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Extended Research Article

High-flow nasal cannula therapy versus continuous positive airway pressure for non-invasive respiratory support in paediatric critical care: the FIRST-ABC RCTs

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This article

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Abstract

Background: Despite the increasing use of non-invasive respiratory support in paediatric intensive care units, there are no large randomised controlled trials comparing two commonly used non-invasive respiratory support modes, continuous positive airway pressure and high-flow nasal cannula therapy.

Objective: To evaluate the non-inferiority of high-flow nasal cannula, compared with continuous positive airway pressure, when used as the first-line mode of non-invasive respiratory support in acutely ill children and following extubation, on time to liberation from respiratory support, defined as the start of a 48-hour period during which the child was free of respiratory support (non-invasive and invasive).

Design: A master protocol comprising two pragmatic, multicentre, parallel-group, non-inferiority randomised controlled trials (step-up and step-down) with shared infrastructure, including internal pilot and integrated health economic evaluation.

Setting: Twenty-five National Health Service paediatric critical care units (paediatric intensive care units and/or high-dependency units) across England, Wales and Scotland.

Participants: Critically ill children assessed by the treating clinician to require non-invasive respiratory support for (1) acute illness (step-up randomised controlled trial) or (2) within 72 hours of extubation (step-down randomised controlled trial).

Interventions: High-flow nasal cannula delivered at a flow rate based on patient weight (Intervention) compared to continuous positive airway pressure of 7–8 cm H_2O pressure (Control).

Main outcome measures: The primary clinical outcome was time to liberation from respiratory support. The primary cost-effectiveness outcome was 180-day incremental net monetary benefit. Secondary outcomes included mortality at paediatric intensive care unit/high-dependency unit discharge, day 60 and day 180; (re)intubation rate at 48 hours; duration of paediatric intensive care unit/high-dependency unit and hospital stay; patient comfort; sedation use; parental stress; and health-related quality of life at 180 days.

Results: In the step-up randomised controlled trial, out of 600 children randomised, 573 were included in the primary analysis (median age 9 months). Median time to liberation was 52.9 hours for high-flow nasal cannula (95% confidence interval 46.0 to 60.9 hours) and 47.9 hours (95% confidence interval 40.5 to 55.7 hours) for continuous positive airway pressure (adjusted hazard ratio 1.03, one-sided 97.5% confidence interval 0.86 to ∞). The high-flow nasal cannula group had lower use of sedation (27.7% vs. 37%) and mean duration of acute hospital stay (13.8 days vs. 19.5 days). In the step-down randomised controlled trial, of the 600 children randomised, 553 were included in the primary analysis (median age 3 months). Median time to liberation for high-flow nasal cannula was 50.5 hours (95% confidence interval, 43.0 to 67.9) versus 42.9 hours (95% confidence interval 30.5 to 48.2) for continuous positive airway pressure (adjusted hazard ratio 0.83, one-sided 97.5% confidence interval 0.70 to ∞). Mortality at day 180 was significantly higher for high-flow nasal cannula [5.6% vs. 2.4% for continuous positive airway pressure, adjusted odds ratio, 3.07 (95% confidence interval, 1.1 to 8.8)].

Limitations: The interventions were unblinded. A heterogeneous cohort of children with a range of diagnoses and severity of illness were included.

Conclusions: Among acutely ill children requiring non-invasive respiratory support, high-flow nasal cannula met the criterion for non-inferiority compared with continuous positive airway pressure for time to liberation from respiratory support whereas in critically ill children requiring non-invasive respiratory support following extubation, the non-inferiority of high-flow nasal cannula could not be demonstrated.

Future work: (1) Identify risk factors for treatment failure. (2) Compare protocolised approaches to post-extubation non-invasive respiratory support, with standard care. (3) Explore alternative approaches for evaluating heterogeneity of treatment effect. (4) Explore reasons for increased mortality in high-flow nasal cannula group within step-down randomised controlled trial.

Study registration: Current Controlled Trials ISRCTN60048867.

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Supplementary material can be found on the NIHR Journals Library report page (https://doi.org/10.3310/PDBG1495).

Supplementary material has been provided by the authors to support the report and any files provided at submission will have been seen by peer reviewers, but not extensively reviewed. Any supplementary material provided at a later stage in the process may not have been peer reviewed.

List of abbreviations

AE	adverse event
CEA	cost-effectiveness analysis
CHU-9D	The Child Health Utility 9 Dimension
CPAP	continuous positive airway pressure
CRF	case report form
CTU	Clinical Trials Unit
FIRST-ABC	FIRST-line support for Assistance in Breathing in Children
GP	general practitioner
HDU	high-dependency unit
HES	Hospital Episode Statistics
HFNC	high-flow nasal cannula
HRQoL	health-related quality of life
HRG	Healthcare Resource Group
HSQ	Health Services Questionnaire
ICNARC	Intensive Care National Audit & Research Centre
IMV	invasive mechanical ventilation
INB	incremental net benefit
ITT	intention to treat
MICE	multivariate imputation via chained equations
mITT	modified intention to treat
NIHR	National Institute for Health and Care Research
NRS	non-invasive respiratory support
PedsQL	Paediatric Quality of Life Inventory
PI	principal investigator
PICANet	The Paediatric Intensive Care Audit Network
PICU	paediatric intensive care unit
PIS	participant information sheet
PPI	patient and public involvement
PSS:PICU	Parental Stressor Scale: PICU
PSSRU	Personal Social Services Research Unit
QALYs	quality-adjusted life-years
RCT	randomised controlled trial
REC	Research Ethics Committee
SAE	serious adverse event
TMG	Trial Management Group

Plain language summary

Non-invasive forms of breathing support, mainly continuous positive airway pressure and high-flow nasal cannula, are used commonly in children's intensive care units. High-flow nasal cannula is easier to use, requires less nursing input and is more comfortable for children. However, few clinical trials have compared their effectiveness in sick children.

The aim of the FIRST-line support for Assistance in Breathing in Children clinical trials was to test if high-flow nasal cannula was non-inferior (not unacceptably worse) compared to continuous positive airway pressure in terms of how quickly children were able to come off breathing support, and whether high-flow nasal cannula provided value for money for the National Health Service. The trials were carried out in two groups of children in whom doctors usually start non-invasive breathing support: (1) acutely ill children and (2) children coming off a ventilator.

A total of 1200 children (600 acutely ill and 600 following extubation) were entered into the trials. Half were randomly assigned to high-flow nasal cannula and the other half to continuous positive airway pressure.

Complete information was available in 573 of 600 acutely ill children included in the trial. The average time taken to come off all breathing support was 5 hours longer with high-flow nasal cannula, judged as acceptable considering its benefits (fewer children on high-flow nasal cannula needed sedative medicines and developed pressure sores in the nose, and children spent a shorter time in hospital).

Complete information was available in 553 children of 600 children needing breathing support following extubation. Average time taken to come off all breathing support was 8 hours longer with high-flow nasal cannula, not considered an acceptable difference, since there were few benefits of using high-flow nasal cannula. On average, high-flow nasal cannula saved a small amount of money for the National Health Service.

The FIRST-line support for Assistance in Breathing in Children trials showed that high-flow nasal cannula was an acceptable first choice in acutely ill children needing breathing support, but continuous positive airway pressure was the most effective first choice in children needing breathing support after extubation.

Scientific summary

Background

Nearly 75% of the 18,000 critically ill children admitted annually to UK paediatric intensive care units (PICUs) receive invasive or non-invasive respiratory support (NRA). NRS is used commonly in PICUs, usually to support acutely ill children with respiratory failure or to provide post-extubation support.

Although there are no randomised controlled trials (RCTs), continuous positive airway pressure (CPAP) has been widely used for NRS; however, it can be uncomfortable and associated with complications such as air leak and nasal trauma. An alternate mode of NRS, high-flow nasal cannula (HFNC), which is easy to use and is well tolerated by children, has gained popularity. The potential benefits of HFNC (patient comfort, safety profile and ease of nursing care) must be balanced against its potential risks (air leak, abdominal distension and nosocomial infection). To date, there have been no large RCTs comparing HFNC with CPAP in the PICU setting.

Following a successful pilot RCT, which supported the feasibility of performing a large pragmatic clinical trial comparing CPAP and HFNC in critically ill children, and informed its design and conduct, the FIRST-line support for Assistance in Breathing in Children (FIRST-ABC) was set up as a master protocol to answer the research question: in a child requiring NRS, either for acute illness or post-extubation support, which first-line mode of NRS is the most clinically and cost-effective treatment?

Aims and objectives

Aim

To evaluate the clinical and cost-effectiveness of HFNC when used as the first-line mode in critically ill children requiring NRS: (1) for an acute illness (step-up RCT) and (2) 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 all forms of respiratory support (invasive and/or non-invasive).

Methods

Trial design and governance

FIRST-line support for Assistance in Breathing in Children was a master protocol comprising two pragmatic, multicentre, 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. The trial was approved by East of England – Cambridge South Research Ethics Committee and the UK Health Research Authority. The National Institute for Health Research convened a majority independent Trial Steering Committee and an independent Data Monitoring and Ethics Committee. The trial was sponsored by Great Ormond Street Hospital NHS Foundation Trust and co-ordinated by the Intensive Care National Audit & Research Centre Clinical Trials Unit.

Participants: sites and patients

To achieve 90% power with a type I error rate of 2.5% (one-sided) to exclude the prespecified non-inferiority margin of hazard ratio (HR) = 0.75, 508 events were required to be observed. Anticipating 5% censoring for death or transfer, allowing for withdrawal/refusal of consent, and for exclusion due to non-adherence in the per-protocol population, we planned to recruit a total sample size of 600 patients in each RCT.

Children were screened and randomised if they were:

- admitted/accepted for admission to a participating PICU/high-dependency unit (HDU)
- aged > 36 weeks corrected gestational age and < 16 years
- assessed by the treating clinician to require NRS
- for an acute illness (step-up RCT)
- within 72 hours of extubation following a period of invasive ventilation (step-down RCT).

Owing to the emergency and time-sensitive nature of respiratory support, the Research Ethics Committee approved a 'research without prior consent' model, meaning that consent was sought after randomisation. Patients were randomised to HFNC or CPAP (by telephone/internet) in a 1 : 1 ratio, using permuted block sizes of 2 and 4, stratified by site and age (< 12 months vs. ≥ 12 months).

Treatment groups

High-flow nasal cannula

High-flow nasal cannula was delivered at the prescribed gas flow rates (based on patient weight) during the trial period. To standardise treatment, clinical criteria and guidance for the initiation, maintenance and weaning of HFNC were provided in a trial algorithm. As per the algorithm, patients were assessed for response to the treatment, readiness to wean and for stopping HFNC at least twice per day.

Continuous positive airway pressure

Continuous positive airway pressure could be started using any approved medical device and patient interface at a set expiratory pressure of 7–8 cm H_2O. To standardise treatment, clinical criteria and guidance for the initiation, maintenance and weaning of CPAP were provided in a trial algorithm. As per the CPAP algorithm, patients were assessed for response to the treatment, readiness to wean and for stopping CPAP at least twice per day.

Clinical practice

As the medical devices and interfaces that deliver HFNC and CPAP were easily distinguishable from each other, it was not possible to blind the patient, parents/guardians or clinical staff. Clinicians were permitted to stop HFNC/CPAP and switch to the other treatment or escalate to other forms of respiratory support, if clinically deemed necessary. Patients who switched or escalated treatments remained in the trial and continued to be monitored until liberation from respiratory support. All other usual care (e.g. sedation, feeding) was at the discretion of the treating clinical team.

Outcome measures

The primary clinical outcome was time to liberation from respiratory support. The primary cost-effectiveness outcome was 180-day incremental net monetary benefit.

Secondary outcomes included mortality at PICU/HDU discharge, day 60 and day 180; (re)intubation rate at 48 hours; duration of PICU/HDU and hospital stay; patient comfort assessed during NRS using the COMFORT Behavior (COMFORT-B) score; proportion of children in whom sedation was used during NRS; parental stress measured, in hospital at/around the time of consent at 24–48 hours, using the validated questionnaire Parental Stress Score: PICU; and health-related quality of life (HRQoL) at 180 days measured using age-appropriate Paediatric Quality of Life Inventory (PedsQL) and Child Health Utility 9 Dimension (CHU-9D) questionnaires.

Data sources

A secure, dedicated electronic case report form was used for trial data entry. To maximise efficiency, trial data were linked to the Paediatric Intensive Care Audit Network data, Hospital Episode Statistics and national death registrations (via NHS Digital). Surviving patients were mailed questionnaires at 180 days, with telephone follow-up to non-responders.

Clinical effectiveness analysis

Analyses were undertaken independently for each RCT. Analyses of primary and secondary outcomes were performed according to the randomisation group in all consented patients who commenced any respiratory support following

randomisation (primary analysis set), and in all consented patients who met eligibility criteria and commenced the randomised treatment (per-protocol analysis). Agreement of results from both analyses was required to conclude non-inferiority.

The primary analysis was performed using Cox regression to calculate a HR with one-sided 97.5% confidence intervals (CIs), adjusted for prespecified baseline covariates. *Both RCTs*: age (< 12 months vs. ≥ 12 months); SpO_2 : FiO_2 ratio; comorbidities (none vs. neurological/neuromuscular vs. other); severity of respiratory distress (severe vs. mild/moderate) and site (treated as a random factor using shared frailty). Additionally in *step-up RCT*: reason for admission (bronchiolitis vs. other respiratory vs. cardiac vs. other); and receipt of NRS at randomisation (yes/no) and in *step-down RCT*: length of prior invasive mechanical ventilation (IMV; < 5 days vs. ≥ 5 days); and reason for IMV (cardiac vs. other). HFNC was considered non-inferior to CPAP if the bound of the one-sided 97.5% CI for the adjusted HR was > 0.75 in both the primary and per-protocol analyses.

Cost-effectiveness analysis

Cost-effectiveness analysis (CEA) was based on an NHS and Personal Social Services perspective. Total costs per patient for up to 6 months post randomisation were reported. Data from PedsQL and CHU-9D at 6 months were combined with survival data to report quality-adjusted life-years (QALYs) at 6 months. The CEA followed the intention-to-treat principle and reported the mean (95% CI) incremental costs, QALYs and net monetary benefit at 6 months. The CEA used multilevel linear regression models that allowed for clustering of patients at site. The analysis adjusted for key baseline covariates at both patient and site level.

Results

Step-up randomised controlled trial

Sites and patients

Of the 18,976 admitted children screened across 24 sites, 1449 were deemed eligible for the trial, of whom 600 (41%) were randomised between 10 August 2019 and 7 November 2021. Consent was in place for 595 children. The primary analysis set consisted of 573 children in whom respiratory support was commenced (HFNC: 295; CPAP: 278). The randomised groups had similar baseline characteristics. The median age of participants was around 9 months, 60% were male, and nearly 50% had bronchiolitis. The per-protocol analysis included 533 children (HFNC: 288; CPAP: 245); baseline characteristics were similar to the primary analysis.

Clinical management

In both groups, the allocated treatment was started in most children who started respiratory support (HFNC: 98.3% and CPAP: 88.5%). The starting HFNC gas flow rate and CPAP pressure followed the trial algorithms. Treatment failure requiring either a switch or escalation occurred in 96/290 children (33.1%) for HFNC and in 131/246 children (53.3%) for CPAP after a median of 6.1 hours (HFNC) and 4.5 hours (CPAP) following randomisation. More patients switched from CPAP to HFNC (30.9%) than from HFNC to CPAP (20.0%). Reasons for switching were mainly related to clinical deterioration in the HFNC group and to patient discomfort in the CPAP group.

Clinical effectiveness

Primary outcome

The median time from randomisation to liberation from respiratory support was 52.9 hours (95% CI 46.0 to 60.9 hours) for HFNC and 47.9 hours (95% CI 40.5 to 55.7 hours) for CPAP, with an absolute difference of 5.0 hours (95% CI −10.1 to 17.4 hours). The adjusted HR was 1.03 (one-sided 97.5% CI 0.86 to ∞). In prespecified subgroup analyses, there was a significant difference in effect between patients who were receiving respiratory support at randomisation (in whom CPAP was more effective) and those who were not. Planned sensitivity analyses did not alter the interpretation of the primary analyses.

Secondary outcomes

The rate of intubation within 48 hours was not significantly different between the groups [HFNC group: 15.4%; CPAP group: 15.9%; adjusted odds ratio (OR), 0.99; 95% CI 0.61 to 1.62]. Sedation use was significantly lower in the HFNC group (27.7% vs. 37.0% for CPAP; adjusted OR 0.59; 95% CI 0.39 to 0.88) as was duration of critical care unit stay [mean, 5 days vs. 7.4 days for CPAP; adjusted mean difference, −3.1 days (95% CI −5.1 to −1.0 days)]. The Parental Stress Score and COMFORT-B score were similar between groups.

Cost-effectiveness

At 180 days, the total costs were higher for CPAP compared to HFNC (£24,142 vs. £20,335). The HRQoL at 6 months was high but similar in both groups; the mean QALYs were slightly lower in the HFNC group. After adjustment for baseline characteristics, the estimated incremental cost of HFNC compared to CPAP was −£5702, with wide 95% CI. The cost-effectiveness plane showed most points representing incremental costs and incremental QALYs fell in the third quadrant (south-west) of the cost-effectiveness plane, indicating that HFNC resulted in lower QALYs and lower costs. At £20,000 per QALY, the incremental net benefit (INB) from adjusted analysis was positive for HFNC although with wide CIs (£5628, 95% CI −£8 to £11,264).

Step-down randomised controlled trial

Sites and patients

Out of 3121 extubated children screened in the 22 participating PICUs, 1051 fulfilled eligibility criteria and 600 (57%) were randomised between 8 August 2019 and 18 May 2020; consent was available in 587 children. The primary analysis set comprised 553 children (HFNC: 281; CPAP: 272) in whom respiratory support was started. The randomised groups had similar baseline characteristics, except for a higher proportion of children receiving ventilation for cardiac reasons in the HFNC group (28.8% vs. 20.2% in the CPAP group). The per-protocol population included 523 children (HFNC: 271; CPAP: 252); baseline characteristics were similar to the primary analysis set.

Clinical management

In both groups, most children who started any respiratory support were started with the allocated treatment (HFNC: 96.8%; CPAP: 92.6%). The starting HFNC gas flow rate and CPAP pressure were as per the trial algorithms. Treatment failure requiring a switch or escalation occurred in 101/272 children (37.1%) for HFNC and 85/252 children (33.7%) for CPAP after a median of 10 hours (HFNC) and 7.8 hours (CPAP) after randomisation. Reasons for treatment failure, particularly switch, were mainly related to clinical deterioration for HFNC and for patient discomfort for CPAP.

Clinical effectiveness

Primary outcome

The median time from randomisation to liberation from respiratory support was 50.5 hours (95% CI 43.0 to 67.9) for HFNC and 42.9 hours (95% CI 30.5 to 48.2) for CPAP (adjusted HR 0.83, one-sided 97.5% CI 0.70 to ∞). Similar results were observed in the per-protocol analysis and in prespecified subgroup analyses. Planned sensitivity analyses did not alter the interpretation of the primary analyses.

Secondary outcomes

Mortality by day 180 was significantly higher in the HFNC group: 5.6% versus 2.4% for CPAP [adjusted OR, 3.07 (95% CI 1.1 to 8.8)]. None of the other secondary outcomes, including rate of reintubation within 48 hours, were significantly different between the groups.

Cost-effectiveness

At 180 days, the total costs were higher for CPAP compared to HFNC (£30,303 vs. £28,275). The HRQoL at 6 months was high but similar in both groups; the mean QALYs were slightly lower in the HFNC group. After adjustment for baseline characteristics, the estimated incremental cost of HFNC compared to CPAP was −£4565, with wide 95% CI. The cost-effectiveness plane showed most points representing incremental costs and incremental QALYs fell in the third quadrant (south-west) of the cost-effectiveness plane, indicating that HFNC resulted in lower QALYs and lower costs. At £20,000 per QALY, the INB from adjusted analysis was positive for HFNC although with wide CIs (£4388, 95% CI −£2551 to £11,307).

Conclusions

Among acutely ill children requiring NRS, HFNC met the criterion for non-inferiority compared with CPAP for time to liberation from respiratory support, whereas in critically ill children requiring NRS following extubation, the non-inferiority of HFNC could not be demonstrated.

Implications for health care

High-flow nasal cannula is a reasonable first-line option for NRS in an acutely ill child requiring NRS. Around one in three children will fail HFNC, mainly due to clinical deterioration, and will require a switch to CPAP or escalation. On the other hand, in the post-extubation setting, CPAP is a reasonable first-line option for NRS. Around one in three children will fail CPAP, mainly due to patient discomfort.

Recommendations for research

Recommendation 1
Secondary analyses exploring patient characteristics and patterns of physiological parameters that predict treatment failure, including intubation.

Recommendation 2
Compare protocolised approaches to initiation of post-extubation respiratory support with standard care in future clinical trials.

Recommendation 3
Explore alternative approaches for evaluating heterogeneity of treatment effect both from a clinical and cost-effectiveness point of view.

Recommendation 4
Explore reasons for increased mortality in HFNC group within step-down RCT.

Study registration

Current Controlled Trials ISRCTN60048867.

