Number of patients analysed but not started treatment, n (% of randomised)			
Group A	XX (XX.X)	XX (XX.X)	XX (XX.X)
Group B:			
Planned	XX (XX.X)	XX (XX.X)	XX (XX.X)
Rescued	XX (XX.X)	XX (XX.X)	XX (XX.X)
Total	XX (XX.X)	XX (XX.X)	XX (XX.X)

n: Number of patients; %: Percentage of patients; N: Total number of patients

Table 2a: Baseline characteristics and clinical variables by treatment group

Variables	HFNC	CPAP
	N = XXX	N = XXX
Demography		
Age (years)		
Mean (SD)	XX.X (XX.X)	XX.X (XX.X)
Median (IQR)	XX (XX,XX)	XX (XX,XX)
Age group, n (%)		
<1 year	XX (XX.X)	XX (XX.X)
1 to 2 years	XX (XX.X)	XX (XX.X)
3 to 4 years	XX (XX.X)	XX (XX.X)
5 to 9 years	XX (XX.X)	XX (XX.X)
10 years and over	XX (XX.X)	XX (XX.X)
Gender, n (%)		
Female	XX (XX.X)	XX (XX.X)
Male	XX (XX.X)	XX (XX.X)
Weight (kg)		
Mean (SD)	XX.X (XX.X)	XX.X (XX.X)
Median (IQR)	XX (XX,XX)	XX (XX,XX)
Ethnicity, n (%)		
White	XX (XX.X)	XX (XX.X)
Mixed	XX (XX.X)	XX (XX.X)
Asian/Asian British	XX (XX.X)	XX (XX.X)
Black/Black British	XX (XX.X)	XX (XX.X)
Other	XX (XX.X)	XX (XX.X)
Diagnosis		
Primary reason for PICU admission, n (%)		
Bronchiolitis	XX (XX.X)	XX (XX.X)
Asthma/Wheeze	XX (XX.X)	XX (XX.X)
Lung disease	XX (XX.X)	XX (XX.X)
Upper airway obstruction	XX (XX.X)	XX (XX.X)
Neuromuscular disorder	XX (XX.X)	XX (XX.X)
Cardiac	XX (XX.X)	XX (XX.X)
Other	XX (XX.X)	XX (XX.X)
Prior treatment		
Length of invasive ventilation prior to extubation (days) (Group B only)		
Mean (SD)	XX.X (XX.X)	XX.X (XX.X)
Median (IQR)	XX (XX,XX)	XX (XX,XX)
Modified COMFORT score at baseline		
Mean (SD)	XX.X (XX.X)	XX.X (XX.X)
Median (IQR)	XX (XX,XX)	XX (XX,XX)
Physiology at baseline		
Respiratory rate (breaths min^{-1})		
Mean (SD)	XX.X (XX.X)	XX.X (XX.X)
Median (IQR)	XX (XX,XX)	XX (XX,XX)
Heart rate (beats min^{-1})		
Mean (SD)	XX.X (XX.X)	XX.X (XX.X)
Median (IQR)	XX (XX,XX)	XX (XX,XX)
SpO_2 (%)		
Mean (SD)	XX.X (XX.X)	XX.X (XX.X)
Median (IQR)	XX (XX,XX)	XX (XX,XX)
PaO_2 (kPa)		
Mean (SD)	X.X (X.X)	X.X (X.X)

	Median (IQR)	X.X (X.X,X.X)	X.X (X.X,X.X)
FiO_2			
	Mean (SD)	X.XX (X.XX)	X.XX (X.XX)
	Median (IQR)	X.XX (X.XX,X.XX)	X.XX (X.XX,X.XX)
pH			
	Mean (SD)	X.XX (X.XX)	X.XX (X.XX)
	Median (IQR)	X.XX (X.XX,X.XX)	X.XX (X.XX,X.XX)
pCO_2 (kPa)			
	Mean (SD)	X.X (X.X)	X.X (X.X)
	Median (IQR)	X.X (X.X,X.X)	X.X (X.X,X.X)
Work of breathing			
Respiratory distress, n (%)			
	None	XX (XX.X)	XX (XX.X)
	Mild	XX (XX.X)	XX (XX.X)
	Moderate	XX (XX.X)	XX (XX.X)
	Severe	XX (XX.X)	XX (XX.X)

n: Number of patients; %: Percentage of patients; N: Total number of patients;
SD: Standard deviation; IQR: Inter-quartile range

Table 2b: Baseline characteristics and clinical variables by treatment group – Group A

Variables		HFNC	CPAP
		N = XXX	N = XXX
Demography			
Age (years)			
	Mean (SD)	XX.X (XX.X)	XX.X (XX.X)
	Median (IQR)	XX (XX,XX)	XX (XX,XX)
Age group, n (%)			
	<1 year	XX (XX.X)	XX (XX.X)
	1 to 2 years	XX (XX.X)	XX (XX.X)
	3 to 4 years	XX (XX.X)	XX (XX.X)
	5 to 9 years	XX (XX.X)	XX (XX.X)
	10 years and over	XX (XX.X)	XX (XX.X)
Gender, n (%)			
	Female	XX (XX.X)	XX (XX.X)
	Male	XX (XX.X)	XX (XX.X)
Weight (kg)			
	Mean (SD)	XX.X (XX.X)	XX.X (XX.X)
	Median (IQR)	XX (XX,XX)	XX (XX,XX)
Ethnicity, n (%)			
	White	XX (XX.X)	XX (XX.X)
	Mixed	XX (XX.X)	XX (XX.X)
	Asian/Asian British	XX (XX.X)	XX (XX.X)
	Black/Black British	XX (XX.X)	XX (XX.X)
	Other	XX (XX.X)	XX (XX.X)
Diagnosis			
Primary reason for PICU admission, n (%)			
	Bronchiolitis	XX (XX.X)	XX (XX.X)
	Asthma/Wheeze	XX (XX.X)	XX (XX.X)
	Lung disease	XX (XX.X)	XX (XX.X)
	Upper airway obstruction	XX (XX.X)	XX (XX.X)
	Neuromuscular disorder	XX (XX.X)	XX (XX.X)
	Cardiac	XX (XX.X)	XX (XX.X)
	Other	XX (XX.X)	XX (XX.X)
Prior treatment			
Modified COMFORT score at baseline			
	Mean (SD)	XX.X (XX.X)	XX.X (XX.X)
	Median (IQR)	XX (XX,XX)	XX (XX,XX)
Physiology at baseline			
Respiratory rate (breaths min^{-1})			
	Mean (SD)	XX.X (XX.X)	XX.X (XX.X)
	Median (IQR)	XX (XX,XX)	XX (XX,XX)
Heart rate (beats min^{-1})			
	Mean (SD)	XX.X (XX.X)	XX.X (XX.X)
	Median (IQR)	XX (XX,XX)	XX (XX,XX)
SpO_2 (%)			
	Mean (SD)	XX.X (XX.X)	XX.X (XX.X)
	Median (IQR)	XX (XX,XX)	XX (XX,XX)
PaO_2 (kPa)			
	Mean (SD)	X.X (X.X)	X.X (X.X)
	Median (IQR)	X.X (X.X,X.X)	X.X (X.X,X.X)
FiO_2			
	Mean (SD)	X.XX (X.XX)	X.XX (X.XX)
	Median (IQR)	X.XX	X.XX

		(X.XX,X.XX)	(X.XX,X.XX)
pH			
	Mean (SD)	X.XX (X.XX)	X.XX (X.XX)
	Median (IQR)	X.XX (X.XX,X.XX)	X.XX (X.XX,X.XX)
pCO_2 (kPa)			
	Mean (SD)	X.X (X.X)	X.X (X.X)
	Median (IQR)	X.X (X.X,X.X)	X.X (X.X,X.X)
Work of breathing			
Respiratory distress, n (%)			
	None	XX (XX.X)	XX (XX.X)
	Mild	XX (XX.X)	XX (XX.X)
	Moderate	XX (XX.X)	XX (XX.X)
	Severe	XX (XX.X)	XX (XX.X)

n: Number of patients; %: Percentage of patients; N: Total number of patients;
SD: Standard deviation; IQR: Inter-quartile range