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Chapter 1 Introduction

Background and rationale

Over 18,000 critically ill children are admitted to paediatric intensive care units (PICUs) in the UK each year.[2] Respiratory support is the most common intervention undertaken in UK PICUs: national audit data from the Paediatric Intensive Care Audit Network (PICANet) show that nearly 75% of admissions between 2017 and 2019 received either invasive (via an endotracheal tube or tracheostomy) and/or non-invasive respiratory support (NRS) during their PICU stay.[2] Although invasive ventilation can be life-saving, there are concerns regarding its complications, such as ventilator-induced lung injury, need for prolonged sedation and nosocomial respiratory tract infections.[3] This has encouraged the greater adoption of NRS techniques in PICUs worldwide.[4–6] In critically ill adults and premature newborns, evidence from randomised controlled trials (RCTs) supports the early use of NRS to reduce invasive ventilation and improve survival in specific patient subgroups.[7–10] In critically ill infants and children, there is a dearth of high-quality RCT evidence; yet the use of NRS has increased over the years in UK PICUs as well as internationally.[2,11,12]

Non-invasive respiratory support is currently used in two distinct clinical scenarios: (1) in acutely ill children, to prevent intubation and ventilation (step-up treatment), and (2) in children who have just come off invasive ventilation, to prevent reintubation (step-down treatment). Traditionally, the first-line mode of NRS used in the PICU setting has been continuous positive airway pressure (CPAP), which involves the delivery of pressurised oxygen/air through a face mask or nasal prongs.[13] Despite the absence of large RCTs to confirm the effectiveness of CPAP, it is a mode of NRS that PICU clinicians have been familiar with and has used for over three decades. However, CPAP has two main limitations: (1) the need for a tight-fitting patient interface such as face mask, hood or nasal prongs to avoid leakage of gas from the ventilator circuit (which frequently causes patient discomfort/agitation as well as nasal and facial pressure sores with prolonged use, leading to treatment failure) and (2) the risk of serious complications such as pneumothorax or pneumomediastinum (which usually necessitates close monitoring and a high level of skilled nursing input).

Over the past decade, a novel mode of NRS called high-flow nasal cannula therapy (HFNC), which involves the delivery of heated and humidified air/oxygen through thin-bore nasal cannula, has rapidly gained popularity. This is despite the absence of RCT evidence to support its effectiveness in the PICU setting.[14,15] The main reason for its increasing use is related to patient comfort and ease of use.[15] Heating and humidification of gases during HFNC therapy prevent rapid drying of airway mucosa and decreases the metabolic work of breathing, and the high gas flow rate used (typically 8–10× minute ventilation) enables the reliable delivery of the set fraction of inspired oxygen (FiO_2). HFNC does not require a tight seal, and its patient interface (nasal prongs) is well tolerated by children. Delivery of heated and humidified medical gases to the patient at high gas flow rates (matching or exceeding the patient's own peak inspiratory flow rate) has been shown to confer a diverse range of beneficial effects such as reduction of airway resistance, reduction of dead space by nasopharyngeal washout with fresh gas, as well as delivery of positive airway pressure (like CPAP).[15,16] There is strong evidence from physiological and observational studies to support the use of HFNC in PICU: studies in infants and children confirm that HFNC reduces the work of breathing and improves oxygenation and ventilation.[17,18] In single-centre observational studies, the use of HFNC has been shown to be associated with a dramatic reduction in the rate of intubation and invasive ventilation.[19–21]

Prior to the FIRST-line support for Assistance in Breathing in Children (FIRST-ABC) RCTs, there were two Cochrane reviews (published in 2014) that examined the effectiveness of HFNC in children – both found no RCTs comparing HFNC with CPAP.[22,23] The first review focused on bronchiolitis only, and the second covered all other causes of

respiratory failure. Subsequently, two RCTs had been completed comparing HFNC with CPAP. The first was a single-centre RCT from Bangladesh and the second was a multicentre non-inferiority trial in bronchiolitis conducted in France.

In premature newborns, several RCTs had compared HFNC with CPAP; however, an evidence synthesis (HTA 14/151/03) concluded that there was a lack of convincing evidence that HFNC is superior or inferior to nasal CPAP and recommended more RCTs.[24] In adult critical care, Cochrane and other systematic reviews did not find sufficient evidence from good quality studies to determine if HFNC was effective compared to non-invasive ventilation.[25,26]

The evidence available from the two paediatric RCTs did not definitively support the effectiveness of either HFNC or CPAP in critically ill children. Relatively small numbers of patients were enrolled in these trials, resulting in wide confidence intervals (CIs); and different definitions of a composite, subjective primary outcome ('treatment failure') were used that did not correlate with more objective patient-centred outcomes, such as rate of intubation or duration of respiratory support. The 'treatment failure' rates reported also differ from treatment failure rates seen in routine practice. Importantly, the RCTs did not study the effectiveness of HFNC for step-up as well as step-down (post-extubation) care in children with a range of diagnoses, making it impossible to generalise their findings to contemporary practice in UK PICUs.

Widespread dissemination of HFNC in the absence of high-quality evidence would represent premature adoption of a technology without rigorous evaluation of associated risks and benefits. In particular, the benefits of HFNC (improved patient comfort, safety profile and ease of nursing care) need to be balanced against its potential risks (serious complications such as air leak, abdominal distension and nosocomial infection as well as excess mortality from delayed intubation and unnecessary prolongation of PICU/hospital stay).[27–29]

Our trial hypothesis was that in critically ill children assessed by the treating clinician to require NRS, first-line use of HFNC is non-inferior to CPAP in terms of time to liberation from respiratory support.

Aims and objectives

The aim of the FIRST-ABC RCTs was to evaluate the clinical and cost-effectiveness of the use of HFNC as the first-line mode of NRS in critically ill children: (1) with an acute illness and (2) within 72 hours of being extubated following a period of invasive ventilation (step-down RCT).

The primary objective was to evaluate the non-inferiority of HFNC, as compared with CPAP, when used as the first-line mode of NRS in children, both as a step-up and as a step-down treatment, 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 [non-invasive (HFNC, CPAP, pressure support and bilevel support) as well as invasive mechanical ventilation (IMV)].

Chapter 2 Methods

Trial design

FIRST-line support for Assistance in Breathing in Children was a master protocol comprising two pragmatic, multicentre, parallel-group, non-inferiority RCTs (step-up RCT and step-down RCT) with shared infrastructure, including an internal pilot stage and integrated health economic evaluation.[1]

The master protocol design allowed the research question to be addressed in each of the two important populations (step-up and step-down NRS) in an efficient way by minimising time and infrastructure costs as compared with conducting two sequential RCTs.[33]

The non-inferiority design was chosen based on previous RCTs on this topic as well as feedback from 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 it was shown not to be superior to CPAP.

The pragmatic design ensures that research findings can be more easily generalised to real-world practice.

Setting

The trial was set in NHS paediatric critical care units [PICUs and/or high-dependency units (HDUs)] across England, Wales and Scotland.

Trial sites

The trial aimed to recruit eligible patients from a representation sample of 25 paediatric critical care units (PICUs and/or HDUs). Trial sites could be either general (medical-surgical), cardiac or mixed (general-cardiac) units.

Sites were required to commit to the following criteria to take part in FIRST-ABC:

- identify a principal investigator (PI) to lead FIRST-ABC locally, supported by a research nurse with responsibility for day-to-day local trial co-ordination
- able to provide both treatments (HFNC and CPAP) to trial participants
- confirm collective equipoise regarding the choice of first-line NRS
- agree to incorporate FIRST-ABC into routine paediatric critical care clinical practice, highlighting the importance of systematic screening for potential eligible patients and prompt randomisation
- active participation in the PICANet for the UK and Ireland audit or able to collect detailed data on patient interventions and outcomes

- compliance with all responsibilities and requirements as stated in the trial protocol and FIRST-ABC Clinical Trial Site Agreement
- compliance with the UK Policy Framework for Health and Social Care Research and International Conference on Harmonization Guidelines on Good Clinical Practice.

Site identification, initiation and activation

Site identification commenced in February 2019 with an e-mail from the chief investigator (PR) to potential site investigators. A FIRST-ABC Collaborators' Meeting was also held in London in June 2019 with representatives from the clinical and research teams from potential sites to raise awareness of the trial and to gather feedback on the proposed trial procedures, including the algorithms for the delivery of CPAP and HFNC.

A staggered opening of sites was used to allow for in-person site initiation visits to be conducted at each participating site. Site initiation visits were facilitated by the chief investigator (PR) and/or trial manager (ARB) and attended by research and clinical team members at the site. During each visit, the background/rationale for the trial was presented and training was provided in the trial procedures for screening, randomisation, delivery of HFNC and CPAP, consent, data collection and safety monitoring. An investigator site file, containing all essential trial documents [e.g. trial protocol, standard operating procedures, participant information sheets (PISs) and consent forms, case report forms (CRFs) and relevant approvals], was also provided.

A 'green light' e-mail was issued to the local PI and research team by the Intensive Care National Audit & Research Centre (ICNARC) Clinical Trials Unit (CTU), authorising the commencement of screening and recruitment, once the following were in place:

- completed site initiation visit
- local confirmation of capacity and capability (e.g. local research and development department approval)
- fully signed FIRST-ABC Clinical Trial Site Agreement
- copy of the signed off delegation log submitted to the ICNARC CTU.

Patients

Eligibility

The target population was critically ill children requiring NRS for (1) an acute illness (step-up RCT) or (2) following extubation after a period of invasive ventilation (step-down RCT). Patients were considered eligible if they met all inclusion criteria and none of the exclusion criteria.

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 NRS, 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 the FIRST-ABC trial.
9. Clinician decision to start other form of NRS (i.e. not HFNC or CPAP).

Exclusion criterion 9 was added following an early amendment to the protocol (see *Health Research Authority and research ethics application* for details).

Screening

Potentially eligible patients admitted/accepted for admission to the participating unit were to be screened against the inclusion/exclusion criteria by the local clinical team, supported by the site research team. In the step-up RCT, all admissions to the critical care unit were to be screened. In the step-down RCT, all patients extubated during critical care admission were to be screened. In each RCT, screening and enrolment logs recorded screened patients, detailing which patients were randomised, reasons for exclusion and reasons for non-enrolment of eligible patients.

Randomisation

Randomisation of patients was performed after confirming eligibility and as soon as possible to the anticipated start of the randomised treatment.

In each RCT, eligible patients were randomised on a 1 : 1 basis to either CPAP or HFNC using a dedicated, centralised 24 hours/7 days per week telephone/web-based randomisation service hosted by Sealed Envelope Ltd (https://sealedenvelope.com/). The randomisation sequence was computer generated by Sealed Envelope and used variable block sizes of 4 and 6 to strengthen allocation concealment. Randomisation was stratified by site and age (< 12 months vs. ≥ 12 months) to minimise imbalance arising from unit practices and interface selection.

Following randomisation, the allocated treatment was commenced as soon as practically possible, each participant was assigned a unique FIRST-ABC trial number, and the local site research team were notified of the randomisation by e-mail.

Treatment groups

High-flow nasal cannula

Any approved medical device capable of delivering heated, humidified, high-flow through nasal cannulae was used to provide HFNC at prescribed gas flow rates (based on patient weight) during the trial period. To standardise treatment, clinical criteria and guidance for the initiation, maintenance and weaning of HFNC (and CPAP) were provided in a trial algorithm (*Figure 1*). The trial algorithms were developed iteratively in consultation with paediatric critical care clinicians across the UK (both via e-mail and in person at a Collaborators' Meeting held prior to the start of the trial). The trial recommended that patients were assessed for response to the treatment, readiness to wean and for stopping HFNC, as per the HFNC algorithm, at least twice per day (e.g. at ward rounds).

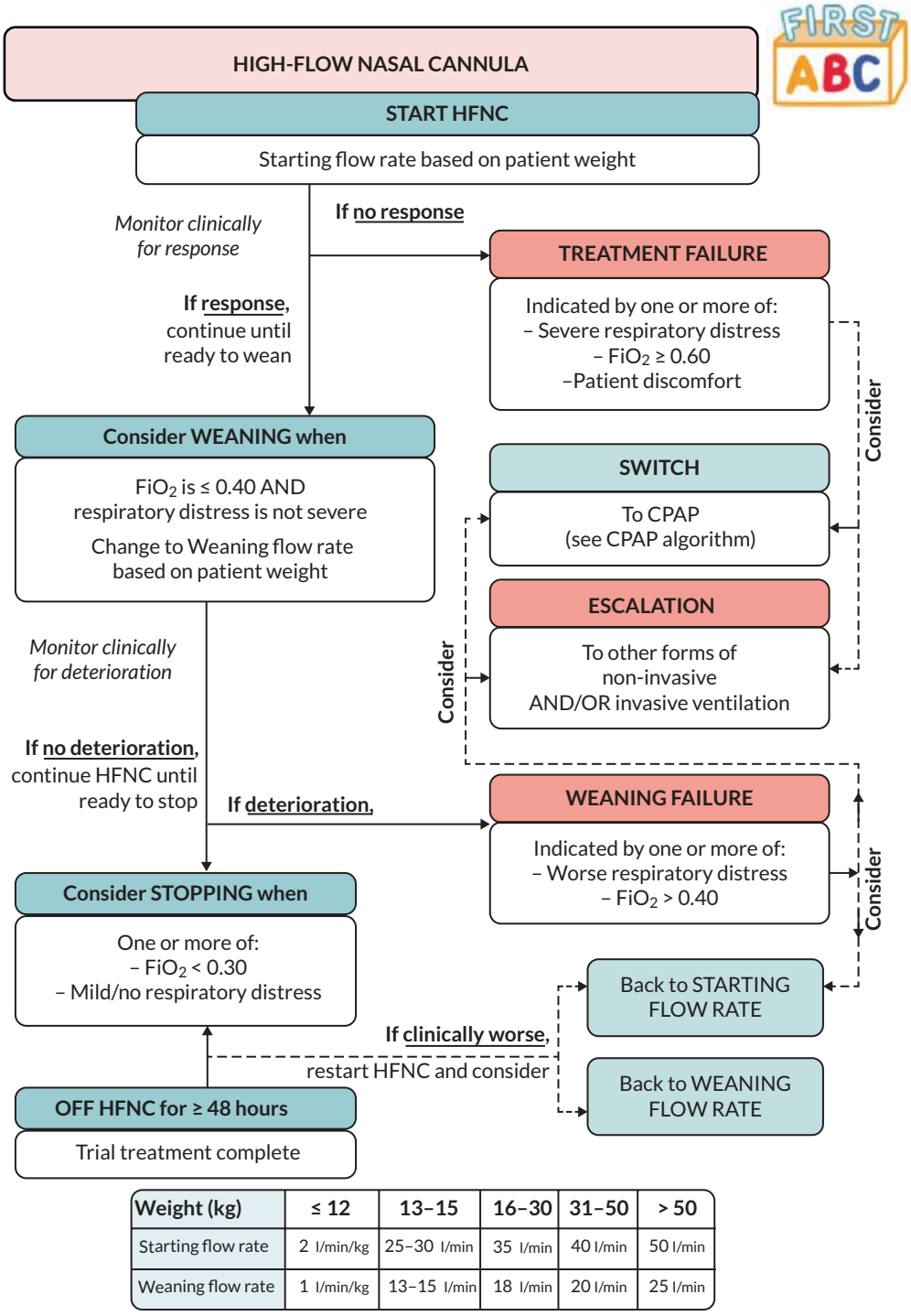
Continuous positive airway pressure

Continuous positive airway pressure was started using an approved medical device at a set expiratory pressure of 7–8 cm H_2O. The trial did 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 were provided in a trial algorithm (*Figure 2*). It was recommended that patients were 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 used HFNC and CPAP, no additional central training related to the use of HFNC or CPAP was provided for the trial, but resources for training in the trial algorithms were provided. As the medical devices and interfaces that deliver HFNC and CPAP are easily distinguishable from each other, it was not possible to blind the patient, parents/guardians or clinical staff.

The trial algorithms were to be followed until the patient has been liberated from all forms of respiratory support for at least 48 continuous hours. As per current clinical practice, clinicians were able to stop HFNC/CPAP and switch



Weight (kg)	≤ 12	13–15	16–30	31–50	> 50
Starting flow rate	2 l/min/kg	25–30 l/min	35 l/min	40 l/min	50 l/min
Weaning flow rate	1 l/min/kg	13–15 l/min	18 l/min	20 l/min	25 l/min

FIGURE 1 Trial algorithm for the delivery of HFNC. Reproduced from Richards-Belle *et al.*[1] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) licence, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: http://creativecommons.org/licenses/by/4.0/. Includes additions and changes to the original.

to the other treatment or escalate to other forms of respiratory support, if clinically deemed necessary. Prespecified objective criteria to identify non-responders to HFNC/CPAP were provided in the algorithms as a guide for clinicians considering switching or escalating respiratory support. Reasons for switches or escalations were recorded on the CRF. Patients who switched or escalated treatments remained in the trial and continued to be monitored until liberation from respiratory support.

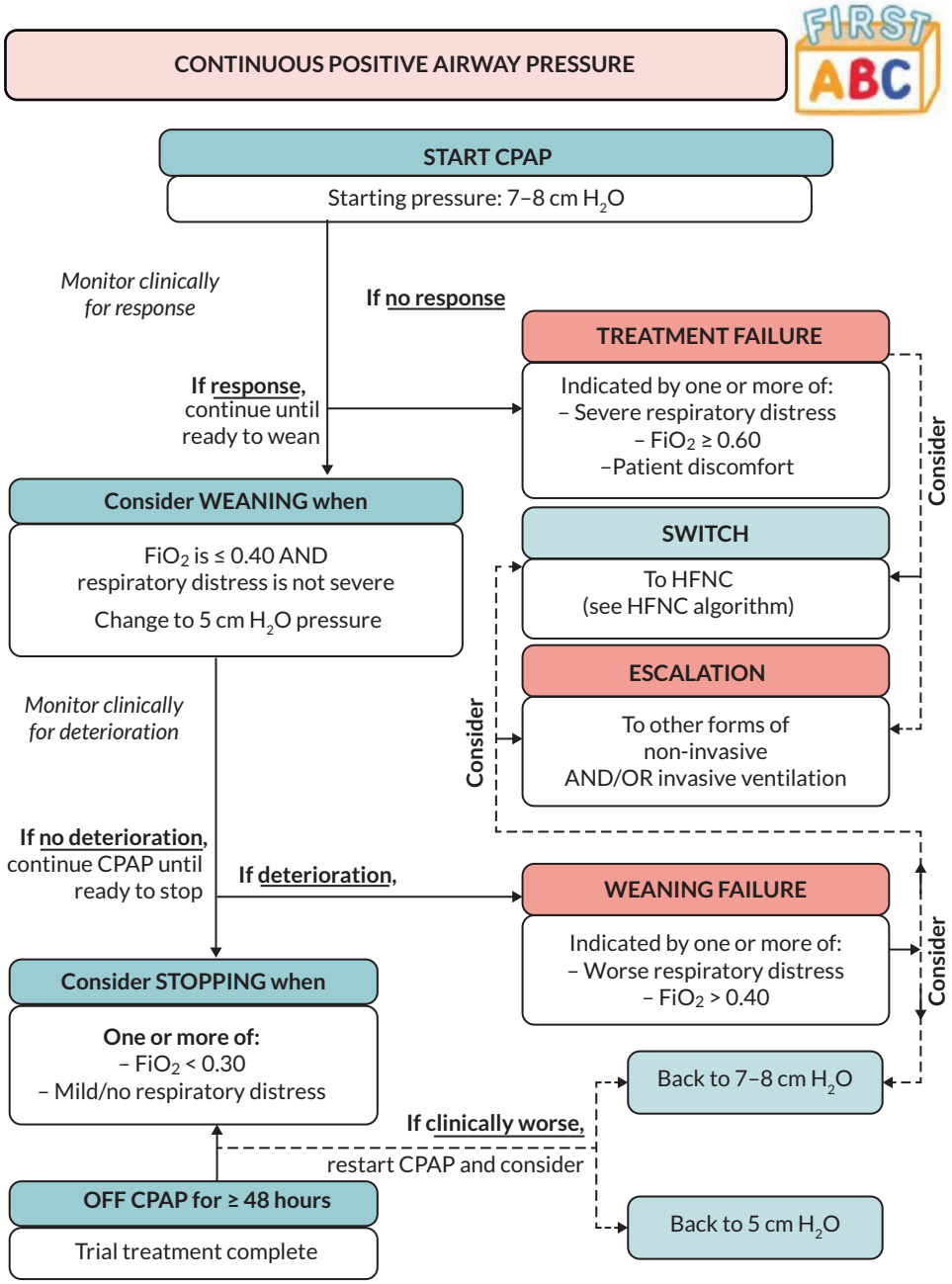


FIGURE 2 Trial algorithm for the delivery of CPAP. Reproduced from Richards-Belle *et al.*[1] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) licence, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: http://creativecommons.org/licenses/by/4.0/. Includes additions and changes to the original.

Co-interventions

All other usual care (e.g. sedation, feeding, etc.) was provided at the discretion of the treating clinical team, as per local practice. Note that respiratory support, as defined for the purposes of FIRST-ABC, did not include supplemental/low-flow oxygen.

Consent procedures

Consent was sought for the child (patient) from their parent/legal guardian. Children became 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 was granted ethical approval by the East of England – Cambridge South Research Ethics Committee (REC) to use a model of research without prior consent. Once a patient was screened and confirmed as eligible for the trial, they were randomised, and the allocated treatment (CPAP or HFNC) was commenced as soon as possible. This model, developed in line with the CONseNt methods in paediatric Emergency and urgent Care Trials (CONNECT) guidance,[34] has been found acceptable to parents/guardians and clinicians in several recent RCTs in the PICU setting[35–40] and is informed by experience/feedback from the pilot RCT.[40]

Following randomisation, a trained, delegated member of the local research team approached the child's parents/guardians as soon as appropriate and practically possible to discuss the trial (usually within 24–48 hours of randomisation). Before approaching the parent/legal guardian, the research team member would check with the relevant clinical staff that the participant was stable and that the timing was appropriate. If the participant's condition had not stabilised, additional time was given before approaching the parent/guardian. Once approached, a PIS was provided (see *Report Supplementary Material 1*), 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 (see *Report Supplementary Material 2*) was provided, indicating that: the information given had been read and understood; participation was voluntary and consent could be withdrawn at any time without consequence; and consent was 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. Parents/guardians were given time to read the information sheet, invited to ask any questions that they may have had about their child's participation, and the opportunity to discuss with other family members or friends before confirming their decision. Due to age and severity of illness, it was not possible to involve the patient in the consenting process. Instead, assent was to be obtained prior to hospital discharge if their condition allowed (e.g. they regained mental capacity).

A modification of the consent procedure would be utilised for two rarer situations where either the patient: (1) was discharged from hospital prior to obtaining consent or (2) died prior to consent being sought.[38,41] In the former, the local research team followed up with the parent/guardian, initially by phone and then by post, for consent. Postal contact was made again if there was no response after 4 weeks. If no consent form was received within 4 weeks of the second letter, the participant was to be included in the trial unless they notified the research team otherwise. In the latter situation, the local research team obtained information from colleagues and bereavement counsellors to establish the most appropriate clinical/research team member to notify the parents/guardians of involvement in the trial. If approach for consent was deemed not appropriate prior to the parent/guardian's departure from hospital, then they were approached by post 4 weeks post randomisation. The letter explained how to opt out of the trial. Postal contact was made again if there was no response after 4 weeks. If no consent form was received within 4 weeks of the second letter, the participant's data were included in the trial.

If informed consent was refused or withdrawn, this decision was respected and abided by, and no further contact made. All data occurring up to the point of this decision would be retained in the trial, unless parents/guardians requested otherwise.

Safety monitoring

Adverse event (AE) reporting followed the Health Research Authority guidelines on safety reporting in studies which do not use Investigational Medicinal Products (non-CTIMPs). The following events were prespecified 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:

- nasal trauma
- facial/neck trauma
- abdominal distension
- pneumothorax
- pneumomediastinum
- subcutaneous emphysema
- facial thermal injury
- respiratory arrest

- cardiac arrest
- aspiration.

Occurrences of the above specified, expected AEs were recorded for all randomised patients. Considering that eligible patients were critically ill and at increased risk of experiencing AEs, occurrences of other, non-specified, AEs were only reported if considered to be related to either CPAP or HFNC (i.e. 'possibly', 'probably' or 'definitely' related). The following events were not reported as AEs or serious adverse events (SAEs) as they were instead collected as study outcomes:

- intubation or reintubation
- sedation
- death (note that death itself was not reported as a SAE, but the suspected cause of death was assessed for severity, relatedness and expectedness).

Each event was assessed for its severity, according to the below definitions:

- 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 or permanent functional limitation.
- Life-threatening: complication that may lead to death or where the participant died as a direct result of the complication/AE.

Any reportable event classified as 'severe' or 'life-threatening' in severity was considered a SAE and was reported to the ICNARC CTU. If a SAE was evaluated by a clinical member of the Trial Management Group (TMG) as a related and unexpected SAE, then the ICNARC CTU submitted a report to the REC within 15 calendar days.

Questionnaire follow-up

At 6 months, after assessing the child's survival status, each consenting parent was sent a questionnaire (via e-mail or post) by the ICNARC CTU to assess health-related quality of life (HRQoL) and health service/resource use. If a parent requested a questionnaire to be sent via post, then a pen and self-addressed stamped envelope was provided for ease of return. Non-responders were followed up via telephone by a trained member of the FIRST-ABC team from the ICNARC CTU 3 weeks later.

If a patient was an inpatient at a participating site at the 6-month time point, then the site research team approached the parent/guardian to complete the questionnaire.

Clinical outcomes

Primary clinical outcome

Time to liberation from respiratory support

The primary outcome was the time from randomisation 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. In this definition, respiratory support included HFNC, CPAP, other forms of NRS (e.g. bilevel positive airway pressure, pressure support, etc.) and invasive ventilation. It did not include the administration of supplemental oxygen alone.

Secondary clinical outcomes

Rate of reintubation at 48 hours

Reintubation at 48 hours is defined as occurring if the child has started invasive ventilation at any time up to and including 48 hours and 0 minutes after the 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 48 hours following randomisation. Patients discharged from PICU/HDU before 48 hours are assumed not to have been invasively ventilated post-discharge.

Duration of paediatric intensive care unit/high-dependency unit and acute hospital stay

Duration of PICU/HDU stay was 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 a critical care unit (or ultimate discharge from critical care if transferred directly to another critical care unit) or to death in the critical care unit.

Patient comfort, during randomised treatment and during non-invasive respiratory support (i.e. high-flow nasal cannula and/or continuous positive airway pressure), measured using the COMFORT Behavior score

Patient comfort was measured during HFNC or CPAP using the COMFORT Behavior (COMFORT-B)[42] score and summarised at the patient level using the median of all recorded scores. Patient comfort was reported in all patients with at least one recorded COMFORT-B score in the first 6 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.

Proportion of patients in whom sedation is used during non-invasive respiratory support

Sedation was defined as any medication given with the intention of improving patient comfort (analgesics/sedatives) while on NRS. These included (but were not limited to): chloral hydrate, alimemazine, opiates (e.g. morphine, fentanyl), benzodiazepines (e.g. midazolam, lorazepam), clonidine and dexmedetomidine. Examples of analgesics which would not be considered a sedative were ibuprofen and paracetamol.

Need for sedation was reported as the proportion of patients in whom sedation was used during NRS at any point from randomisation until liberation from respiratory support. Patients were be included in the denominator if they had a minimum of three non-missing observations in the first 6 hours of respiratory support.

Parental stress, in hospital at/around the time of consent, measured using the Parental Stressor Scale: paediatric intensive care unit

Parental stress was measured using the validated Parental Stressor Scale: PICU (PSS:PICU)[43] in hospital at/around the time of consent (anticipated to be within 24–48 hours post randomisation). This scale consists of 37 items, each scored in whole numbers from 1 (not stressful) to 5 (extremely stressful). A total score was calculated as the mean of all completed items.

Mortality at paediatric intensive care unit/high-dependency unit discharge, day 60 and day 180

Mortality at discharge from the PICU/HDU was defined as death due to any cause before discharge to any location providing a level of care less than Level 2 (high dependency care). Mortality at days 60 and 180 was calculated as binary end points using all patients with known survival status at those times and additionally using time-to-event methods with surviving patients censored at the date last known to be alive (to a maximum of day 180).

Data collection and management

Case report forms

Case report forms were developed to capture important data fields for the RCTs relating to: confirming eligibility, consent and patient details (to enable data linkage and follow-up), baseline observations and comorbidities,

delivery of respiratory support (including switches and escalations, weaning from HFNC or CPAP, and liberation), critical care and hospital discharge details, and safety monitoring. The trial data collection schedule is shown in *Table 1*.

A dedicated, secure, electronic CRF was developed to enable site staff to enter and submit the trial data. Access to the electronic CRF was centrally managed, with access granted only to authorised site staff (as per the delegation log).

Data management

Data validation checks were built into the electronic CRF, such that only values that were physically possible could be saved as well as checks to identify and query unusual or missing data items. Sites were contacted throughout the trial period with potential data queries in an attempt for data to be validated and cleaned as early as possible.

Data linkage: The Paediatric Intensive Care Audit Network and National Health Service Digital

To reduce the burden of data collection on sites, FIRST-ABC data were linked to PICANet and NHS Digital. Linkage with PICANet provided further data on interventions delivered during critical care admissions within the first 6 months following randomisation (a separate CRF was developed for sites not participating in PICANet). Following the signing of a data-sharing agreement with NHS Digital, FIRST-ABC data were linked to Hospital Episode Statistics (HES; admitted patient care, outpatients and emergency care data sets), to provide data on resource use, and to civil registrations, to identify any deaths, both within the 6 months following randomisation.

Governance, management and oversight

Health Research Authority and research ethics application

Following submission of an application for Health Research Authority approval and REC favourable opinion on 26 April 2019, a research ethics committee meeting was scheduled for 23 May 2019 and attended by ARB and PM. Provisional

TABLE 1 Patient data collection schedule

	Baseline	At time of consent	During NRS	End of PICU/HDU stay	End of hospital stay	At 6 months
In hospital						
Clinical/baseline data	✔					
Patient/parent details		✔				
Types of respiratory support received[a]	✔		✔			
Patient comfort and sedation use			✔			
Parental stress		✔				
Discharge data				✔	✔	
Safety monitoring data			✔			
At follow-up						
PedsQL						✔
CHU-9D						✔
Health services/resource use						✔

PedsQL, Pediatric Quality of Life Inventory; CHU-9D, Child Health Utility 9 Dimension questionnaire.
a Including weaning, switches and escalations from HFNC/CPAP.

Note
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opinion was issued on 12 June 2019 and full Health Research Authority approval and REC favourable opinion given on 26 July 2019.

Amendments to the protocol

There was one amendment to the protocol (substantial amendment 1). The main purpose of this amendment was to:

- add an exclusion criterion ('clinical decision to start other forms of NRS i.e. not HFNC or CPAP')
    - As FIRST-ABC investigated HFNC and CPAP, patients deemed to require other forms of NRS (such as bilevel support) were not eligible. This message was reinforced in study training materials; however, some participating sites requested this be added as an explicit exclusion criterion for clarity among their teams.
- remove the step-down RCT interim analysis
    - Considering a higher-than-expected recruitment rate in the step-down RCT, a decision was agreed with the DMEC that no formal interim analysis would be performed given that the trial would have almost completed recruitment by the time the first 300 patients had been followed up to 60 days (the prespecified time point for the interim analysis). Instead, safety data (counts and percentages of AEs by arm, and a line listing of SAEs) was made available for scrutiny by the DMEC by the end of the internal pilot stage. There were no changes to the planned interim analysis of the step-up RCT.

This amendment was submitted on 6 February 2020 and received Health Research Authority approval and Research Ethics Committee favourable opinion on 27 February 2020.

Local governance

Prior to the commencement of patient recruitment, each participating NHS trust/health board signed a Clinical Trial Site Agreement, based on the model agreement for non-commercial research in the NHS, with the sponsor and issued confirmation of capacity and capability to deliver the trial.

Trial registration

FIRST-line support for Assistance in Breathing in Children was prospectively registered with the ISRCTN Registry on 19 June 2019 (reference: ISRCTN60048867).

Patient and public involvement

Two parent representatives with experience of paediatric intensive care contributed to the design of FIRST-ABC and were co-investigators on the grant. One parent representative continued their involvement through membership of the TMG, and contributed to reviewing and advising on participant documents, consent procedures and interpretation of the results. The TSC included two patient and public involvement (PPI) members.

Trial monitoring

The trial team members at the ICNARC CTU had regular communication with sites via e-mail, telephone, teleconferences and regular newsletters. The local PI was responsible for ensuring all queries were addressed and for overall quality of their site data. Adherence to the protocol was paramount in the central monitoring plan, including a review of eligibility data and adherence to the HFNC and CPAP algorithms.

The on-site monitoring plan followed a risk-based strategy. The timing and frequency of visits to sites were based on risk assessment, with a view to visiting ~ 25% of sites at least once during the recruitment period. In total, 6 of 26 (23%) were visited for a monitoring visit. Additional visits were not possible due to restrictions introduced following the start of the COVID-19 pandemic. During these visits, the investigator site file was checked for completeness, consent forms were reviewed, and source data verification was carried out on a random sample of patient CRFs. The visits were also used to discuss progress on delivering the trial at the site, including identifying any potential barriers or difficulties and suggesting potential solutions. Following each visit, a report was sent to the site by the trial monitor summarising the findings and any outstanding actions.

Trial Management Group

The TMG, led by the chief investigator (PR), was responsible for the management of the trial. The chief investigator (PR) took overall responsibility for the delivery of the trial and oversaw progress against timelines. The TMG included paediatric critical care clinicians, trialists and PPI representation. The trial manager (ARB) was responsible for the day-to-day management of the trial, supported by the trial co-ordinator (LD), data manager (MS) and trial statisticians (KT, IO).

Trial Steering Committee

An independently chaired and majority independent Trial Steering Committee was convened by the National Institute for Health and Care Research (NIHR) to provide overall supervision of the trial on behalf of the funder and sponsor. The committee was chaired by Professor Carrol Gamble (University of Liverpool).

Data Monitoring and Ethics Committee

An independent Data Monitoring and Ethics Committee was convened by the NIHR in order to monitor recruitment, protocol adherence and patient safety. The committee was chaired by Professor Neal Thomas (Penn State University).

Sponsorship

FIRST-line support for Assistance in Breathing in Children was sponsored by Great Ormond Street Hospital for Children NHS Foundation Trust (reference: 17IA05).

Network support

FIRST-line support for Assistance in Breathing in Children was adopted onto the NIHR Central Portfolio Management System on 17 May 2019 (reference: 42112).

Statistical analysis

Analysis principles

The primary clinical outcomes were tested for non-inferiority. Other secondary outcomes were tested for superiority, where testing was specified, or analysed using descriptive statistics only if no testing was specified in the statistical analysis plan. All analyses were performed separately for each of the two trials, and any results were not combined.

Statistical tests will be two-sided with significance set at $p < 0.05$ unless otherwise specified. Effect estimates will be reported with 95% CIs. There will be no adjustment for multiple testing. The results of subgroup analyses were interpreted taking into account accepted criteria for credible subgroup effects.[44,45]

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 end point ('primary analysis set'), consisting of the ITT populations excluding those with no recorded respiratory support post randomisation.

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

Sample size calculation

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 non-inferiority 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,[40] 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 per-protocol population, we aimed to recruit a total sample size of 600 patients in each of the two RCTs.

Internal pilot

The internal pilot phase was evaluated 6 months after the first site opened to recruitment. At this point, the following key progression criteria were assessed and classified as green, amber or red (*Table 2*).

All progression criteria in both RCTs were classified as green and so both proceeded to the full sample size as planned.

Interim analyses

A single interim analysis was planned for each RCT, after recruitment and follow-up to day 60 of 300 patients. At this point, the following end points were to 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 was shown to be superior with $p < 0.05$.

For this interim analysis, patients discharged 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.

Due to a higher than anticipated recruitment rate, the step-down RCT interim analysis was not performed (see *Amendments to the protocol*).

Clinical effectiveness analysis

Screening

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 percentage of patients who did not meet inclusion criteria, overall and by criteria.
- Of the patients who met the inclusion criteria, number and percentage 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 percentage not randomised, overall and by reason (if known).

TABLE 2 Internal pilot progression criteria

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[a]	Over 90%	75–90%	Less than 75%
Changes to another form of NRS, escalation and weaning carried out as per protocol[b]	At least two-thirds	Between one-third and two-thirds of cases	Less than one-third of cases

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

Recruitment
Consolidated Standards of Reporting Trials flow diagrams for the ITT and per-protocol populations will be completed for each trial.

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 hours 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 NHS Digital 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 have already been obtained via linkage from PICANet or NHS Digital, these 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 end point.

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.

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 (SD), 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_2O as a continuous variable, and grouped as < 7 cm, 7–8 cm, > 8 cm), by hour during the first 6 hours from randomisation.
- In patients randomised to HNFC, flow rate (as percentage 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.

Protocol adherence
The number and percentage 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 are not met in last recorded observation prior to weaning.
- Respiratory support is discontinued while FiO_2 ≥ 0.3 and moderate or severe respiratory distress is present.

Safety
Adverse events (nasal trauma, facial/neck trauma, abdominal distension, pneumothorax, pneumomediastinum, subcutaneous emphysema, facial thermal injury, respiratory arrest, cardiac arrest), and any other possibly related AE, 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 AEs in patients who commenced respiratory support post randomisation will be compared between groups using Fisher's exact test. Counts and percentages of AEs, and SAEs, overall and by type, will be presented by allocated treatment group.

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.

Timing of outcome assessments

Following randomisation, details of respiratory support (type of support, flow rate/pressure), physiological parameters (respiratory rate, heart rate, SpO_2, FiO_2) 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 6 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 PSS at the time of consent, which is expected to be within 24–48 hours of randomisation. Pediatric Quality of Life Inventory (PedsQL) and the Child Health Utility 9 Dimension (CHU-9D) and health services/resource use is assessed at 6 months post randomisation.

Analysis methods

Baseline patient characteristics

Baseline data are 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 per-protocol populations, by allocated treatment group (using mean, SD, median and IQR, or counts and percentages for binary and categorical variables) but not subjected to statistical testing:

In both RCTs

- Age (years) – median and IQR, and number and percentage 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 percentage.
- Respiratory distress at randomisation – number and percentage by category.
- Heart rate at randomisation (both as absolute values, and converted to centile for age) – median and IQR, mean and SD.
- SpO_2 at randomisation – median and IQR, mean and SD.
- FiO_2 at randomisation – median and IQR, mean and SD.
- Ratio of SpO_2 : FiO_2 at randomisation – median and IQR, mean and SD.
- COMFORT-B score at randomisation (last available) – mean and IQR, number and percentage with COMFORT-B score ≥ 23 (representing possible distress[1]).
- Comorbidities – number and percentageby type of comorbidities (as specified on the CRF).

Step-up RCT only

- Main reason for admission to critical care – number and percentage.
- Any respiratory support received in 24 hours prior to randomisation (overall, and by type and duration of support) – number and percentage.
- Whether on respiratory support at time of randomisation – number and percentage.

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

Step-down RCT only

- Main reason for invasive ventilation.
- Duration of invasive ventilation – median and IQR, and number and percentage with duration < 5 days, number and percentage with duration ≥ 5 days.

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 RCTs

- Age (< 12 months vs. ≥ 12 months).
- Severity of respiratory distress at randomisation (severe vs. mild/moderate).
- SpO_2 : FiO_2 ratio at randomisation (linear).
- Comorbidities (none vs. neurological/neuromuscular vs. other).

Step-up RCT only

- Reason for admission [bronchiolitis vs. other respiratory (airway problem, asthma/wheeze or any other respiratory) vs. cardiac vs. other (neurological, sepsis/infection, any other)].
- Whether the patient was on NRS at randomisation (yes/no).

Step-down RCT only

- Length of prior IMV (< 5 days vs. ≥ 5 days).
- Reason for IMV (cardiac vs. other).

The primary effect estimate will be the adjusted HR, reported with a 95% CI. HFNC will be considered non-inferior to CPAP if the lower bound of the 95% CI is above 0.75 in both the mITT and per-protocol populations. Patients without a recorded time of liberation will be censored at date and time of death (for patients who died while on treatment) or at date and 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:

In both RCTs

- Age.
- Severity of respiratory distress at randomisation.
- SF ratio at randomisation.
- Comorbidities.

Step-up RCT only

- Reason for admission.
- Whether the patient was on NRS at randomisation.

Step-down RCT 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) versus 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 HR within five categories at quintiles of the continuous variable.

Planned sensitivity analyses included a repeat of the primary analysis using alternative durations: from start of respiratory support to liberation from respiratory support; from randomisation to start of weaning; and from randomisation to meeting weaning criteria. A post hoc analysis was performed to assess the effect of patients who did not start any respiratory support by including them in a sensitivity analysis of the primary end point that assigned them to a nominal 2 hours of respiratory support.

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 per-protocol and mITT populations. Absolute risk reduction and unadjusted odds ratios (ORs) will be reported with 95% CIs. Multilevel logistic regression (adjusted for the same baseline variables as the adjusted analysis of the primary outcome) will be used to calculate adjusted ORs with 95% CIs.

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

Duration of survival to day 180 will be plotted as Kaplan–Meier survival curves, in the per-protocol and mITT populations, and unadjusted and adjusted HRs with 95% CIs will be calculated using Cox regression models.

Parent-/patient-reported outcomes (PSS:PICU score, PedsQL score) will be summarised by treatment groups, in the per-protocol and mITT populations. Mean difference between groups will be calculated, with 95% CI 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 percentage of patients with any recorded COMFORT-B score ≥ 23 while on randomised treatment, and the number and percentage of patients with any recorded COMFORT-B score ≥ 23 while on either HFNC or CPAP will be reported. Mean difference between groups will be calculated, with 95% CI using bootstrapping to account for anticipated non-normality in the distribution. Linear regression will be used to calculate adjusted mean differences.

Health economic analysis

Methods overview

A full cost-effectiveness analysis (CEA) was undertaken to assess the relative cost-effectiveness of HFNC versus CPAP in acutely ill children admitted to a critical care unit clinically assessed to require NRS. The CEA was undertaken for both step-up and step-down RCTs and compared the costs and health economic outcomes of treatment comparators within each trial over 6 months after randomisation. The CEA used patient-level healthcare resource use and outcome data collected as part of the trial databases linked to routine data from PICANet (the national clinical audit of PICUs) and

NHS Digital's HES data sets and through completion of the follow-up Health Services Questionnaire (HSQ) to report cost-effectiveness at 6 months. The cost analysis adopted a health and personal health services perspective.[46]

Health-related quality of life was measured using the age-appropriate Pediatric Quality of Life Generic Core Scales (PedsQL) questionnaire, which was then mapped onto preference-based CHU-9D score to estimate HRQoL. HRQoL data were combined with survival data to report preference weighted quality-adjusted life-years (QALYs), which is the preferred outcome measure for CEA. The base-case CEA followed the mITT principle and reported the mean (95% CI) incremental costs, QALYs and incremental net monetary benefit (INB) at 6 months of HFNC versus CPAP, overall and for the same prespecified subgroups as for the evaluation of clinical effectiveness. Patients who did not consent to being sent the questionnaire or to their data being used in the CEA were not included in this part of the study. The main assumptions of the CEA were subjected to extensive sensitivity analyses. The study used similar CEA methods for the step-up and step-down RCTs, which are described below.

Resource use and costs at 6 months

The resource use associated with hospital stays (index admission and re-admissions up to 6 months), and visits to outpatients and community healthcare services were chosen a priori as possible drivers of incremental costs. The interventions, CPAP and HFNC, are provided in the usual care practice and their costs are assumed to be included within the hospital bed-day costs. No additional intervention costs, such as cost of device, consumables or staff time were deemed required for delivering the interventions in PICU/HDU. Total costs were calculated by combining the resource use with unit costs at 2020–1 prices (£ GBP).