Table 2c: Baseline characteristics and clinical variables by treatment group – Group B

Variables	Planned		Rescued	
	HFNC	CPAP	HFNC	CPAP
	N = XXX	N = XXX	N = XXX	N = XXX
Demography				
Age (years)				
Mean (SD)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)
Median (IQR)	XX (XX,XX)	XX (XX,XX)	XX (XX,XX)	XX (XX,XX)
Age group, n (%)				
<1 year	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
1 to 2 years	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
3 to 4 years	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
5 to 9 years	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
10 years and over	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Gender, n (%)				
Female	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Male	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Weight (kg)				
Mean (SD)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)
Median (IQR)	XX (XX,XX)	XX (XX,XX)	XX (XX,XX)	XX (XX,XX)
Ethnicity, n (%)				
White	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Mixed	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Asian/Asian British	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Black/Black British	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Other	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Diagnosis				
Primary reason for PICU admission, n (%)				
Bronchiolitis	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Asthma/Wheeze	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Lung disease	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Upper airway obstruction	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Neuromuscular disorder	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Cardiac	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Other	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Prior treatment				
Length of invasive ventilation prior to extubation (days)				
Mean (SD)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)
Median (IQR)	XX (XX,XX)	XX (XX,XX)	XX (XX,XX)	XX (XX,XX)
Modified COMFORT score at baseline				
Mean (SD)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)
Median (IQR)	XX (XX,XX)	XX (XX,XX)	XX (XX,XX)	XX (XX,XX)
Physiology at baseline				
Respiratory rate (breaths min^{-1})				
Mean (SD)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)
Median (IQR)	XX (XX,XX)	XX (XX,XX)	XX (XX,XX)	XX (XX,XX)
Heart rate (beats min^{-1})				
Mean (SD)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)
Median (IQR)	XX (XX,XX)	XX (XX,XX)	XX (XX,XX)	XX (XX,XX)
SpO_2 (%)				

Mean (SD)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)
Median (IQR)	XX (XX,XX)	XX (XX,XX)	XX (XX,XX)	XX (XX,XX)
PaO_2 (kPa)				
Mean (SD)	X.X (X.X)	X.X (X.X)	X.X (X.X)	X.X (X.X)
Median (IQR)	X.X (X.X,X.X)	X.X (X.X,X.X)	X.X (X.X,X.X)	X.X (X.X,X.X)
FiO_2				
Mean (SD)	X.XX (X.XX)	X.XX (X.XX)	X.XX (X.XX)	X.XX (X.XX)
Median (IQR)	X.XX (X.XX,X.XX)	X.XX (X.XX,X.XX)	X.XX (X.XX,X.XX)	X.XX (X.XX,X.XX)
pH				
Mean (SD)	X.XX (X.XX)	X.XX (X.XX)	X.XX (X.XX)	X.XX (X.XX)
Median (IQR)	X.XX (X.XX,X.XX)	X.XX (X.XX,X.XX)	X.XX (X.XX,X.XX)	X.XX (X.XX,X.XX)
pCO_2 (kPa)				
Mean (SD)	X.X (X.X)	X.X (X.X)	X.X (X.X)	X.X (X.X)
Median (IQR)	X.X (X.X,X.X)	X.X (X.X,X.X)	X.X (X.X,X.X)	X.X (X.X,X.X)
Work of breathing				
Respiratory distress, n (%)				
None	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Mild	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Moderate	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Severe	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)

n: Number of patients; %: Percentage of patients; N: Total number of patients;
SD: Standard deviation; IQR: Inter-quartile range