The length of stay within PICU/HDU and general medical ward from index and re-admission were extracted from FIRST-ABC CRFs linked to PICANet database and follow-up HSQ. The duration and location of the index hospital admission, that is, the combined duration of any stay in PICU/HDU and in the general medical ward following randomisation, were recorded for each patient on the CRF. The length of stay in the initial PICU/HDU admission during the index admission was calculated as the total duration in days (including fractions of days), from the date and time of randomisation until the time of discharge to the medical ward or death, including duration of transfers to other critical care units. Subsequent re-admissions into PICU/HDU units following initial discharge to the ward were also measured. Each activity day within paediatric critical care was assigned a Healthcare Resource Group (HRG) applying the 2019–20 HRG4+ Grouper algorithm.[47] The cost of paediatric critical care bed-days was valued according to realistic scenarios reflecting workload. Patients receiving HFNC or CPAP in a PICU or HDU were considered to receive the same level of care. Intermediate paediatric critical care (XB06Z HRG code) was considered the appropriate level of critical care associated with providing the interventions. The cost of HFNC use in the paediatric ward following discharge from HDU/PICU was costed as basic critical care (XB07Z HRG code).

A hospital re-admission was defined as a further hospital admission following ultimate discharge from the index hospital admission. Information on re-admissions was collected from two sources. Firstly, data on re-admissions to critical care were accessed from the trial CRFs linked to the PICANet database.[48] From these databases, information was accessed on the duration of stay within the critical care unit as well as the total hospital stay including subsequent transfers to other care areas (e.g. general medical wards) within the same hospital and to other hospitals. Secondly, information on re-admissions that did not include a further stay in critical care wards was collated from responses to the HSQ administered to patients surviving to 6 months post randomisation.

The resource use associated with re-admissions to hospital, hospital outpatient visits and community services use following discharge from the index hospital admission but before 6 months post randomisation were collected via HSQ. In sensitivity analysis, use of health services following discharge from the index hospital admission was derived from HES.

Unit cost

The unit costs required for valuing the resource use data were taken from national unit cost databases and are listed in *Appendix 1*. The costs per critical care bed-day by HRG and general medical bed-day were taken from the NHS benchmark prices (personal communication). Unit costs for hospital outpatient visits and community service use were obtained from a recommended published source for health and social care costs.[49] All unit costs were reported in 2020–1 prices.

Health-related quality of life, life-years and quality-adjusted life-years up to 6 months

Health-related quality of life data were collected via age-appropriate Pediatric Quality of Life Generic Core Scales (PedsQL™) questionnaires sent to patients at 6 months post randomisation.[50] The responses to PedsQL questionnaires from eligible surviving patients at 6 months were mapped onto the CHU-9D index score.[51,52]

FIRST-line support for Assistance in Breathing in Children trial data were linked with national death registrations using the Medical Research Information Service Database Administrative System held by NHS Digital. Information on the date and time of deaths was used to calculate the survival time and life-years up to 6 months for each randomised patient. QALYs at 6 months post randomisation were calculated by valuing each patient's survival time by their HRQoL (CHU-9D utility score) at 6 months according to the 'area under the curve' approach.[53] For 6-month survivors, QALYs was calculated using the CHU-9D scores at 6 months, assuming a CHU-9D score of zero at randomisation, and a linear interpolation between randomisation and 6 months. An alternative published algorithm for mapping PedsQL to the CHU-9D index score was considered in a sensitivity analysis. For decedents between randomisation and 6 months, a zero QALY was assumed for the 6-month period.

Incremental net monetary benefit at 6 months

The INB of HFNC compared to CPAP at 6 months was calculated by multiplying the mean gain or loss in QALYs by a recommended cost-effectiveness threshold in the UK (£20,000 per QALY gained) and subtracting the difference in costs.[46]

Statistical analysis of cost-effectiveness analysis at 6 months

Cost-effectiveness analyses for both step-up and step-down RCTs followed the mITT principle, and reported incremental costs, QALYs and cost-effectiveness up to 6 months, according to randomised group. Missing data in baseline covariates, resource use and outcomes (see *Appendix 2* and *Appendix 3*) were handled with multivariate imputation via chained equations (MICE).[54] Under this approach, each variable was imputed conditional on fully observed baseline variables, resource use, outcomes and all other imputed variables. Patients who did not return or fully completed the PedsQL questionnaire administered at 6 months had their HRQoL scores imputed from those survivors who did fully complete the questionnaire. Similarly, for those eligible patients who did not return the HSQ, information on the use of outpatient services up to 6 months post randomisation was imputed from those patients who completed and returned the HSQ.

Analysis of uncertainty and sensitivity in cost-effectiveness at 6 months

We estimated the incremental costs and QALYs from the imputed data sets with a single-level bivariate seemingly unrelated regression model to allow for correlation between costs and QALYs. The incremental results from multiply imputed data sets were summarised using Rubin's rule.[55] The economic analysis was adjusted for same baseline covariates as for the clinical analysis to adjust for baseline imbalances between the randomised arms (see *Clinical effectiveness analysis* section for further details). To express the uncertainty in the estimation of the incremental costs and QALYs, we used the estimates of the means, and variances from the single-level regression model, to generate 800 estimates of incremental costs and QALYs from the joint distribution of these end points, assuming asymptotic normality. The uncertainty around the differences in average costs and QALYs at 6 months between the treatment groups was illustrated on the cost-effectiveness plane.[56]

Subgroup analyses

We undertook prespecified subgroup analysis as per analysis of clinical effectiveness, for both step-up and step-down RCTs and reported INBs for each subgroup.

Sensitivity analyses

The main assumptions made in the base-case analysis and how they were relaxed in sensitivity analyses are described below (see also *Table 3*).

- *Analysis principle*: The base-case analysis followed the mITT population as per the primary clinical analysis. The sensitivity analysis was performed according to the ITT principle.

TABLE 3 Alternative assumptions for cost-effectiveness sensitivity analyses for both step-up and step-down RCTs

	Base case	Sensitivity analysis
Analysis sample	mITT	ITT
Intervention costs	Location based	Intervention based
Follow-up costs	HSQ	HES database
Unit costs of resources	NHS benchmark prices and PSSRU costs in 2021/22	± 10% increase/decrease in all unit costs
CHU-9D mapping	Mapping algorithm from UK population applied	Mapping algorithm from Australian population applied
Analysis model and missing data	Full cohort using missing imputation methods	Complete cases only
Distributional assumptions	Costs and QALYs normally distributed	Costs and QALYs gamma distributed
Modelling assumption	Single-level bivariate regression model	Multilevel bivariate regression model to allow for clustering of patients at sites

- *Intervention costs irrespective of location*: The base-case analysis considered intervention costs of HFNC or CPAP to be the same across locations (PICU or HDU) and equivalent to the cost of intermediate paediatric critical care (XB06Z HRG code). In the sensitivity analysis, we examined whether the cost-effectiveness results are sensitive to intervention base costs irrespective of location, by assuming the cost of HFNC is equivalent to basic critical care (XB07Z HRG code) and CPAP is equivalent to intermediate critical care (XB06Z HRG code).
- *Follow-up costs from HES database:* The base-case analysis included follow-up costs calculated from responses to the HSQ. In the sensitivity analysis, follow-up costs derived from resource use information from HES databases were used.
- *Unit costs of resources*: The unit costs of resources in the base-case analysis were taken from NHS benchmark prices and Personal Social Services Research Unit (PSSRU) costs in 2020–1. In the sensitivity analysis, unit costs were increased/decreased by 10% to allow for possible changes in unit costs in recent years.
- *CHU-9D mapping*: The HRQoL in the base-case analysis was derived using a mapping algorithm of PedsQL responses to the CHU-9D utility score derived in the UK context.[51] In the sensitivity analysis, we consider an alternative mapping algorithm derived using responses to both questionnaires from a paediatric population from Australia.[57]
- *Distributional assumptions for costs and QALYs:* The base-case analysis assumed that costs and QALYs were normally distributed when reporting the 95% CIs around incremental costs, QALYs and INB. In a sensitivity analysis, we assessed the robustness of CEA results to alternative distributional assumptions about both outcomes. Following methodological guidance,[58,59] the sensitivity analysis considered a gamma distribution for costs given the observed right-skewed distribution.[60] The sensitivity analysis also considered a gamma distribution for QALYs given the large proportion of decedents with zero QALYs and the observed right-skewed distribution of QALYs for patients who were alive at 6 months.
- *Modelling assumption:* The base-case analysis model followed single-level bivariate regression model to allow for correlation between costs and QALY. The sensitivity analysis followed a multilevel bivariate regression model to allow for clustering of patients at sites.
- *Analysis model and missing data:* The base-case analysis was based on full eligible trial participants in which missing data were imputed using MI methods. In the sensitivity analysis, complete case analysis was performed excluding patients whose costs/outcome data were missing.

The results of the sensitivity analyses were reported as mean INBs with corresponding 95% CIs.

Handling of missing data

As the primary end point 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 NRS. 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 conditional on the observed data. Multiple imputation will be undertaken using the MICE 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 data set and results combined using Rubin's rules.[55]

Statistical software

All analyses were conducted in Stata/SE Version 14.2 64-bit x86-64 (StataCorp LP, College Station, TX, USA). Some additional CEAs were carried out in R (The R Foundation for Statistical Computing, Vienna, Austria) as required.

Chapter 3 Results: step-up randomised controlled trial

Sites and patients

Site selection and set-up

Expressions of interest and completed site feasibility questionnaires were received from 26 potential sites across England, Wales and Scotland. All sites were invited to take part in the trial, of which two were ultimately not able to progress with set-up (one due to research capacity issues and one due to equipoise issues).

In total, 24 sites, covering 25 critical care units, recruited patients into the FIRST-ABC step-up RCT. The first sites opened in August 2019, on schedule, and the final site opened in July 2021. By the end of the internal pilot, 22 sites were open to recruitment. The characteristics of the sites are shown in *Table 4*.

In relation to research governance, the median time from provision of the final local information pack to the issuing of local confirmation of capacity and capability was 46 (IQR 29.5–99.5) days. The median time from local confirmation of capacity and capability to the start of patient screening at sites was 13 (IQR 4–26) days. The median time from the start of patient screening to the first patient recruited at sites was 11 (IQR 2–42) days. In total, the process from provision of the final local information pack to first patient recruited took a median of 113 (IQR 64–142) days.

Of the 22 sites that were open prior to the COVID-19 outbreak, 18 formally paused recruitment at least once due to the impact of COVID-19 on clinical and research activity. The majority of these sites paused in March 2020 due to the COVID-19 first wave, and most had reopened to recruitment by September 2020. Two additional sites were

TABLE 4 Characteristics of participating UK NHS critical care units

Characteristic	Critical care units (*n* = 24)
Country/region	
England	
London	7 (29.2)
North East and Yorkshire	4 (16.7)
North West	3 (12.5)
Midlands	2 (8.3)
South East	3 (12.5)
South West	1 (4.2)
East of England	2 (8.3)
Wales	1 (4.2)
Scotland	1 (4.2)
Northern Ireland	0 (0.0)
Type of unit	
Combined PICU/HDU	19 (79.2)
HDU	5 (20.8)

Note
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opened after the initial COVID-19 period in order to mitigate some resultant impact on the trial timeline. Overall, two sites formally closed ahead of the completion of recruitment – with all other sites remaining open until the end of the recruitment period. In total, each site participated in the step-up RCT for a median (IQR) of 19.4 (17.1–22.3) months.

Patient screening, randomisation and consent

Between August 2019 and November 2021, 18,976 patients were admitted to participating PICU/HDUs and screened for inclusion in the step-up RCT, from which 3825 were deemed to meet inclusion criteria (*Figure 3*). Of those not meeting inclusion criteria (*n* = 15,151), most did not require NRS for an acute illness (*n* = 15,026, 99.2%).

Of patients meeting inclusion criteria, 2376 additionally met exclusion criteria and were not eligible for the trial. The most common reasons for exclusion were prior receipt of HFNC or CPAP for > 2 hours in the prior 24 hours (*n* = 1085, 45.7%); receipt of home non-invasive ventilation prior to admission (*n* = 509, 21.4%); and a clinical decision to commence a form of NRS other than HFNC or CPAP (*n* = 393, 16.5%).

Of the remaining 1449 eligible patients, 600 (41.4%) were randomised into the trial and 849 (58.6%) were not. The most common reasons for eligible patients not being enrolled in the trial were that patients were either missed or identified too late for recruitment (*n* = 438, 51.6%) or a clinical decision was made not to enrol the patient (*n* = 325, 38.3%). The full sample was recruited 2 months ahead of the schedule (*Figure 4*). The overall site recruitment rate was 1.7 patients per month with a median recruitment rate of 1.1 (IQR 0.3–1.8) patients across sites.

Among the 600 enrolled, 301 were randomised to the HFNC group and 299 to the CPAP group. After accounting for complete withdrawals, 300 in the HFNC group and 295 in the CPAP group formed the ITT population. In the HFNC group, 295 started respiratory support following randomisation compared with 278 in the CPAP group, forming the primary analysis set. Of those randomised to HFNC, 290 started HFNC, while 246 in the CPAP group started CPAP as randomised, forming the per-protocol population (see *Appendix 4*).

In the primary analysis set, the primary outcome was observed in 264 in the HFNC group and in 281 in the CPAP group, with 14 censored in each group. In the per-protocol population, the primary outcome was observed in 275 in the HFNC group and in 236 in the CPAP group.

Baseline characteristics

The randomised groups had similar characteristics at baseline (*Table 5*). In the primary analysis set, the median (IQR) age in months was 10 (2–31) and 9 (1–27) in the HFNC and CPAP groups, respectively. Just under 40% were female in both groups and around half had at least one comorbidity (HFNC: 48.5%, CPAP: 46.2%).

Overall, the main reasons for admission to critical care were either bronchiolitis (HFNC: 48.5%, CPAP: 49.8%) or another respiratory condition (HFNC: 18.6%, CPAP: 20.6%). At the time of randomisation, most patients were in moderate respiratory distress (HFNC: 57.4%, CPAP: 59.9%), with similar oxygen requirements [median (IQR) fraction of inspired oxygen, HFNC: 0.30 (0.21–0.48), CPAP: 0.30 (0.21–0.44)].

Baseline characteristics were similar in the per-protocol population and are shown in *Table 6*. The baseline characteristics of the full ITT population (i.e. including the small number of patients who did not start any respiratory support following randomisation) are shown in *Appendix 5*.

Clinical management

In both groups, the randomised treatment was started in the majority of children who started respiratory support [HFNC: 290/295 (98.3%), CPAP: 246/278 (88.5%)] - see Figure 7. A variety of devices and interfaces were used to delivery HFNC and CPAP (see *Appendix 6*).

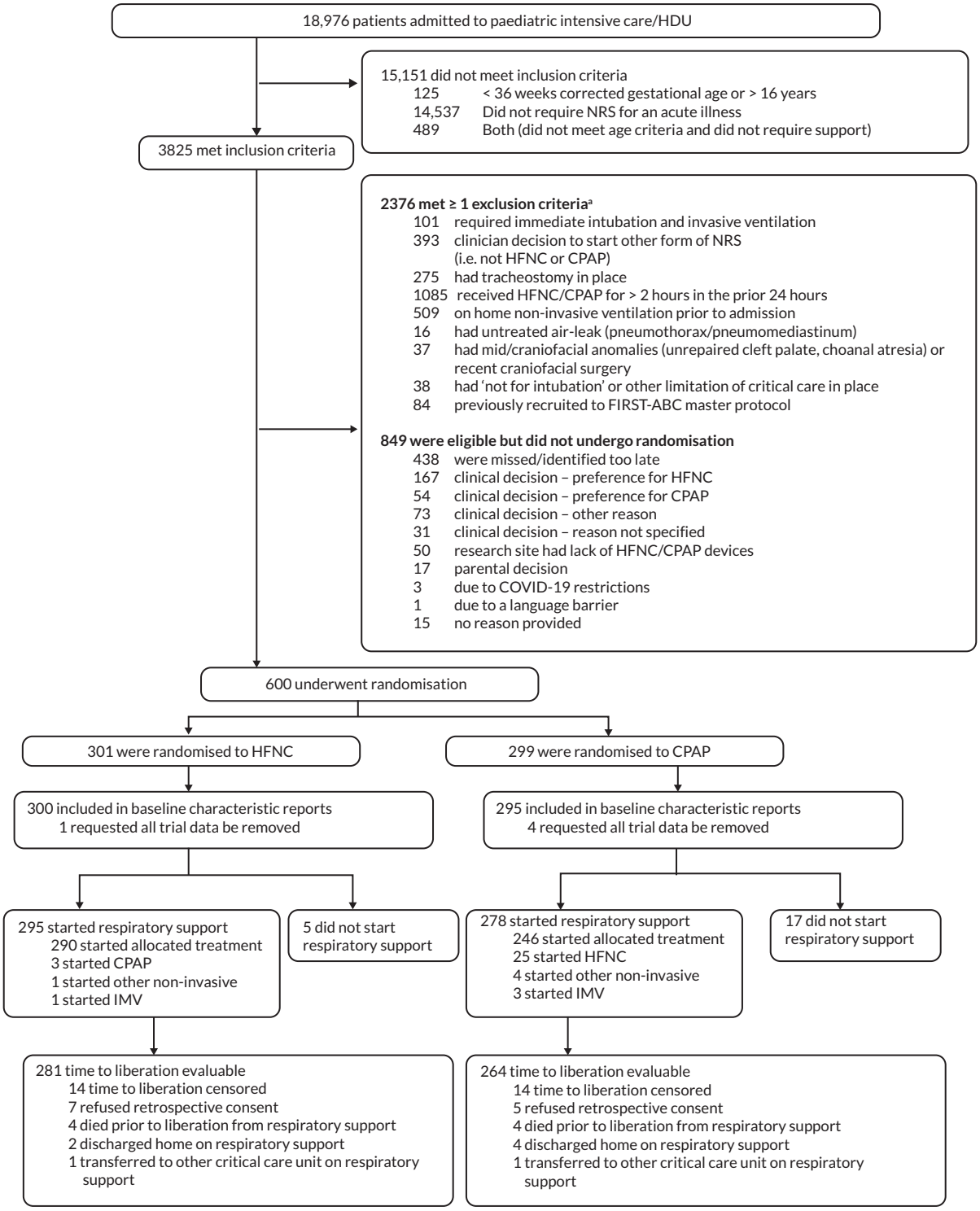

FIGURE 3 Consolidated Standards of Reporting Trials flow of screening, randomisation and follow-up through the step-up RCT. Reproduced with permission from Ramnarayan *et al.*[31] Copyright © 2022 JAMA. All rights reserved.

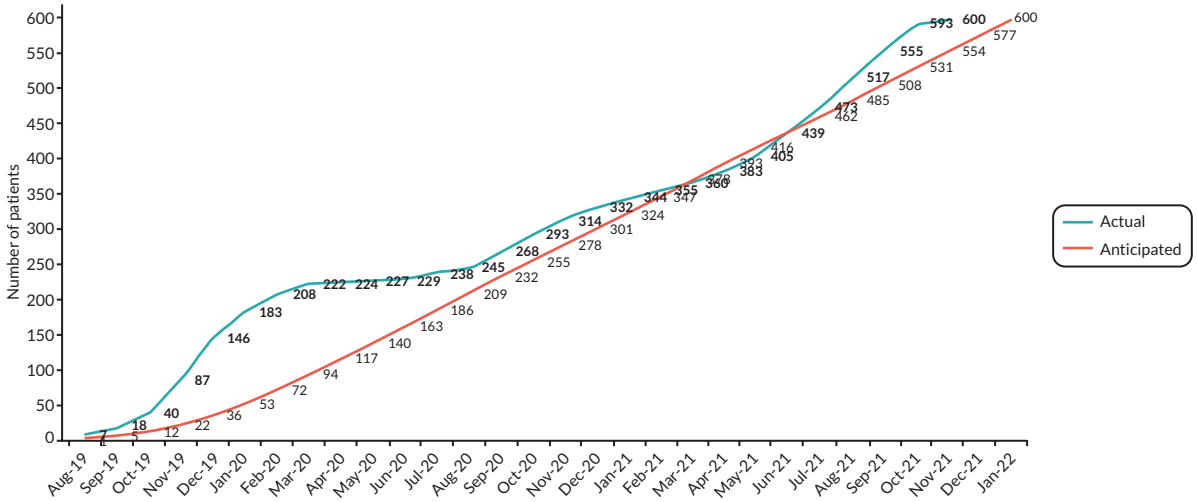

FIGURE 4 Step-up RCT – actual vs. anticipated patient randomisation. Comparison of actual vs. anticipated cumulative randomisation of patients into the FIRST-ABC step-up RCT. During the first wave of the COVID-19 epidemic in the UK, 17 (of 24) sites suspended recruitment for an average of 4.8 months. During the second wave, five sites suspended recruitment for an average of 2.6 months. Reproduced with permission from Ramnarayan *et al.*[31] Copyright © 2022 JAMA. All rights reserved.

TABLE 5 Step-up RCT – baseline characteristics in the primary analysis set

Characteristic	HFNC (*N* = 295)	CPAP (*N* = 278)
Age, median (IQR), months	10 (2–31)	9 (1–27)
Age, no. (%)		
≤ 28 days	31 (10.5)	37 (13.3)
29–180 days	87 (29.5)	80 (28.8)
181–364 days	49 (16.6)	43 (15.5)
1 year	41 (13.9)	44 (15.8)
2–4 years	40 (13.5)	27 (9.7)
5–10 years	29 (9.8)	26 (9.4)
11–15 years	18 (6.1)	21 (7.6)
Sex, no. (%)		
Female	116 (39.3)	110 (39.6)
Male	179 (60.7)	168 (60.4)
Ethnicity, no. (%)	*n = 221*	*n = 205*
Asian	28 (12.7)	33 (16.1)
Black	20 (9.0)	13 (6.3)
Mixed	13 (5.9)	11 (5.4)
White	148 (67.0)	139 (67.8)
Other	12 (5.4)	9 (4.4)
Geographical location of patient residence, no. (%)	*n = 260*	*n = 246*
Urban	235 (90.4)	222 (90.2)
Rural	25 (9.6)	24 (9.8)

TABLE 5 Step-up RCT – baseline characteristics in the primary analysis set (*continued*)

Characteristic	HFNC (*N* = 295)	CPAP (*N* = 278)
Comorbidities, no. (%)		
None	152 (51.5)	149 (53.8)
At least one	143 (48.5)	128 (46.2)
Missing	0 (0.0)	1 (0.4)
Airway/respiratory	59 (20.0)	48 (17.3)
Cardiac/vascular	40 (13.6)	33 (11.9)
Neurological/neuromuscular	46 (15.6)	39 (14.0)
Congenital/genetic/syndrome	33 (11.2)	39 (14.0)
Gastro/surgical	24 (8.1)	30 (10.8)
Haematology/oncology	20 (6.8)	21 (7.6)
Metabolic/endocrine	9 (3.1)	14 (5.0)
Immunodeficiency	10 (3.4)	9 (3.2)
Prematurity	8 (2.7)	7 (2.5)
Other	17 (5.8)	11 (4.0)
Type of admission, no. (%)	*n = 245*	*n = 234*
Planned, following surgery	8 (3.3)	6 (2.6)
Unplanned, following surgery	6 (2.4)	3 (1.3)
Planned, not following surgery	5 (2.0)	13 (5.6)
Unplanned, not following surgery	226 (92.2)	212 (90.6)
Source of admission, no. (%)	*n = 245*	*n = 233*
Same hospital	215 (87.8)	210 (90.1)
Other hospital	11 (4.5)	9 (3.9)
Home	19 (7.8)	14 (6.0)
Missing	50 (16.9)	45 (19.3)
Main reason for admission, no. (%)	*n = 295*	*n = 277*
Bronchiolitis	143 (48.5)	138 (49.8)
Other respiratory condition	55 (18.6)	57 (20.6)
Asthma/wheeze	31 (10.5)	20 (7.2)
Sepsis/infection	24 (8.1)	23 (8.3)
Cardiac	17 (5.8)	12 (4.3)
Upper airway problem	15 (5.1)	12 (4.3)
Neurological	4 (1.4)	2 (0.7)
Other	6 (2.0)	13 (4.7)
On NRS at randomisation, no. (%)		
No	229 (77.6)	213 (76.6)
Yes	66 (22.4)	65 (23.4)

continued

TABLE 5 Step-up RCT – baseline characteristics in the primary analysis set (*continued*)

Characteristic	HFNC (*N* = 295)	CPAP (*N* = 278)
Clinical characteristics at randomisation[a]		
Respiratory distress, no./N (%)[b]	*n = 244*	*n = 227*
None	14 (5.7)	12 (5.3)
Mild	47 (19.3)	39 (17.2)
Moderate	140 (57.4)	136 (59.9)
Severe	43 (17.6)	40 (17.6)
Respiratory rate, median (IQR), (*N*), breaths per minute	48 (38–60), (*N* = 286)	49 (39–60), (*N* = 272)
SpO_2 (%), median (IQR), (*N*)	97 (94–99), (*N* = 285)	97 (94–99), (*N* = 275)
FiO_2, median (IQR), (*N*)	0.30 (0.21–0.48), (*N* = 288)	0.30 (0.21–0.44), (*N* = 271)
SpO_2/FiO_2 ratio, median (IQR), (*N*)	313 (198–424), (*N* = 287)	330 (218–438) (*N* = 271)
Heart rate, median (IQR), (*N*), beats per minute	155 (140–171), (*N* = 291)	154 (140–173) (*N* = 272)
COMFORT-B score[c]	*n = 79*	*n = 60*
Mean (SD) (*N*)	16.2 (4.7)	15.3 (5.5)
Median (IQR) (*N*)	16.0 (12.0–20.0)	14.0 (11.0–18.5)
< 10	5 (6.3)	6 (10.0)
10–12	17 (21.5)	18 (30.0)
13–17	25 (31.6)	17 (28.3)
> 17	32 (40.5)	19 (31.7)

a Data were recorded at or within 1 hour prior to randomisation, except for COMFORT Behavior Scale score, which was the last recorded value prior to randomisation.
b Respiratory distress was defined as mild (one accessory muscle used, mild indrawing of subcostal and intercostal muscles, mild tachypnoea, no grunting); moderate (two accessory muscles used, moderate indrawing of subcostal and intercostal muscles, moderate tachypnoea, occasional grunting); or severe (use of all accessory muscles, severe indrawing of subcostal and intercostal muscles, severe tachypnoea, regular grunting). Data on severity of respiratory distress were missing for 102 children, 60% of whom were from 3 of the 24 sites.
c COMFORT Behavior Scale scores range from 5 (most sedated) to 30 (least sedated). A mean value of 15 indicates a comfortable patient who is easily rousable and is not agitated. Data on COMFORT Behavior Scale scores were missing for 434 children, mainly because some sites did not collect COMFORT Behavior Scale scores when children were randomised prior to critical care unit admission.

Note

TABLE 6 Step-up RCT – baseline characteristics in the per-protocol population

Characteristic	HFNC (*N* = 288)	CPAP (*N* = 245)
Age, months		
Median (IQR)	10 (2–32)	8 (1–25)
Age (categories), no. (%)		
≤ 28 days	29 (10.1)	32 (13.1)
29–180 days	83 (28.8)	72 (29.4)
181–364 days	49 (17.0)	40 (16.3)
1 year	40 (13.9)	38 (15.5)

TABLE 6 Step-up RCT – baseline characteristics in the per-protocol population (*continued*)

Characteristic	HFNC (*N* = 288)	CPAP (*N* = 245)
2 years	24 (8.3)	14 (5.7)
3 years	13 (4.5)	7 (2.9)
4 years	3 (1.0)	2 (0.8)
5–10 years	29 (10.1)	24 (9.8)
11–15 years	18 (6.3)	16 (6.5)
Sex, no. (%)		
Female	113 (39.2)	98 (40.0)
Male	175 (60.8)	147 (60.0)
Ethnicity, no. (%)	*n = 214*	*n = 182*
Asian	28 (13.1)	26 (14.3)
Black	19 (8.9)	11 (6.0)
Mixed	13 (6.1)	10 (5.5)
White	142 (66.4)	126 (69.2)
Other	12 (5.6)	9 (4.9)
Geographical location of patient residence, no. (%)	*n = 253*	*n = 215*
Urban	228 (90.1)	193 (89.8)
Rural	25 (9.9)	22 (10.2)
Comorbidities, no. (%)		
None	148 (51.4)	132 (54.1)
At least one	140 (48.6)	112 (45.9)
Missing	0 (0.0)	1 (0.4)
Airway/respiratory	58 (20.1)	40 (16.3)
Cardiac/vascular	38 (13.2)	30 (12.2)
Neurological/neuromuscular	45 (15.6)	35 (14.3)
Congenital/genetic/syndrome	32 (11.1)	35 (14.3)
Gastro/surgical	22 (7.6)	26 (10.6)
Haematology/oncology	20 (6.9)	17 (6.9)
Metabolic/endocrine	8 (2.8)	13 (5.3)
Immunodeficiency	10 (3.5)	7 (2.9)
Prematurity	7 (2.4)	4 (1.6)
Other	17 (5.9)	10 (4.1)
Type of admission, no. (%)	*n = 240*	*n = 210*
Planned, following surgery	8 (3.3)	4 (1.9)
Unplanned, following surgery	5 (2.1)	3 (1.4)
Planned, not following surgery	5 (2.1)	12 (5.7)

continued

TABLE 6 Step-up RCT – Baseline characteristics in the per-protocol population (*continued*)

Characteristic	HFNC (*N* = 288)	CPAP (*N* = 245)
Unplanned, not following surgery	222 (92.5)	191 (91.0)
Source of admission, no. (%)	*n = 240*	*n = 210*
Same hospital	210 (87.5)	190 (90.5)
Other hospital	11 (4.6)	8 (3.8)
Home	19 (7.9)	12 (5.7)
Clinical characteristics at randomisation[a]		
Respiratory distress,[b] *no. (%)*	*n = 238*	*n = 202*
None	13 (5.5)	9 (4.5)
Mild	46 (19.3)	37 (18.3)
Moderate	138 (58.0)	119 (58.9)
Severe	41 (17.2)	37 (18.3)
Respiratory rate, median (IQR), (*N*), breaths per minute	48 (38–60), (*N* = 280)	50 (40–60), (*N* = 240)
SpO_2 (%), median (IQR), (*N*)	97 (94–99), (*N* = 283)	97 (94–99), (*N* = 243)
FiO_2, median (IQR), (*N*)	0.30 (0.21–0.48), (*N* = 281)	0.30 (0.21–0.44), (*N* = 241)
SpO2/FiO2 ratio	*n = 280*	*n = 241*
Median (IQR)	308 (198–424)	333 (218–443)
> 350	114 (40.7)	109 (45.2)
301–350	28 (10.0)	22 (9.1)
266–300	16 (5.7)	8 (3.3)
220–265	38 (13.6)	34 (14.1)
< 220	84 (30.0)	68 (28.2)
Heart rate, median (IQR), (*N*), beats per minute	155 (140–171), (*N* = 284)	154 (140–172), (*N* = 240)
COMFORT-B score[c]	*n = 79*	*n = 59*
Median (IQR)	16.0 (12.0–20.0)	14.0 (11.0–18.5)
< 10	5 (6.3)	5 (8.9)
10–12	17 (21.5)	17 (30.4)
13–17	25 (31.6)	17 (30.4)
> 17	32 (40.5)	17 (30.4)

a Data were recorded at or within 1 hour prior to randomisation, except for COMFORT Behavior Scale score, which was the last recorded value prior to randomisation.
b Respiratory distress was defined as Mild: one accessory muscle used, mild indrawing of subcostal and intercostal muscles, mild tachypnoea, no grunting. Moderate: two accessory muscles used, moderate indrawing of subcostal and intercostal muscles, moderate tachypnoea, occasional grunting. Severe: use of all accessory muscles, severe indrawing of subcostal and intercostal muscles, severe tachypnoea, regular grunting.
c COMFORT Behavior Scale scores range from 5 to 30 (most sedated to least sedated).

Note

Initiation of HFNC was quicker than was the initiation of CPAP (median 25.0 vs. 55.5 minutes) (*Table 7*). Adherence to the trial algorithms was good, with most patients receiving HFNC at the prescribed gas flow rates (*Figure 5*) and CPAP at the specified pressure level (*Figure 6*).

More patients (109/246, 44.3%) in the CPAP group switched to HFNC than patients in the HFNC group switched to CPAP (74/290, 25.5%) (Figure 10 and *Table 7*). Patients in the CPAP group primarily switched for patient discomfort reasons, whereas patients in the HFNC group primarily switched due to severe respiratory distress (see *Appendix 7*).

TABLE 7 Step-up RCT – adherence with trial algorithms in children who started the allocated treatment

Characteristic	HFNC (*N* = 290)	CPAP (*N* = 246)
Starting NRS		
Time from randomisation to starting support, median (IQR), minutes	25.0 (1.0–58.0)	55.5 (30.0–85.0)
Started on ≥ 75% of the trial-recommended gas flow rate, no./total (%)	272 (93.8)	NA
Started on pressure of ≥ 7 cm H_2O, no./total (%)	NA	170 (69.1)
Switch events		
All recorded switch events, total	74	109
Switch recorded as the first event, no./total (%)	58	76
Evidence of switch as per protocol, no./total (%)	51 (68.9)	82 (75.2)
No evidence of switch as per protocol, no./total (%)	23 (31.1)	27 (24.8)
Clinical deterioration, criteria not documented	16 (21.6)	2 (1.8)
Switch for weaning purposes, not for treatment failure	7 (9.5)	7 (6.4)
Switch to HFNC to allow discharge	0 (0.0)	3 (2.8)
Interface issues	0 (0.0)	6 (5.5)
Non-adherent	0 (0.0)	9 (8.3)
Reasons for switch, no. (% of switch events)[a]		
Severe respiratory distress	38 (51.4)	14 (12.8)
FiO_2 ≥ 0.60	11 (14.9)	5 (4.6)
Patient discomfort	15 (20.3)	72 (66.1)
Other reason	25 (33.8)	27 (24.8)
Escalation events		
All recorded escalation events, total	121	114
Escalation recorded as the first event, no./total (%)	17	37
Evidence of escalation as per protocol, no./total (%)	84 (69.4)	77 (67.5)
No evidence of escalation as per protocol, no./total (%)	37 (30.6)	37 (32.5)
Clinical deterioration, criteria not met	32 (26.4)	35 (30.7)
Non-adherent	5 (4.1)	2 (1.8)

continued

TABLE 7 Step-up RCT – adherence with trial algorithms in children who started the allocated treatment (*continued*)

Characteristic	HFNC (*N* = 290)	CPAP (*N* = 246)
Reasons for escalation, no. (% of escalation events)[a]		
Severe respiratory distress	62 (51.2)	53 (46.5)
FiO_2 ≥ 0.60	24 (19.8)	19 (16.7)
Patient discomfort	9 (7.4)	8 (7.0)
Other reason	47 (38.8)	43 (37.7)
Weaning events		
All recorded weaning events, total	248	175
Evidence of weaning as per protocol, no./total (%)	231 (93.1)	170 (97.1)
No evidence of escalation as per protocol, no./total (%)	17 (6.9)	5 (2.9)
Non-adherent	17 (6.9)	5 (2.9)

a More than one reason could be selected.

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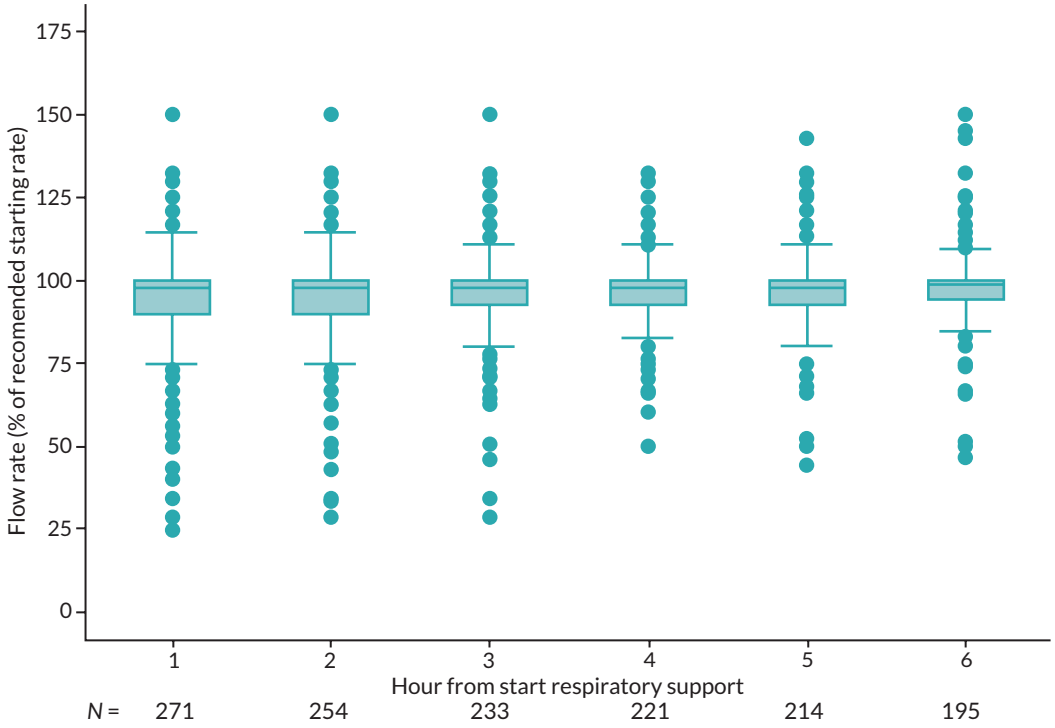

FIGURE 5 Step-up RCT – HFNC flow rates during the first 6 hours of treatment. Reproduced with permission from Ramnarayan *et al.*[31] Copyright © 2022 JAMA. All rights reserved.

Clinical effectiveness

Primary outcome

The median time from randomisation to liberation from respiratory support was 52.9 hours (95% CI 46.0 to 60.9 hours) in the HFNC group and 47.9 hours (95% CI 40.5 to 55.7 hours) in the CPAP group [absolute difference 5.0 hours (95% CI −10.1 to 17.4 hours); adjusted HR 1.03, one-sided 97.5% CI 0.86 to ∞] (*Figure 8*). The bound of the one-sided 97.5%

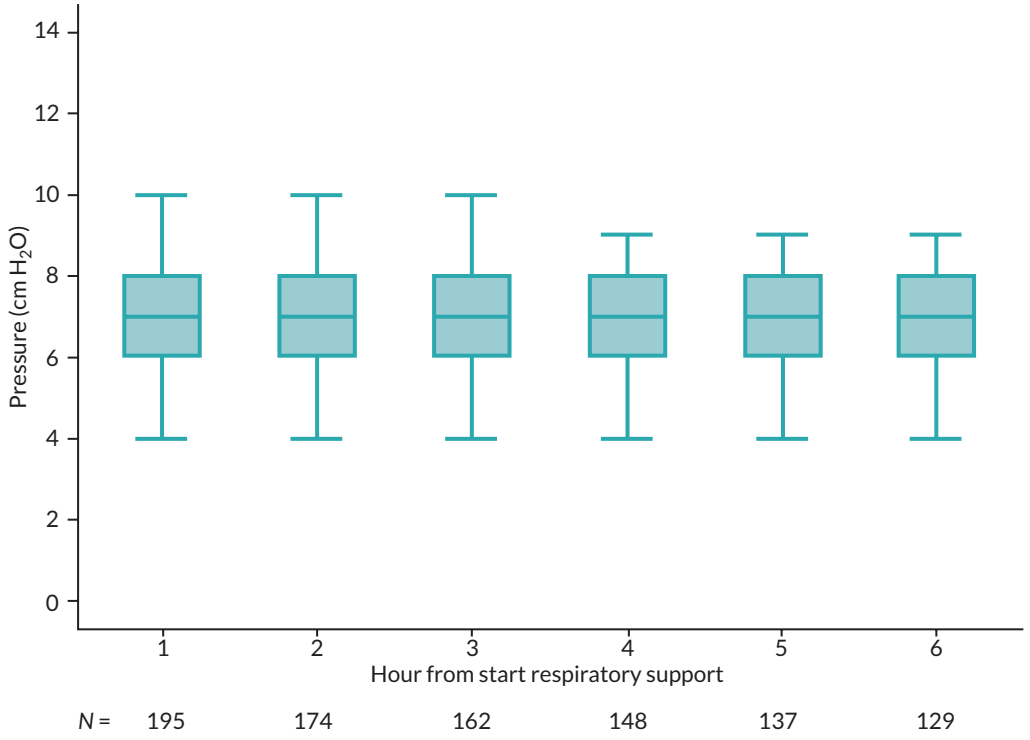

FIGURE 6 Step-up RCT – CPAP pressures during the first 6 hours of treatment. Reproduced with permission from Ramnarayan *et al.*[31] Copyright © 2022 JAMA. All rights reserved.

CI fell within the prespecified non-inferiority margin. Results were similar in the per-protocol analysis (adjusted HR, HR 1.03, 95% CI 0.86 to 1.23) (*Table 8*; *Figure 9*). Proportional hazards assumptions were checked by examining plots of −ln[−ln(survival)] over time and scaled Schoenfeld residuals from each Cox proportional hazards model. No evidence of departures from proportional hazards was observed.

The time to liberation according to whether treatment failure occurred is shown in *Appendix 8*. Patients experiencing treatment failure had a much longer median (IQR) time to liberation than did patients without treatment failure – more so for the HFNC group compared to the CPAP group [79.8 (48.0–146.8) vs. 56.0 (26.1–134.0)].

Subgroup analyses

In prespecified subgroup analyses, there was a significant difference in treatment effect between patients who were receiving respiratory support at randomisation, in whom CPAP was more effective, and those who were not, in whom CPAP was less effective (*Figure 11*). There was no significant heterogeneity across other patient subgroups.

Secondary outcomes

There was no significant difference in the rate of intubation by 48 hours, with 15.4% intubated in the HFNC group and 15.9% in the CPAP group (adjusted OR 0.99, 95% CI 0.61 to 1.62), but there was a significant difference in the use of sedation while receiving HFNC or CPAP – with less sedation use in the HFNC group (27.7% vs. 37.0%), equating to an adjusted OR of 0.59 (95% CI 0.39 to 0.88). The durations of critical care unit and acute hospital stay were shorter in the HFNC group compared with the CPAP group [mean (SD) acute hospital stay: 13.8 (26.8) for HFNC and 19.5 (47.7) for CPAP]. COMFORT-B scores were similar between the groups, as was the level of parental stress at/around the time of consent.

Adverse events

The number of participants with one or more AEs was low in both groups, occurring in 17 out of 295 (5.8%) in the HFNC group and in 30 out of 278 (10.8%) in the CPAP group (*Table 9*). A total of four SAEs were reported – all were cardiac arrests, one in the HFNC group and three in the CPAP group.