Table 3: Adherence by treatment groups

Variables	HFNC N = XXX	CPAP N = XXX
Initiation:		
Randomised treatment started, n/N (%)		
Group A	XX/XX (XX.X)	XX/XX (XX.X)
Group B	XX/XX (XX.X)	XX/XX (XX.X)
Total	XX/XX (XX.X)	XX/XX (XX.X)
Time from randomisation to initiation (hours)		
Mean (SD)		
Group A	XX.X (XX.X)	XX.X (XX.X)
Group B:		
Planned	XX.X (XX.X)	XX.X (XX.X)
Rescued	XX.X (XX.X)	XX.X (XX.X)
Total	XX.X (XX.X)	XX.X (XX.X)
Median (IQR)		
Group A	XX (XX,XX)	XX (XX,XX)
Group B:		
Planned	XX (XX,XX)	XX (XX,XX)
Rescued	XX (XX,XX)	XX (XX,XX)
Total	XX (XX,XX)	XX (XX,XX)
Maintenance:		
At correct pressure/flow rate by Hour 2, n/N (%)		
Group A	XX/XX (XX.X)	XX/XX (XX.X)
Group B	XX/XX (XX.X)	XX/XX (XX.X)
Total	XX/XX (XX.X)	XX/XX (XX.X)
Treated >50% of time at correct pressure/flow rate in first 6 hours, n/N (%)		
Group A	XX/XX (XX.X)	XX/XX (XX.X)
Group B	XX/XX (XX.X)	XX/XX (XX.X)
Total	XX/XX (XX.X)	XX/XX (XX.X)
Weaning:		
Proportion started weaning in whom FiO_2 was <0.40, n/N (%)		
Group A	XX/XX (XX.X)	XX/XX (XX.X)
Group B	XX/XX (XX.X)	XX/XX (XX.X)
Total	XX/XX (XX.X)	XX/XX (XX.X)
Proportion weaned by correct amount, n/N (%)		
Group A	XX/XX (XX.X)	XX/XX (XX.X)
Group B	XX/XX (XX.X)	XX/XX (XX.X)
Total	XX/XX (XX.X)	XX/XX (XX.X)

n: Number of patients; %: Percentage of patients; N: Total number of patients;
SD: Standard deviation; IQR: Inter-quartile range

Table 4: Modified COMFORT score and PSS:PICU by treatment group

Variables	HFNC	CPAP
	N = XXX	N = XXX
Modified COMFORT score:		
Modified COMFORT score completed, n/N (% of all eligible time points)		
Group A	XX (XX.X)	XX (XX.X)
Group B	XX (XX.X)	XX (XX.X)
Total	XX (XX.X)	XX (XX.X)
Patients with at least one modified COMFORT score completed, n/N (%)		
Group A	XX (XX.X)	XX (XX.X)
Group B	XX (XX.X)	XX (XX.X)
Total	XX (XX.X)	XX (XX.X)
Modified COMFORT score (Hour 1-6) by tolerating randomised treatment at individual time points, mean (SD) [N]		
Group A		
Yes	XX.X (XX.X) [XX]	XX.X (XX.X) [XX]
No	XX.X (XX.X) [XX]	XX.X (XX.X) [XX]
Group B		
Yes	XX.X (XX.X) [XX]	XX.X (XX.X) [XX]
No	XX.X (XX.X) [XX]	XX.X (XX.X) [XX]
Mean modified COMFORT score (Hour 1-6) by patient's highest level of respiratory distress, mean (SD) [N]		
Group A		
None/Mild	XX.X (XX.X) [XX]	XX.X (XX.X) [XX]
Moderate/Severe	XX.X (XX.X) [XX]	XX.X (XX.X) [XX]
Group B		
None/Mild	XX.X (XX.X) [XX]	XX.X (XX.X) [XX]
Moderate/Severe	XX.X (XX.X) [XX]	XX.X (XX.X) [XX]
Use of sedative agents, n (%):		
Group A	XX (XX.X)	XX (XX.X)
Group B	XX (XX.X)	XX (XX.X)
Total	XX (XX.X)	XX (XX.X)
PSS:PICU:		
PSS:PICU questionnaire returned, n/N (%)		
Group A	XX (XX.X)	XX (XX.X)
Group B	XX (XX.X)	XX (XX.X)
Total	XX (XX.X)	XX (XX.X)
PSS:PICU questionnaire 100% complete, n/N (%)		
Group A	XX (XX.X)	XX (XX.X)
Group B	XX (XX.X)	XX (XX.X)
Total	XX (XX.X)	XX (XX.X)
PSS:PICU questionnaire >90% complete, n/N (%)		
Group A	XX (XX.X)	XX (XX.X)