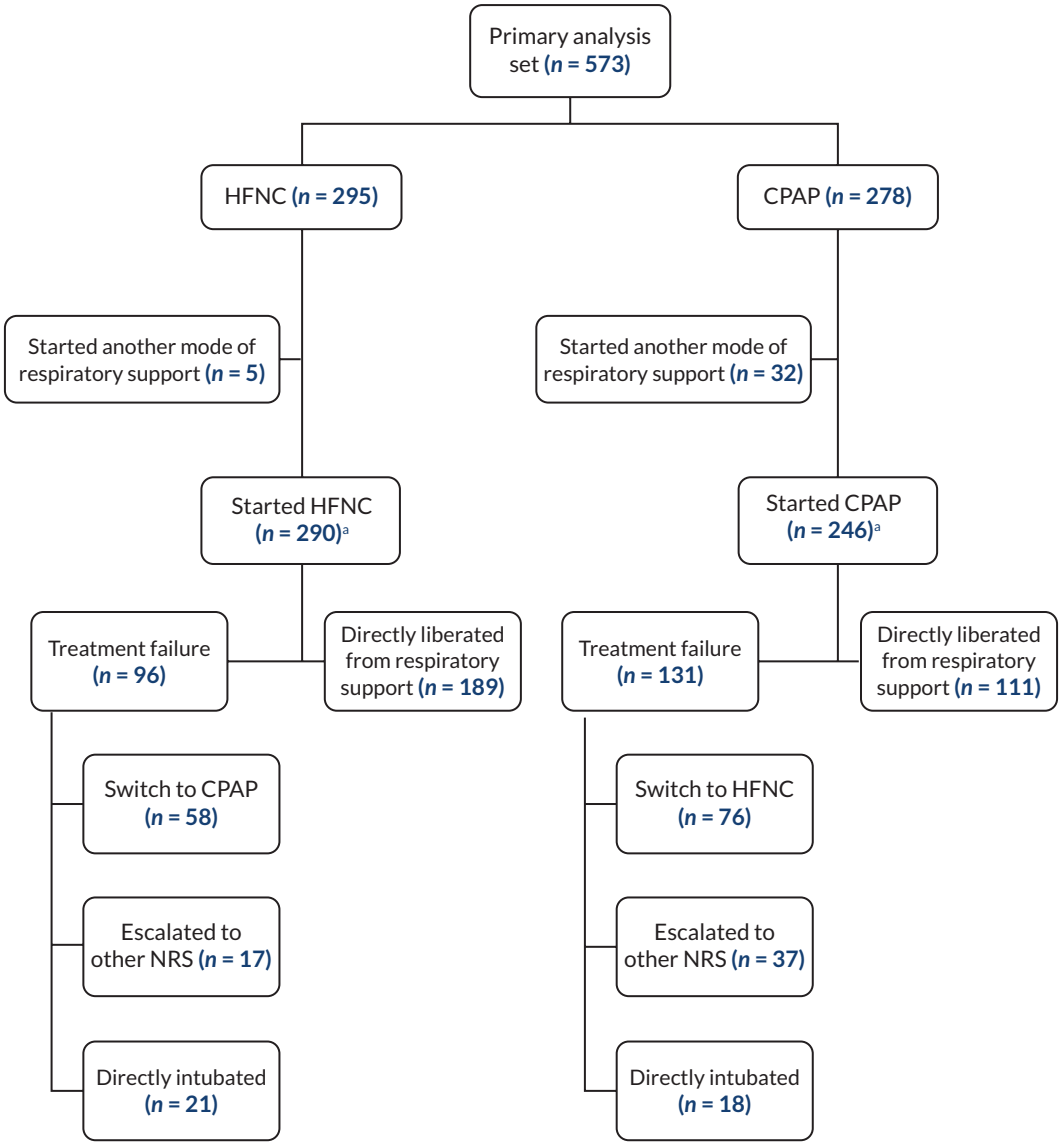

FIGURE 7 Step-up RCT – clinical management of trial patients. a, Time to liberation was censored in five patients started on HFNC and four patients started on CPAP. Reproduced with permission from Ramnarayan *et al.*[31] Copyright © 2022 JAMA. All rights reserved.

Sensitivity analyses

Planned and post hoc sensitivity analyses did not alter interpretation of the primary outcome (see *Appendix 9*). When repeating the primary analysis in the full ITT population (assigning a nominal 2 hours of respiratory support to patients who did not start any respiratory support following randomisation), the adjusted HR was 0.98 (95% CI 0.83 to 1.16) (*Figure 12*).

Cost-effectiveness analysis

Resource use and costs up to 6 months

Resource use up to 6 months post randomisation is reported in *Table 10*. Patients in the HFNC group had, on average, shorter stays in paediatric critical care units (5.08 vs. 7.05 days) and in the general medical ward (9.04 vs. 9.74 days) during the index hospital admission compared to patients in the CPAP group. A larger number of patients in the HFNC group were re-admitted into hospital during the 6 months following ultimate discharge from the index hospital admission compared to the CPAP group (7.80 vs. 6.75% of patients had at least one admission to critical care, 38% vs. 36% had at least one admission to the general ward). The average duration of critical care unit stays during

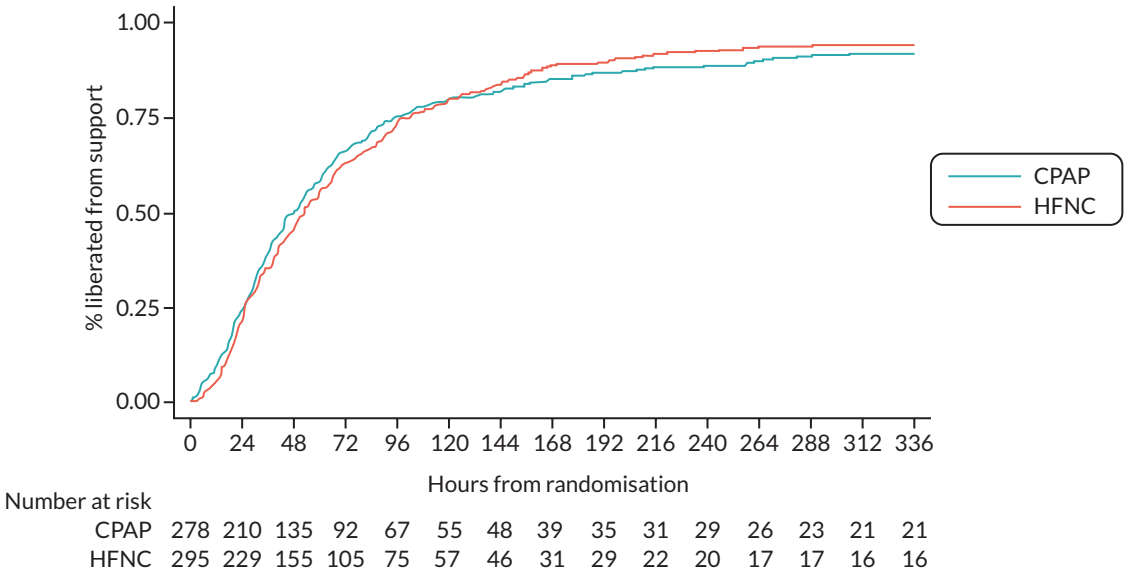

FIGURE 8 Step-up RCT – time to liberation from respiratory support in the primary analysis set. Reproduced with permission from Ramnarayan *et al.*[31] Copyright © 2022 JAMA. All rights reserved.

TABLE 8 Step-up RCT – primary and secondary outcomes

	Primary analysis set					Per-protocol analysis				
				Effect estimate					Effect estimate	
Outcome	HFNC (*N* = 295)	CPAP (*N* = 278)	Difference (95% CI)	Unadjusted (95% CI)	Adjusted (95% CI)	HFNC (*N* = 288)	CPAP (*N* = 245)	Difference (95% CI)	Unadjusted[a] (95% CI)	Adjusted[b] (95% CI)
Primary										
Time from randomisation to liberation from respiratory support, median (IQR), hours	52.9 (46.0–60.9)	47.9 (40.5–55.7)		HR 1.03 (0.87 to 1.22)	HR 1.03 (0.86 to 1.22)	52.7 (45.0–60.1)	45.4 (40.2–53.7)		HR 1.05 (0.88 to 1.25)	HR 1.03 (0.86 to 1.23)
Secondary										
Mortality at critical care discharge, no./total no. (%)	5/292 (1.7)	4/274 (1.5)	AD 0.3 (−1.8 to 2.3)	OR 1.18 (0.31 to 4.43)	OR 1.22 (0.32 to 4.62)	5/285 (1.8)	3/243 (1.2)	AD 0.5 (−1.5 to 2.6)	OR 1.43 (0.34 to 6.04)	OR 1.46 (0.35 to 6.22)
Intubation at 48 hours, no./total no. (%)	45/292 (15.4)	44/276 (15.9)	AD −0.5 (−6.5 to 5.5)	OR 0.96 (0.61 to 1.51)	OR 0.99 (0.61 to 1.62)	43/285 (15.1)	36/243 (14.8)	AD 0.3 (−5.8 to 6.4)	OR 1.02 (0.63 to 1.65)	OR 1.07 (0.64 to 1.81)
Duration of critical care unit stay, mean (SD), (*N*), days	5.0 (8.2), (*n* = 288)	7.4 (18.9), (*n* = 270)	MD −2.4 (−4.8 to 0.0)	–	MD −3.0 (−5.1 to −1.0)	4.7 (7.3), (*n* = 281)	7.7 (19.9), (*n* = 242)	MD −3.0 (−5.7 to −0.3)	–	MD −3.5 (−5.6 to −1.4)
Duration of acute hospital stay, mean (SD), (*N*), days	13.8 (26.8), (*n* = 279)	19.5 (47.7), (*n* = 260)	MD −5.7 (−12.2 to 0.8)	–	MD −7.6 (−13.2 to −1.9)	13.7 (26.9), (*n* = 272)	20.8 (50.3), (*n* = 231)	MD −7.1 (−14.5 to 0.3)	–	MD −8.8 (−14.8 to −2.8)

continued

TABLE 8 Step-up RCT – primary and secondary outcomes (*continued*)

Outcome	Primary analysis set			Effect estimate		Per-protocol analysis			Effect estimate	
	HFNC (*N* = 295)	CPAP (*N* = 278)	Difference (95% CI)	Unadjusted (95% CI)	Adjusted (95% CI)	HFNC (*N* = 288)	CPAP (*N* = 245)	Difference (95% CI)	Unadjusted[a] (95% CI)	Adjusted[b] (95% CI)
COMFORT-B[c] score while on randomised treatment, mean (SD), (*N*)	14.1 (3.6), (*n* = 194)	14.4 (4.8), (*n* = 142)	MD −0.4 (−1.3, to 0.5)	–	MD −0.6 (−1.4 to 0.2)	14.1 (3.6), (*n* = 193)	14.5 (4.7), (*n* = 139)	MD −0.4 (−1.3 to 0.5)	–	MD −0.6 (−1.4 to 0.2)
COMFORT-B[c] score while on HFNC or CPAP, mean (SD), (*N*)	13.9 (3.5), (*n* = 201)	13.7 (3.7), (*n* = 169)	MD 0.2 (−0.6 to 0.9)	–	MD 0.2 (−0.5 to 0.8)	13.9 (3.5), (*n* = 197)	13.6 (3.6), (*n* = 157)	MD 0.3 (−0.5 to 1.0)	–	MD 0.2 (−0.4 to 0.9)
Proportion of patients in whom sedation was used during NRS, no./total no. (%)	81/292 (27.7)	97/262 (37.0)	AD −9.3 (−17.1 to −1.5)	OR 0.65 (0.46 to 0.93)	OR 0.59 (0.39 to 0.88)	80/286 (28.0)	93/237 (39.2)	AD −11.3 (−19.4 to −3.2)	OR 0.60 (0.42 to 0.87)	OR 0.54 (0.35 to 0.81)
Parental stress (PSS:PICU) score,[d] mean (SD), (*N*)	1.5 (0.8), (*n* = 180)	1.6 (0.7), (*n* = 185)	MD 0.0 (−0.2 to 0.1)	–	MD −0.1 (−0.2 to 0.1)	1.5 (0.8), (*n* = 174)	1.6 (0.7), (*n* = 167)	MD 0.0 (−0.2 to 0.1)	=	MD 0.0 (−0.2 to 0.1)
Mortality										
At PICU discharge – no./total no. (%)	5/292 (1.7)	4/274 (1.5)	AD 0.3 (−1.8 to 2.3)	OR 1.18 (0.31 to 4.43)	OR 1.22 (0.32 to 4.62)	5/285 (1.8)	3/243 (1.2)	AD 0.5 (−1.5 to 2.6)	OR 1.43 (0.34 to 6.04)	OR 1.46 (0.35 to 6.22)
At day 60 – no./total no. (%)	4/289 (1.4)	5/271 (1.8)	−0.5 (−2.6 to 1.6)	0.75 (0.20 to 2.81)	0.76 (0.20 to 2.88)	4/282 (1.4)	4/240 (1.7)	−0.2 (−2.4 to 1.9)	0.85 (0.21 to 3.43)	0.76 (0.20 to 2.88)
At day 180 – no./total no. (%)	12/284 (4.2)	6/267 (2.2)	2.0 (−1.0 to 4.9)	1.92 (0.71 to 5.19)	1.95 (0.72 to 5.29)	12/277 (4.3)	5/237 (2.1)	2.2 (−0.8 to 5.2)	2.10 (0.73 to 6.05)	1.95 (0.72 to 5.29)

AD, absolute difference; MD, mean difference.

a Unadjusted effect estimate is not separately reported for some rows, since it is the mean difference as reported in the 'Difference' column.

b Adjusted for pre-baseline factors of age (< 12 months vs. ≥ 12 months), SpO2 : FiO2 ratio, comorbidities (none vs. neurological/neuromuscular vs. other), reason for admission (bronchiolitis vs. other respiratory vs. cardiac vs. other), respiratory support at randomisation (yes/no), severity of respiratory distress (severe vs. mild/moderate) and site (using shared frailty).

c COMFORT Behavior Scale scores were recorded every 6 hours until liberation from respiratory support and were aggregated to patient level using the median of all recorded scores.

d PSS:PICU scores range from 1 to 5 (not stressful to extremely stressful). A mean value of 1.6 indicates a low level of parental stress at the time of completing the questionnaire.

Note

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re-admissions was similar between randomised groups (1.15 vs. 1.24 days), but HFNC patients had slightly longer stays in the general medical ward compared to the CPAP group (4.45 vs. 3.65 days). The mean total length of stay up to 6 months was lower in the HFNC group compared to CPAP (19.71 vs. 21.68 days).

The number of outpatient visits and use of community healthcare services following discharge from hospital up to 6 months for HFNC and CPAP patient groups was derived from responses to the HSQ and is summarised in *Appendix 10*. Patients in the HFNC group had, on average, more contacts with their general practitioner (GP), nurse,

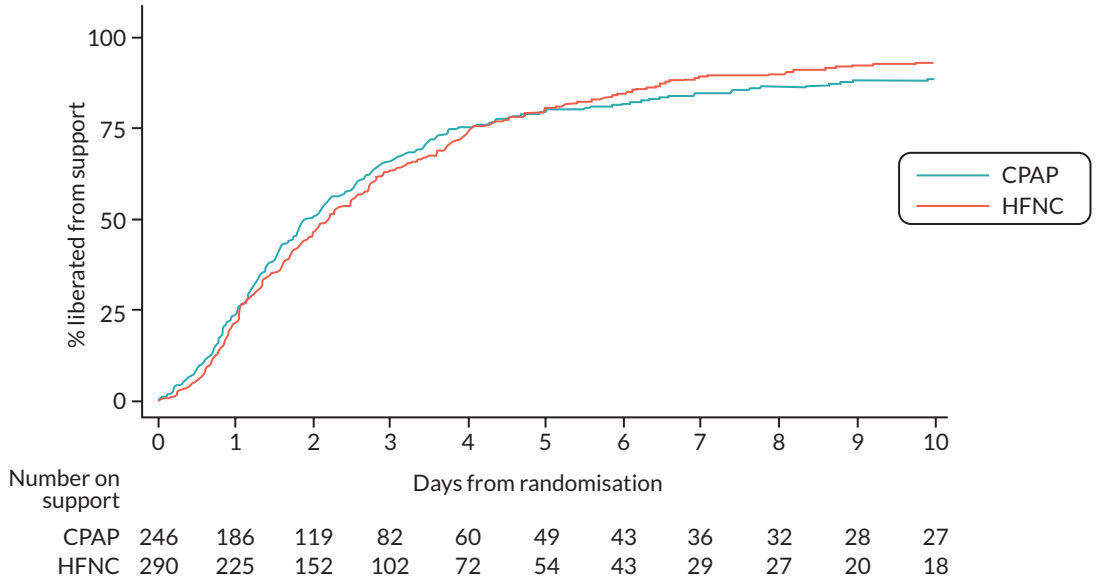

FIGURE 9 Time to liberation from respiratory support in the per-protocol population. Reproduced with permission from Ramnarayan *et al.*[31] Copyright © 2022 JAMA. All rights reserved.

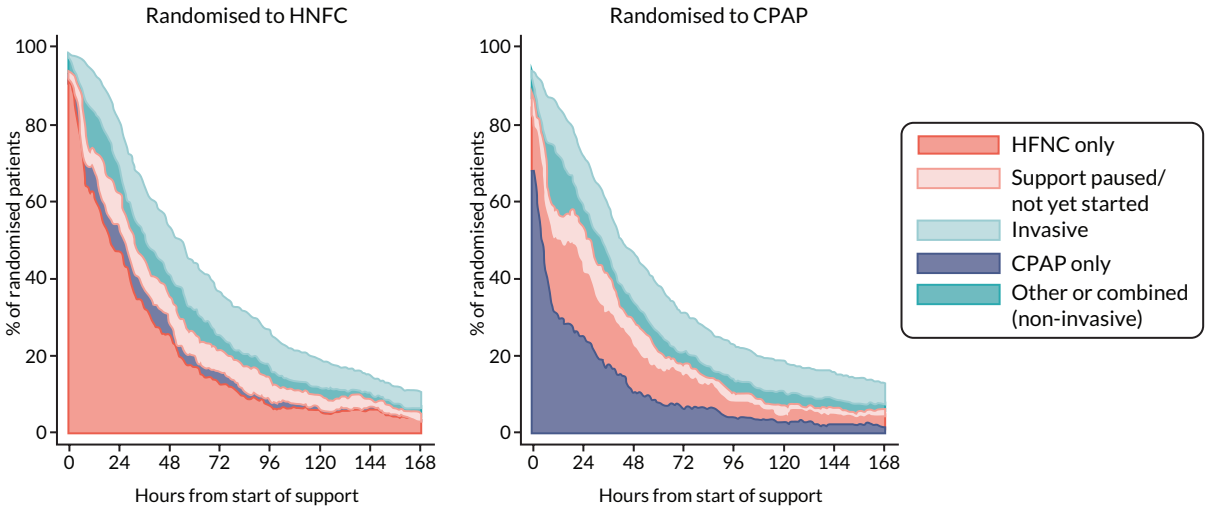

FIGURE 10 Step-up RCT – respiratory support treatments provided overtime to children in the primary analysis set. Reproduced with permission from Ramnarayan *et al.*[31] Copyright © 2022 JAMA. All rights reserved.

health visitor and counsellor services than patients in the CPAP group, but fewer number of outpatient visits and contacts with dietitian, occupational therapy, psychiatric nurse and physiotherapy services. Use of other community care services up to 6 months was low and similar between the two groups.

Total costs (GB£)

Mean total costs per patient at 6 months post randomisation are reported in *Table 11*. The index hospital admission costs were the main driver of the total cost associated with the provision of HFNC and CPAP in this population, accounting for up to 74% and 81%, respectively, of the total costs at 6 months. Within the index admission, the cost of stays in critical care units was lower in the HFNC group compared to CPAP (£8658 vs. £12,584), and higher than those of stays in general medical wards for both groups. The re-admission costs were higher in the HFNC group than in the CPAP group. In re-admissions, the costs of stays in general medical wards were higher than the costs of stays in critical care units for both randomised groups. The costs of outpatient visits and community healthcare services were larger

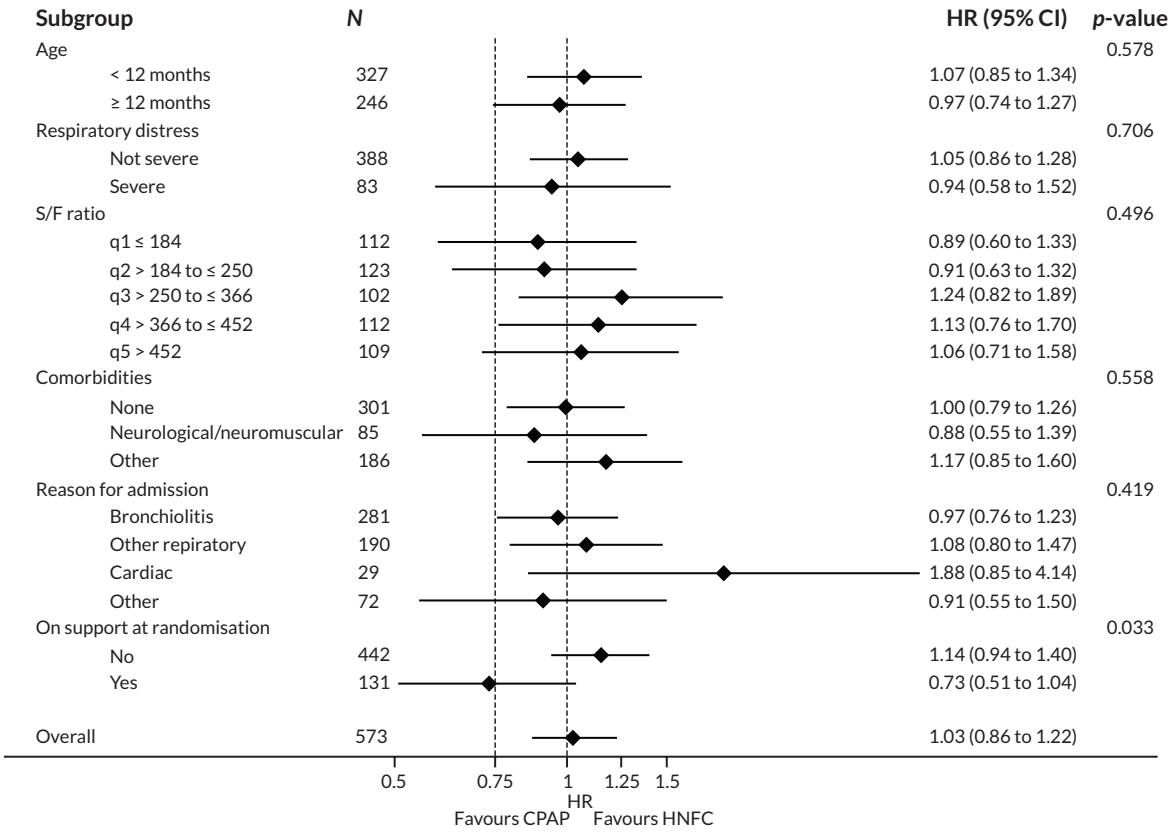

FIGURE 11 Step-up RCT – subgroup analysis of the primary outcome of liberation from respiratory support in the primary analysis set. Median (IQR) observation time. Primary analysis set: HFNC 50.0 hours (25.5, 96.6), CPAP 44.8 hours (24.3, 92.9). Per-protocol analysis: HFNC 49.9 hours (25.4, 95.8), CPAP 44.7 hours (24.3, 90.0). Reproduced with permission from Ramnarayan *et al.*[31] Copyright © 2022 JAMA. All rights reserved.