	Group B	XX (XX.X)	XX (XX.X)
	Total	XX (XX.X)	XX (XX.X)
PSS:PICU			
	Group A:		
	Mean (SD)	XX.X (XX.X)	XX.X (XX.X)
	Median (IQR)	XX (XX,XX)	XX (XX,XX)
	Group B:		
	Mean (SD)	XX.X (XX.X)	XX.X (XX.X)
	Median (IQR)	XX (XX,XX)	XX (XX,XX)

n: Number of patients; %: Percentage of patients; N: Total number of patients;
SD: Standard deviation

Table 5: Treatment failure by treatment group

Variables	HFNC N = XXX	CPAP N = XXX
Treatment failure:		
Crossover or escalation to other forms of ventilation within 72 hours of randomisation, n/N (%)		
Group A	XX/XX (XX.X)	XX/XX (XX.X)
Group B	XX/XX (XX.X)	XX/XX (XX.X)
Total	XX/XX (XX.X)	XX/XX (XX.X)
Crossover:		
Crossover from HFNC to CPAP or CPAP to HFNC, n/N (%)		
Group A	XX/XX (XX.X)	XX/XX (XX.X)
Group B	XX/XX (XX.X)	XX/XX (XX.X)
Total	XX/XX (XX.X)	XX/XX (XX.X)
Treatment escalation:		
Intubation and ventilation, n/N (%)		
Group A	XX/XX (XX.X)	XX/XX (XX.X)
Group B	XX/XX (XX.X)	XX/XX (XX.X)
Total	XX/XX (XX.X)	XX/XX (XX.X)
Non-invasive CPAP/PS, n/N (%)		
Group A	XX/XX (XX.X)	XX/XX (XX.X)
Group B	XX/XX (XX.X)	XX/XX (XX.X)
Total	XX/XX (XX.X)	XX/XX (XX.X)
Non-invasive BiPAP, n/N (%)		
Group A	XX/XX (XX.X)	XX/XX (XX.X)
Group B	XX/XX (XX.X)	XX/XX (XX.X)
Total	XX/XX (XX.X)	XX/XX (XX.X)
Other, n/N (%)		
Group A	XX/XX (XX.X)	XX/XX (XX.X)
Group B	XX/XX (XX.X)	XX/XX (XX.X)
Total	XX/XX (XX.X)	XX/XX (XX.X)

n: Number of patients; %: Percentage of patients; N: Total number of patients

Table 6: Adverse events by treatment group

Variables	HFNC N = XXX	CPAP N = XXX
Safety - Adverse events		
Pneumothorax, n (%)		
Group A	XX (XX.X)	XX (XX.X)
Group B	XX (XX.X)	XX (XX.X)
Total	XX (XX.X)	XX (XX.X)
Pneumomediastinum, n (%)		
Group A	XX (XX.X)	XX (XX.X)
Group B	XX (XX.X)	XX (XX.X)
Total	XX (XX.X)	XX (XX.X)
Subcutaneous emphysema, n (%)		
Group A	XX (XX.X)	XX (XX.X)
Group B	XX (XX.X)	XX (XX.X)
Total	XX (XX.X)	XX (XX.X)
Abdominal distension, n (%)		
Group A	XX (XX.X)	XX (XX.X)
Group B	XX (XX.X)	XX (XX.X)
Total	XX (XX.X)	XX (XX.X)
Nasal trauma, n (%)		
Group A	XX (XX.X)	XX (XX.X)
Group B	XX (XX.X)	XX (XX.X)
Total	XX (XX.X)	XX (XX.X)
Facial trauma, n (%)		
Group A	XX (XX.X)	XX (XX.X)
Group B	XX (XX.X)	XX (XX.X)
Total	XX (XX.X)	XX (XX.X)
Facial thermal injury, n (%)		
Group A	XX (XX.X)	XX (XX.X)
Group B	XX (XX.X)	XX (XX.X)
Total	XX (XX.X)	XX (XX.X)
Respiratory/Cardiac arrest, n (%)		
Group A	XX (XX.X)	XX (XX.X)
Group B	XX (XX.X)	XX (XX.X)
Total	XX (XX.X)	XX (XX.X)
Aspiration, n (%)		
Group A	XX (XX.X)	XX (XX.X)
Group B	XX (XX.X)	XX (XX.X)
Total	XX (XX.X)	XX (XX.X)
Other[a], n (%)		
Group A	XX (XX.X)	XX (XX.X)
Group B	XX (XX.X)	XX (XX.X)
Total	XX (XX.X)	XX (XX.X)

n: Number of patients; %: Percentage of patients; N: Total number of patients
[a] Other reported adverse events were…