TABLE 9 Step-up RCT – summary of AEs and SAEs

Event	HFNC (*N* = 295)	CPAP (*N* = 278)	*p*-value
AE			
Nasal trauma	6 (2.0)	18 (6.5)	
Facial/neck trauma	4 (1.4)	5 (1.8)	
Abdominal distension	6 (2.0)	6 (2.2)	
Pneumothorax	3 (1.0)	1 (0.4)	
Pneumomediastinum	1 (0.3)	0 (0.0)	
Subcutaneous emphysema	1 (0.3)	1 (0.4)	
Respiratory arrest	1 (0.3)	1 (0.4)	
Cardiac arrest	1 (0.3)	3 (1.1)	
Aspiration	1 (0.3)	1 (0.4)	
Other	0 (0.0)	3 (1.1)	
Any one or more event	17 (5.8)	30 (10.8)	0.03
SAE			
Nasal trauma	0 (0.0)	0 (0.0)	
Facial/neck trauma	0 (0.0)	0 (0.0)	

TABLE 9 Step-up RCT – summary of AEs and SAEs (*continued*)

Event	HFNC (*N* = 295)	CPAP (*N* = 278)	*p*-value
Abdominal distension	0 (0.0)	0 (0.0)	
Pneumothorax	0 (0.0)	0 (0.0)	
Pneumomediastinum	0 (0.0)	0 (0.0)	
Subcutaneous emphysema	0 (0.0)	0 (0.0)	
Respiratory arrest	0 (0.0)	0 (0.0)	
Cardiac arrest	1 (0.3)	3 (1.1)	
Aspiration	0 (0.0)	0 (0.0)	
Other	0 (0.0)	0 (0.0)	
Any one or more event	1 (0.3)	3 (1.1)	–

Note

in the HFNC group than in the CPAP group (£418 vs. £355). The mean total costs per patient were lower in the HFNC group (£20,335) compared to the CPAP group (£24,142).

Health-related quality of life

Table 12 reports HRQoL for respondents of the follow-up questionnaires in the HFNC and CPAP groups at 6 months. The mean overall scores across the four PedsQL dimensions were similar between HFNC and CPAP patients (70 vs. 73 in the physical dimension, 71 vs. 68 in the emotional dimension, 81 vs. 81 in the social dimension, and 65 vs. 67 in the school functioning dimension). The mean total PedsQL score at 6 months were high in both randomised groups (71 and 72 in HFNC and CPAP group, respectively).

The mapped CHU-9D utility scores at 6 months were similar between the randomised groups (*Table 13*). At 6 months, HFNC compared to CPAP group had slightly lower life-years. The resultant mean QALYs at 6 months were slightly lower in the HFNC group.

Cost-effectiveness

The unadjusted incremental cost of HFNC compared to CPAC was −£3807, and this estimate was surrounded by a wide 95% CI that included zero (*Table 14*). After adjustment for baseline characteristics, the estimated incremental cost of HFNC compared to CPAP was −£5702, but the 95% CI around it was wide. The incremental life-years and QALYs of HFNC versus CPAP were found to be negative in both the unadjusted and adjusted analysis, but the magnitudes were small in all cases with 95% CIs including zero. The cost-effectiveness plane shows that the majority of points representing incremental costs and incremental QALYs fall in the third quadrant (south-west) of the cost-effectiveness plane, indicating that HFNC resulted in lower QALYs and lower costs, albeit with wide uncertainty (*Figure 13*). The INB for HFNC versus CPAP was positive, but there is statistical uncertainty around the INB; at £20,000 per QALY, the INB from adjusted analysis was £5628 (95% CI −£8 to £11,264).

The results of the subgroup analysis are reported in *Report Supplementary Material 3*. Estimated INBs were similar across all subgroups, except for the subgroup of patients who were admitted due to cardiac reasons. The INB for the cardiac patient subgroup is large relative to all other subgroups. For all other subgroups, as for the overall results, the 95% CIs around the INB included zero.

Report Supplementary Material 4 reports the mean with 95% CI of the INB (at £20,000 per QALY gain) according to alternative assumptions, compared with the base case. The INBs from alternative scenarios are similar to the base-case INB (£5628), with overlapping CIs, suggesting that that the base-case results were robust to the main assumptions made in the base case.

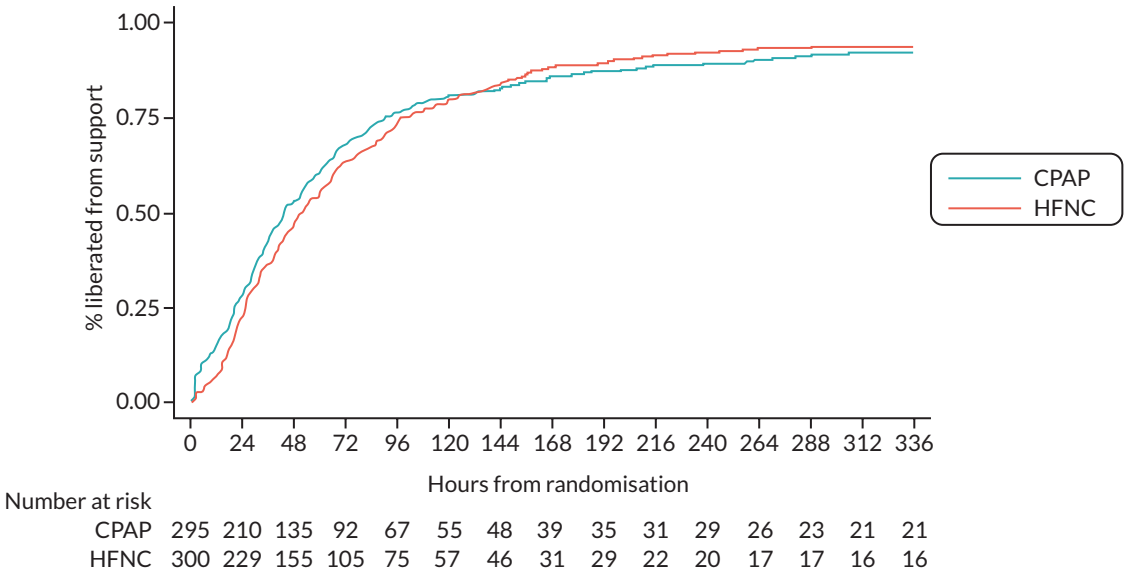

FIGURE 12 Step-up RCT – time to liberation from respiratory support – post hoc sensitivity analysis in all randomised children including those who were not started on respiratory support. To enable the inclusion of all randomised patients we assigned a minimal time to liberation of 2 hours in those who did not start any respiratory support following randomisation, and repeated the primary analysis. Reproduced with permission from Ramnarayan *et al.*[31] Copyright © 2022 JAMA. All rights reserved.

TABLE 10 Step-up RCT – resource use up to 6 months

	HFNC (*n* = 269)	CPAP (*n* = 237)
Index admission		
Days in PICU/HDU[a,b]	5.08 (11.04)	7.05 (17.40)
Days in general medical ward[a]	9.04 (25.41)	9.74 (26.71)
Re-admission		
N (%) re-admission to PICU/HDU	21 (7.80)	16 (6.75)
N (%) to general medical ward	102 (37.85)	85 (36.03)
Days in PICU/HDU[a]	1.15 (6.31)	1.24 (7.59)
Days in general medical[a,c]	4.45 (7.77)	3.65 (8.41)
Total length of stay up to 6 months[a,c]	19.71 (31.06)	21.68 (38.76)

a Data censored at 180 days.
b Including admissions to PICU/HDU following initial discharge to the ward.
c Following multiple imputation to handle missing resource use data. All numbers are mean (SD) unless stated otherwise.

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TABLE 11 Step-up RCT – costs (GB£) up to 6 months, mean (SD)

	HFNC (*n* = 269)	CPAP (*n* = 237)
Hospital costs		
Index admission		
PICU/HDU	8658 (13,798)	12,584 (28,819)
General medical ward	6142 (17,155)	6617 (18,111)

TABLE 11 Step-up RCT – costs (GB£) up to 6 months, mean (SD) (*continued*)

	HFNC (*n* = 269)	CPAP (*n* = 237)
Re-admission[a]		
PICU/HDU[b]	2126 (10,951)	2134 (12,756)
General medical ward[b]	2990 (5221)	2452 (5653)
Outpatient and community costs[a,b]	418 (437)	355 (695)
Total costs up to 6 months[a,b,c]	20,335 (27,207)	24,142 (42,938)

a FIRST-ABC Study and PICANet Database.
b Following multiple imputation to handle missing resource use data.
c HSQ.

Note
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TABLE 12 Step-up RCT – PedsQL score at 6 months, mean (SD)

	HFNC (*n* = 269)	CPAP (*n* = 237)
PedsQL dimension		
Physical score[a]	70 (31)	73 (28)
Emotional score[a]	71 (18)	68 (20)
Social score[a]	81 (20)	81 (23)
School score[a]	65 (28)	67 (30)
PedsQL total score[a]	71 (21)	72 (22)

a Only reported for patients who were alive and completed the follow-up questionnaires at 6 months post randomisation.

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TABLE 13 Step-up RCT – CHU-9D utility score, life-years, and QALYs up to 6 months, mean (SD)

	HFNC (*n* = 269)	CPAP (*n* = 237)
CHU-9D utility score	0.919 (0.033)	0.917 (0.036)
Life-years	0.483 (0.090)	0.494 (0.056)
QALY	0.222 (0.042)	0.226 (0.027)

Note
The CHU-9D score, life-years and QALY results are all reported after applying multiple imputation to handle missing data.
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TABLE 14 Step-up RCT – cost-effectiveness at 6 months: total costs (£ GB), CHU-9D utility score, life-years, QALY and INB

	HFNC (*n* = 269) mean (SD)	CPAP (*n* = 237) mean (SD)	Incremental effect (unadjusted) mean (95% CI)	Incremental effect (adjusted)[a] mean (95% CI)
Costs (£ GB)	20,335 (27,207)	24,142 (42,938)	−3807 (−10,113 to 2500)	−5702 (−11,328 to −75)
CHU-9D utility score (survivors)	0.919 (0.033)	0.917 (0.036)	0.002 (−0.012 to 0.016)	0.002 (−0.011 to 0.016)
Life-years	0.483 (0.090)	0.494 (0.056)	−0.011 (−0.024 to 0.003)	−0.009 (−0.022 to 0.004)
QALY	0.222 (0.042)	0.226 (0.027)	−0.004 (−0.011 to 0.003)	−0.003 (−0.010 to 0.004)
INB (£ GB)[b]			3720 (−2610 to 10,050)	5628 (−8 to 11,264)

a The incremental effects are reported after applying case-mix adjustment.
b The INB is calculated according to National Institute for Health and Care Excellence methods guidance, by multiplying the mean QALY gain (or loss) by £20,000, and subtracting from this the incremental cost.

Note
The cost, CHU-9D, life-years, QALY and INB results are all reported after applying multiple imputation to handle missing data.
All numbers are mean (SD), unless stated otherwise.

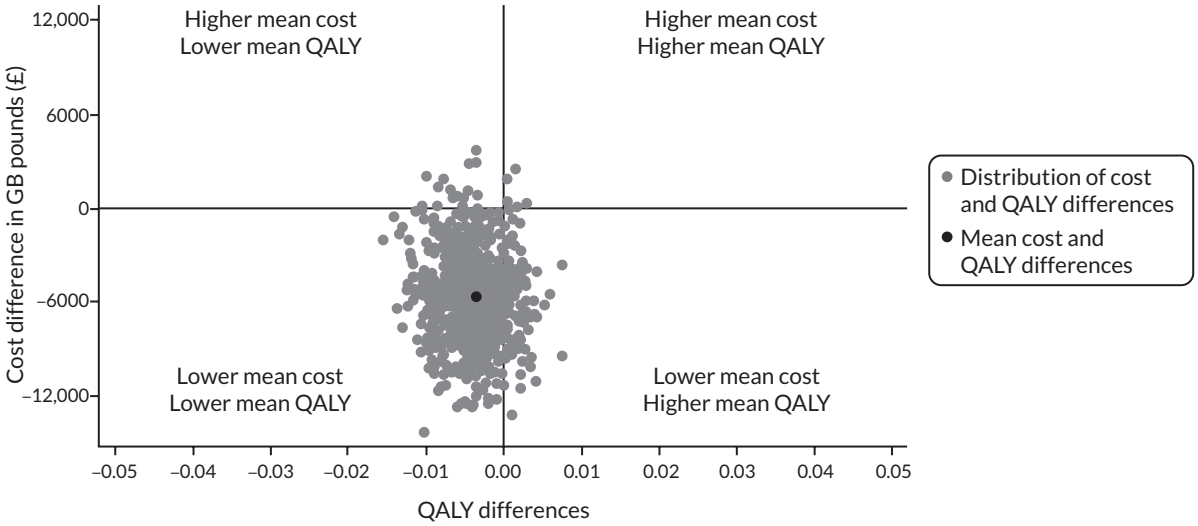

FIGURE 13 Step-up RCT – uncertainty in the mean costs (GB£) and QALY differences and their distribution for HFNC vs. CPAP (within 6 months post randomisation).

Chapter 4 Results: step-down randomised controlled trial

Sites and patients

Site selection and set-up

Expressions of interest and completed site feasibility questionnaires were received from 22 potential sites across England, Wales and Scotland. All sites were invited to take part in the trial, of which two were ultimately not able to progress with set-up (one due to research capacity issues and one due to equipoise issues).

In total, 20 sites, covering 22 PICUs, recruited patients into the FIRST-ABC step-down RCT. The first sites opened in August 2019, on schedule, and the final sites opened in January 2020. By the end of the internal pilot, 20 sites were open to recruitment. Characteristics of the participating PICUs are compared with non-participating PICUs in *Table 15*.

In relation to research governance, the median time from provision of the final local information pack to the issuing of local confirmation of capacity and capability was 39 (IQR 19–98) days. The median time from local confirmation of capacity and capability to the start of patient screening at sites was 18 (IQR 6–59) days. The median time from the start of patient screening to the first patient recruited at sites was 5 (IQR 2–13) days. In total, the process from provision of the final local information pack to first patient recruited took a median of 101 (IQR 64–130) days.

Of the 20 sites, 15 formally paused recruitment at least once due to the impact of COVID-19 on clinical and research activity. However, 91.2% of the sample size were already recruited prior to March 2020, limiting the overall impact on trial recruitment. Overall, each site participated in the step-down RCT for a median (IQR) of 5.6 (4.0–6.6) months.

TABLE 15 Characteristics of participating UK NHS PICUs

Characteristic	Participated in FIRST-ABC step-down RCT (*n* = 22)	Did not participate in FIRST-ABC step-down RCT (*n* = 6)
Country/region		
England		
London	8 (36.4)	0 (0)
North East and Yorkshire	2 (9.1)	3 (50.0)
North West	2 (9.1)	1 (16.7)
Midlands	4 (18.2)	0 (0)
South East	2 (9.1)	0 (0)
South West	1 (4.6)	0 (0)
East of England	1 (4.6)	0 (0)
Wales	1 (4.6)	0 (0)
Scotland	1 (4.6)	1 (16.7)
Northern Ireland	0 (0)	1 (16.7)
Type of unit		
General	14 (63.6)	3 (50.0)
Cardiac	3 (13.6)	1 (16.7)

continued

TABLE 15 Characteristics of participating UK NHS PICUs (*continued*)

Characteristic	Participated in FIRST-ABC step-down RCT (*n* = 22)	Did not participate in FIRST-ABC step-down RCT (*n* = 6)
Mixed	5 (22.7)	2 (33.3)
Annual admissions		
< 500	5 (22.7)	4 (66.7)
500–749	10 (45.5)	1 (16.7)
750–999	4 (18.2)	1 (16.7)
≥ 1000	3 (13.6)	0 (0)
Annual admissions (ventilated)		
< 250	5 (22.7)	3 (50.0)
250–499	10 (45.5)	1 (16.7)
≥ 500	7 (31.8)	2 (33.3)

RCT, randomised controlled trial.

Note

Patient screening, randomisation and consent

Between August 2019 and May 2020, 3121 patients were extubated following a period of IMV at participating PICU/HDUs and screened for inclusion in the step-down RCT, from which 1397 were deemed to meet inclusion criteria (*Figure 14*). Of those not meeting inclusion criteria (*n* = 1724), most did not require NRS within 72 hours of extubation (*n* = 1700, 98.6%).

Of patients meeting inclusion criteria, 346 additionally met exclusion criteria and were not eligible for the trial. The most common reasons for exclusion were: a clinical decision to commence a form of NRS other than HFNC or CPAP (*n* = 153, 44.2%) and receipt of home non-invasive ventilation prior to admission (*n* = 64, 18.5%).

Of the remaining 1051 eligible patients, 600 (57.1%) were randomised into the trial and 451 (42.9%) were not. The most common reasons for eligible patients not being enrolled in the trial were that patients were either missed or identified too late for recruitment (*n* = 157, 34.8%) or a clinical decision was made not to enrol the patient (*n* = 263, 58.3%). Regarding the latter, a greater number of patients were not randomised due to the clinician preferring HFNC rather than CPAP. The full sample were recruited 5 months ahead of the schedule (*Figure 15*).

Among the 600 enrolled, 299 were randomised to the HFNC group and 301 to the CPAP group. After accounting for complete withdrawals, 291 in the HFNC group and 296 in the CPAP group formed the ITT population. In the HFNC group, 281 started respiratory support following randomisation compared with 272 in the CPAP group, forming the primary analysis set. Of those randomised to HFNC, 272 started HFNC, while 252 in the CPAP group started CPAP as randomised, forming the per-protocol population (see *Report Supplementary Material 5*).

In the primary analysis set, the primary outcome was observed in 260 in the CPAP group and in 258 in the HFNC group, with 12 and 23 censored in each group, respectively. In the per-protocol population, the primary outcome was observed in 244 in the CPAP group and in 248 in the HFNC group.

Baseline characteristics

The groups were well matched at baseline (*Table 16*), except for a higher proportion of children receiving ventilation for cardiac reasons in the HFNC group (28.8% vs. 20.2%). The median age in months was 3, and just over three quarters were aged < 1 year, in both groups. The median (IQR) duration of prior IMV was 89 (56–145) hours in the HFNC group and 87 (51–140) hours in the CPAP group, with most patients randomised prior to extubation (63.3%

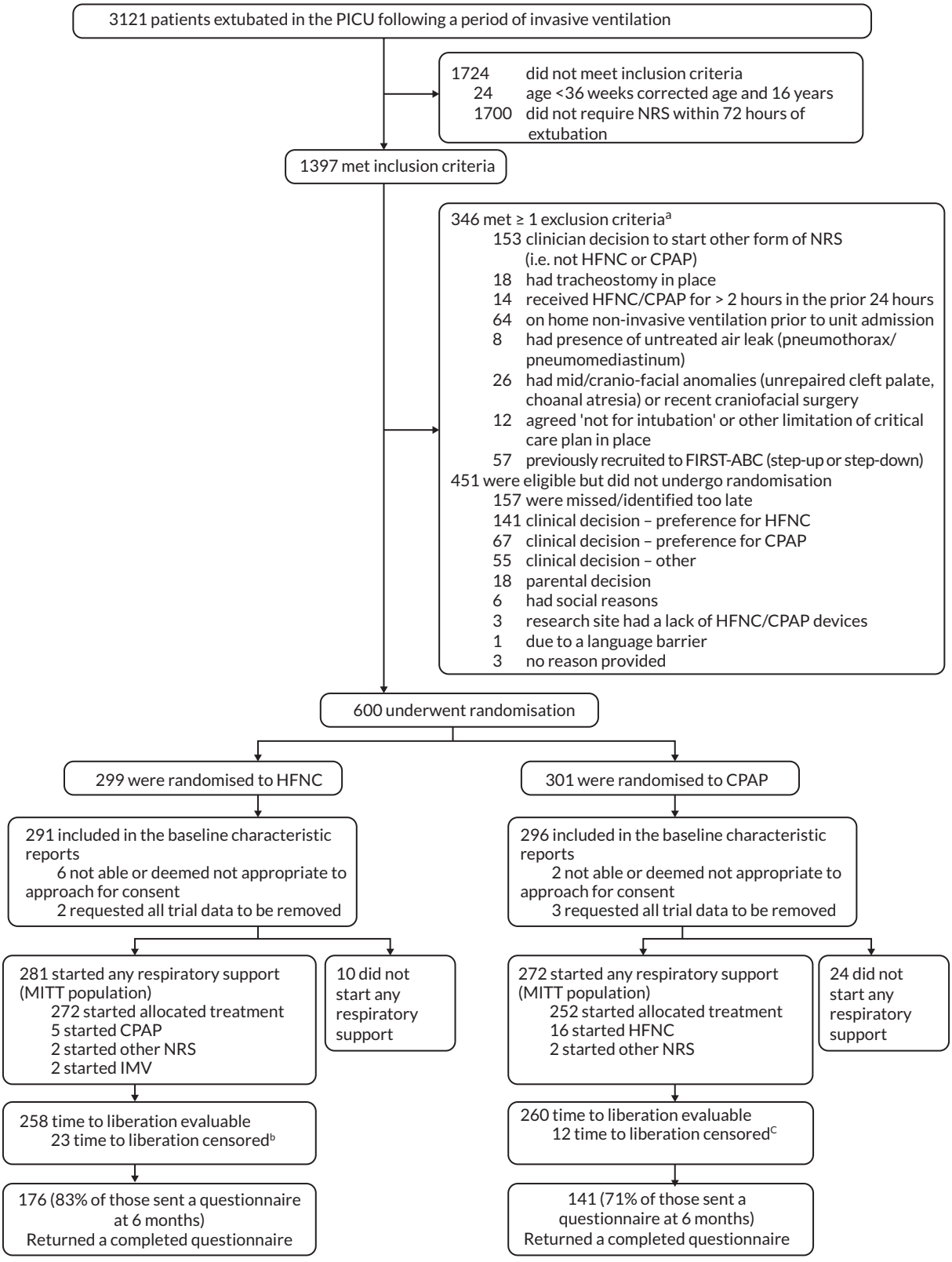

FIGURE 14 Screening, randomisation and follow-up through the step-down RCT. a, Numbers meeting individual exclusion criteria do not add to the total as some patients met > 1 criterion. b, In the HFNC group, time to liberation was censored for 23 patients: 4 refused retrospective consent, 8 died prior to liberation from respiratory support, 10 were discharged from critical care on respiratory support and data are unavailable, 1 patient was transferred to another critical care unit on respiratory support and data are unavailable. c, In the CPAP group, time to liberation was censored for 12 patients: 6 refused retrospective consent, 3 died prior to liberation from respiratory support, 2 were discharged from critical care on respiratory support and data are unavailable, 1 patient was transferred to another critical care unit on respiratory support and data are unavailable. Reproduced with permission from Ramnarayan *et al.*[32] Copyright © 2022 JAMA. All rights reserved.