Table 7: Comparison of outcomes by treatment group

Outcome	HFNC	CPAP	Effect estimates (95% CI)	P value
	N = XXX	N = XXX		
Intubation within 72h				
n (%)	XX (XX.X)	XX (XX.X)	Risk ratio: X.XX (X.XX, X.XX) Absolute risk reduction: XX.X (XX.X, XX.X)	0.XXX
Treatment failure within 72h				
n (%)	XX (XX.X)	XX (XX.X)	Risk ratio: X.XX (X.XX, X.XX) Absolute risk reduction: XX.X (XX.X, XX.X)	0.XXX
Length of PICU stay from randomisation (days):				
Mean (SD)	X.X (X.X)	X.X (X.X)	Mean difference: X.X (X.X,X.X)	0.XXX
Median (IQR)	X.X (X.X,X.X)	X.X (X.X,X.X)		
Length of hospital stay (days)				
Mean (SD)	X.X (X.X)	X.X (X.X)	Mean difference: X.X (X.X,X.X)	0.XXX
Median (IQR)	XX (XX,XX)	XX (XX,XX)		
Length of invasive ventilation (days)				
Mean (SD)	X.X (X.X)	X.X (X.X)	Mean difference: X.X (X.X,X.X)	0.XXX
Median (IQR)	XX (XX,XX)	XX (XX,XX)		
Length of non-invasive respiratory support (days)				
Mean (SD)	X.X (X.X)	X.X (X.X)	Mean difference: X.X (X.X,X.X)	0.XXX
Median (IQR)	XX (XX,XX)	XX (XX,XX)		
Ventilator-free days at day 28				
Mean (SD)	X.X (X.X)	X.X (X.X)	Mean difference: X.X (X.X,X.X)	0.XXX
PICU mortality				
n (%)	XX (XX.X)	XX (XX.X)	Risk ratio: X.XX (X.XX, X.XX) Absolute risk reduction: XX.X (XX.X, XX.X)	0.XXX
Hospital mortality				
n (%)	XX (XX.X)	XX (XX.X)	Risk ratio: X.XX (X.XX, X.XX) Absolute risk reduction: XX.X (XX.X, XX.X)	0.XXX

n: Number of patients; %: Percentage of patients; N: Total number of patients;
SD: Standard deviation; IQR: Inter-quartile range

Figure 1: Study flow diagram
CONSORT flow diagram

Figure 2: Flow rate/pressure over time
Mean (SD) at Hours 0, 1, 2, 3, 4, 5, 6, 12, 24, 36, 48 and 72. Panels for:

- Flow rate (<10 kg vrs ≥10 kg - l kg^{-1} min^{-1}) – HFNC group
- Pressure (cmH_2O) – CPAP group

Figure 3: Physiology/comfort/respiratory distress over time
Mean (SD), unless indicated, by treatment group at Hours 0, 1, 2, 3, 4, 5, 6, 12, 24, 36, 48 and 72. Panels (Group A and Group B) for:

- Respiratory rate (breaths min^{-1})
- Heart rate (beats min^{-1})
- SpO_2 (%)
- PaO_2 (kPa)
- FiO_2
- pH
- pCO_2 (kPa)
- Modified COMFORT score
- Percentage with Moderate/Severe respiratory distress

Numbers at the foot of each figure will indicate the number of patients with measurements at each timepoint.

Figure 4: Forest plot of outcomes
All outcomes from Table 7 reported for Group A, Group B and overall with test of interaction. Panels for (A) binary outcomes (risk ratio); and (B) continuous outcomes (difference in means).