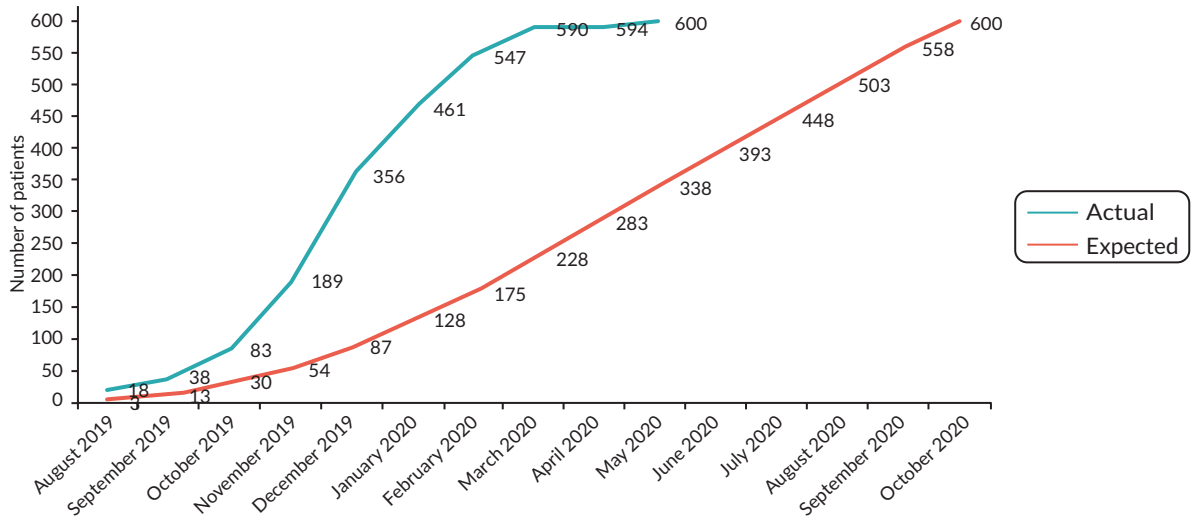

FIGURE 15 Step-down RCT – actual vs. expected patient randomisation. Comparison of actual vs. expected cumulative randomisation of patients into the FIRST-ABC step-down RCT. Reproduced with permission from Ramnarayan *et al.*[32] Copyright © 2022 JAMA. All rights reserved.

vs. 61.8%, respectively), indicating a pre-planned use of NRS post-extubation. Baseline characteristics of the per-protocol population were similar to those of the primary analysis set (*Table 17*). The baseline characteristics of the full ITT population (i.e. including the small number of patients who did not start any respiratory support following randomisation) are shown in *Report Supplementary Material 6*.

Clinical management

In both groups, the randomised treatment was started in the majority of children who started respiratory support [272/281 (96.8%) in the HFNC group, 252/272 (92.6%) in the CPAP group]. A variety of devices and interfaces were used to delivery HFNC and CPAP (*Report Supplementary Material 7*). Adherence to the trial algorithms was good, with most patients receiving HFNC at the prescribed gas flow rates (*Figure 16*) and CPAP at the specified pressure level (*Figure 17*).

A flow of the clinical management in each randomised group is shown in *Figure 18*. More patients (101/272, 37.1%) in the HFNC group experienced treatment failure compared to the CPAP group (85/252, 33.7%) (*Report Supplementary Material 8*). Almost a quarter (23.5%) of those experiencing treatment failure in the HFNC group switched to CPAP, whereas only 12.3% in the CPAP group switched to HFNC. Patients in the HFNC group were most often switched due to severe respiratory distress, whereas patients in the CPAP group were most often switched due to patient discomfort reasons (*Report Supplementary Material 8*).

Clinical effectiveness

Primary outcome

The median time from randomisation to liberation from respiratory support was 50.5 hours (95% CI 43.0 to 67.9) in the HFNC group and 42.9 hours (95% CI 30.5 to 48.2) in the CPAP group (adjusted HR 0.83; one-sided 97.5% CI 0.70 to ∞). The bound of the one-sided 97.5% CI (adjusted HR 0.70) was below the prespecified non-inferiority margin (HR 0.75) (*Figure 19*; see*Table 18*). Results were similar in the per-protocol analysis (adjusted HR 0.82, 95% CI 0.68 to 0.98) (Figure 20; see *Table 18*) (see *Report Supplementary Material 9*). Proportional hazards assumptions were checked by examining plots of −ln(−ln(survival)) over time and scaled Schoenfeld residuals from each Cox proportional hazards model. No evidence of departures from proportional hazards was observed. A breakdown of the duration of invasive

TABLE 16 Step-down RCT – baseline characteristics of the primary analysis set[a]

Characteristic	HFNC (*N* = 281)	CPAP (*N* = 272)
Age, median (IQR), months	3 (1–10)	3 (1–11)
Age, no. (%)		
≤ 28 days	56 (19.9)	37 (13.6)
29–180 days	122 (43.4)	124 (45.6)
181–364 days	37 (13.2)	46 (16.9)
1 year	25 (8.9)	25 (9.2)
2–4 years	17 (6.0)	14 (5.1)
5–10 years	17 (6.0)	12 (4.4)
11–15 years	7 (2.5)	14 (5.1)
Sex, no. (%)		
Female	111 (39.5)	130 (47.8)
Male	170 (60.5)	142 (52.2)
Ethnicity, no. (%)	*n = 193*	*n = 199*
Asian	24 (12.4)	27 (14.9)
Black	9 (4.7)	15 (8.3)
Mixed	12 (6.2)	6 (3.3)
White	138 (71.5)	124 (68.5)
Other	10 (5.2)	9 (5.0)
Type of admission, no. (%)	*n = 279*	*n = 269*
Planned, following surgery	53 (19.0)	46 (17.1)
Unplanned, following surgery	7 (2.5)	6 (2.2)
Planned, not following surgery	15 (5.4)	8 (3.0)
Unplanned, not following surgery	204 (73.1)	209 (77.7)
Source of admission	*n = 279*	*n = 269*
Same hospital	108 (38.7)	96 (35.7)
Other hospital	171 (61.3)	173 (64.3)
Comorbidities, no. (%)		
None	110 (39.1)	117 (43.0)
At least one	171 (60.9)	155 (57.0)
Airway/respiratory	37 (13.2)	38 (14.0)
Cardiac/vascular	105 (37.4)	90 (33.1)
Neurological/neuromuscular	31 (11.0)	32 (11.8)
Congenital/genetic/syndrome	36 (12.8)	39 (14.3)
Gastro/surgical	30 (10.7)	21 (7.7)
Haematology/oncology	4 (1.4)	6 (2.2)

continued

TABLE 16 Step-down RCT – baseline characteristics of the primary analysis set (*continued*)

Characteristic	HFNC (*N* = 281)	CPAP (*N* = 272)
Metabolic/endocrine	9 (3.2)	7 (2.6)
Immunodeficiency	5 (1.8)	5 (1.8)
Prematurity	10 (3.6)	12 (4.4)
Other	29 (10.3)	17 (6.3)
Main reason for IMV, no. (%)		
Upper airway problem	9 (3.2)	13 (4.8)
Bronchiolitis	97 (34.5)	122 (44.9)
Asthma/wheeze	1 (0.4)	5 (1.8)
Other respiratory	42 (14.9)	34 (12.5)
Cardiac	81 (28.8)	55 (20.2)
Neurological	7 (2.5)	13 (4.8)
Sepsis/infection	12 (4.3)	10 (3.7)
Other	32 (11.4)	20 (7.4)
Duration of prior IMV, hours		
Hours, mean (SD)	127 (130)	124 (130)
Hours, median (IQR)	89 (56–145)	87 (51–140)
0–4 days	189 (67.3)	183 (67.3)
5 + days	92 (32.7)	89 (32.7)
Nature of post-extubation NRS, no. (%)		
Planned (randomised before extubation)	178 (63.3)	168 (61.8)
Indeterminate (randomised within 1 hour of extubation)	49 (17.4)	49 (18.0)
Rescue (randomised at least 1 hour after extubation)	54 (19.2)	55 (20.2)
Respiratory distress, no. (%)[b]	*n = 210*	*n = 198*
None	126 (60.0)	112 (56.6)
Mild	58 (27.6)	52 (26.3)
Moderate	22 (10.5)	29 (14.6)
Severe	4 (1.9)	5 (2.5)
Respiratory rate, breaths per minute[c]	*n = 277*	*n = 269*
Median (IQR)	35 (27–45)	36 (28–45)
SpO_2 (%)[d]	*n = 281*	*n = 270*
Median (IQR)	96 (94–98)	97 (94–99)
FiO_2[e]	*n = 278*	*n = 270*
Median (IQR)	0.30 (0.24–0.35)	0.30 (0.25–0.35)
SpO_2/FiO_2 ratio[f]	*n = 278*	*n = 268*
Median (IQR)	327 (271–400)	327 (274–396)

TABLE 16 Step-down RCT – baseline characteristics of the primary analysis set (*continued*)

Characteristic	HFNC (*N* = 281)	CPAP (*N* = 272)
Heart rate, beats per minute[g]	*n = 280*	*n = 272*
Median (IQR)	128 (115–145)	132 (115–147)
COMFORT-B score[h]	*n = 204*	*n = 187*
Mean ± SD	13.8 ± 2.7	14.3 ± 3.2
Median (IQR)	13.0 (12.0–15.5)	14.0 (12.0–16.0)
< 10	4 (2.1)	5 (2.8)
10–12	55 (28.8)	45 (25.3)
13–17	110 (57.6)	101 (56.7)
> 17	22 (11.5)	27 (15.2)

a Excludes 13 patients where parents or legal guardians requested all data be removed from the trial or where consent could not be obtained. Additionally, excludes 10 patients in the HFNC group and 24 patients in the CPAP group who did not start any respiratory support after randomisation. Plus–Minus values are means ± SD.
b Data on respiratory distress were available for 210 patients in the HFNC group and 198 patients in the CPAP group. Mild: one accessory muscle used, mild indrawing of subcostal and intercostal muscles, mild tachypnoea, no grunting. Moderate: two accessory muscles used, moderate indrawing of subcostal and intercostal muscles, moderate tachypnoea, occasional grunting. Severe: use of all accessory muscles, severe indrawing of subcostal and intercostal muscles, severe tachypnoea, regular grunting.
c Data on respiratory rate were missing for four patients in the HFNC group and three patients in the CPAP group.
d Data on peripheral oxygen saturation were missing for two patients in the CPAP group.
e Data on fraction of inspired oxygen were missing for three patients in the HFNC group and two patients in the CPAP group.
f Data on the ratio of peripheral oxygen saturation to fraction of inspired oxygen (SpO_2/FiO_2 ratio) were missing for three patients in the HFNC group and four patients in the CPAP group.
g Data on heart rate were missing for one patient in the HFNC group.
h COMFORT Behavior Scale Scores range from 5 to 30 (most sedated to least sedated). Data on the COMFORT-B score were available for 204 patients in the HFNC group and 187 patients in the CPAP group.

Note
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TABLE 17 Step-down RCT – baseline characteristics in the per-protocol population[a]

Characteristic	HFNC (*N* = 271)	CPAP (*N* = 252)
Age, months		
Median (IQR)	3 (1–11)	3 (1–11)
Age (categories), no. (%)		
≤ 28 days	53 (19.6)	37 (14.7)
29–180 days	116 (42.8)	115 (45.6)
181–364 days	36 (13.3)	40 (15.9)
1 year	25 (9.2)	22 (8.7)
2–4 years	17 (6.3)	14 (5.6)
5–10 years	17 (6.3)	10 (4.0)
11–15 years	7 (2.6)	14 (5.6)
Sex, no. (%)		
Female	104 (38.4)	123 (48.8)
Male	167 (61.6)	129 (51.2)

continued

TABLE 17 Step-down RCT – baseline characteristics in the per-protocol population (*continued*)

Characteristic	HFNC (*N* = 271)	CPAP (*N* = 252)
Ethnicity, no. (%)	*n = 186*	*n = 169*
Asian	24 (12.9)	24 (14.2)
Black	9 (4.8)	13 (7.7)
Mixed	12 (6.5)	5 (3.0)
White	132 (71.0)	119 (70.4)
Other	9 (4.8)	8 (4.7)
Comorbidities, no. (%)		
None	107 (39.5)	109 (43.3)
At least one	164 (60.5)	143 (56.7)
Airway/respiratory	36 (13.3)	35 (13.9)
Cardiac/vascular	101 (37.3)	84 (33.3)
Neurological/neuromuscular	31 (11.4)	29 (11.5)
Congenital/genetic/syndrome	36 (13.3)	37 (14.7)
Gastro/surgical	28 (10.3)	19 (7.5)
Haematology/oncology	4 (1.5)	3 (1.2)
Metabolic/endocrine	9 (3.3)	7 (2.8)
Immunodeficiency	5 (1.8)	4 (1.6)
Prematurity	10 (3.7)	11 (4.4)
Other	26 (9.6)	16 (6.3)
Type of admission, no. (%)	*n = 269*	*n = 249*
Planned, following surgery	53 (19.7)	44 (17.7)
Unplanned, following surgery	6 (2.2)	5 (2.0)
Planned, not following surgery	15 (5.6)	8 (3.2)
Unplanned, not following surgery	195 (72.5)	192 (77.1)
Source of admission, no. (%)	*n = 269*	*n = 249*
Same hospital	103 (38.3)	86 (34.5)
Other hospital	166 (61.7)	163 (65.5)
Main reason for IMV, no. (%)		
Upper airway problem	9 (3.3)	11 (4.4)
Bronchiolitis	92 (33.9)	114 (45.2)
Asthma/wheeze	1 (0.4)	4 (1.6)
Other respiratory	41 (15.1)	30 (11.9)
Cardiac	79 (29.2)	53 (21.0)
Neurological	7 (2.6)	13 (5.2)
Sepsis/infection	12 (4.4)	8 (3.2)

TABLE 17 Step-down RCT – baseline characteristics in the per-protocol population (*continued*)

Characteristic	HFNC (*N* = 271)	CPAP (*N* = 252)
Other	30 (11.1)	19 (7.5)
Duration of prior IMV		
Hours, mean (SD)	128 (132)	121 (131)
Hours, median (IQR)	90 (56–153)	84 (51–137)
0–4 days	180 (66.4)	174 (69.0)
5 + days	91 (33.6)	78 (31.0)
Nature of post-extubation NRS, no. (%)		
Planned (randomised before extubation)	171 (63.1)	159 (63.1)
Indeterminate (randomised within 1 hour of extubation)	46 (17.0)	42 (16.7)
Rescue (randomised at least 1 hour after extubation)	54 (19.9)	51 (20.2)
Respiratory distress[b]	*n = 204*	*n = 184*
None	122 (59.8)	106 (57.6)
Mild	57 (27.9)	47 (25.5)
Moderate	21 (10.3)	26 (14.1)
Severe	4 (2.0)	5 (2.7)
Respiratory rate	*n = 267*	*n = 249*
Median (IQR)	35 (27–45)	35 (28–45)
SpO_2 (%)		*n = 250*
Median (IQR)	96 (94–98)	97 (94–99)
FiO_2	*n = 268*	*n = 251*
Median (IQR)	0.30 (0.24–0.35)	0.30 (0.25–0.35)
SpO_2/FiO_2 ratio	*n = 268*	*n = 249*
Median (IQR)	327 (271–400)	327 (274–396)
> 350	106 (39.6)	104 (41.8)
301–350	73 (27.2)	61 (24.5)
266–300	28 (10.4)	34 (13.7)
220–265	34 (12.7)	24 (9.6)
< 220	27 (10.1)	26 (10.4)
Heart rate	*n = 270*	
Median (IQR)	128 (115–144)	131 (115–147)
COMFORT-B score[c]	*n* = 196	*n* = 175
Mean (SD)	13.8 (2.7)	14.2 (3.2)
Median (IQR)	13.0 (12.0–15.0)	14.0 (12.0–16.0)
< 10	4 (2.0)	5 (2.9)
10–12	66 (33.7)	52 (29.7)

continued

TABLE 17 Step-down RCT – baseline characteristics in the per-protocol population (*continued*)

Characteristic	HFNC (*N* = 271)	CPAP (*N* = 252)
13–17	105 (53.6)	93 (53.1)
> 17	21 (10.7)	25 (14.3)

a The per-protocol population was defined as all patients who consented, met the eligibility criteria and who commenced the randomised treatment.
b Mild: one accessory muscle used, mild indrawing of subcostal and intercostal muscles, mild tachypnoea, no grunting. Moderate: two accessory muscles used, moderate indrawing of subcostal and intercostal muscles, moderate tachypnoea, occasional grunting. Severe: use of all accessory muscles, severe indrawing of subcostal and intercostal muscles, severe tachypnoea, regular grunting.
c COMFORT Behaviour Scale Scores range 5–30, scores ≤ 11 indicate oversedation and ≥ 23 undersedation.

Note

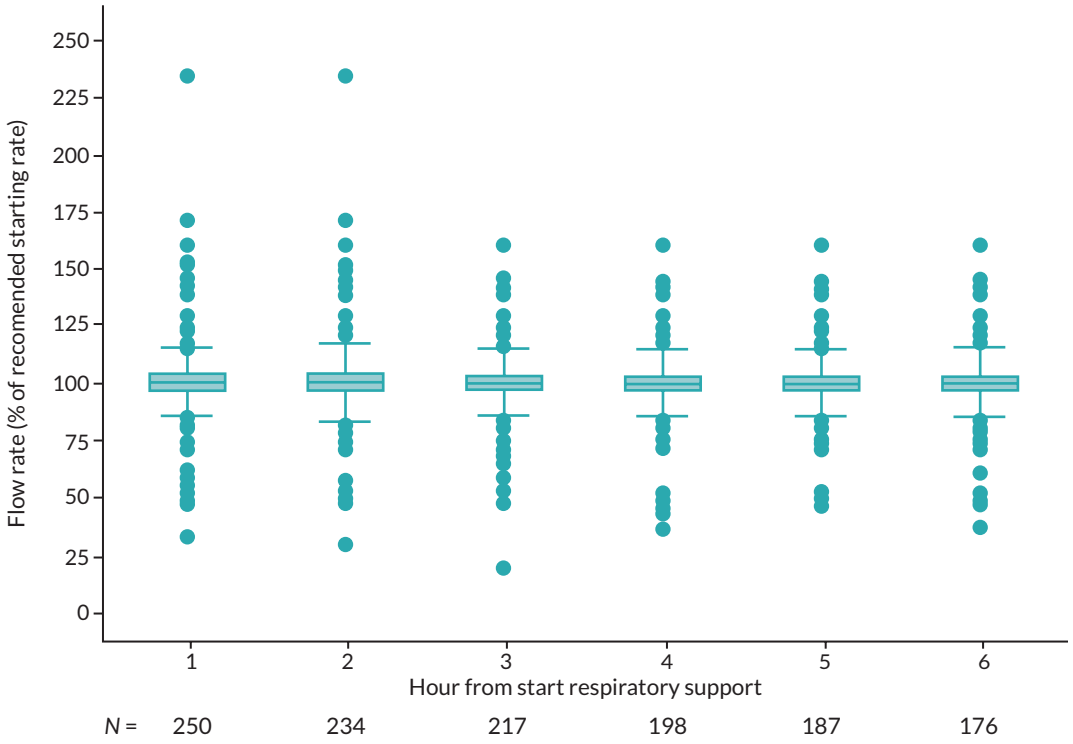

FIGURE 16 Step-down RCT – HFNC flow rates during the first 6 hours of treatment. Reproduced with permission from Ramnarayan *et al.*[32] Copyright © 2022 JAMA. All rights reserved.

and NRS prior to liberation in the primary analysis set is shown in *Table 19* and the time to liberation according to whether treatment failure occurred is shown in *Report Supplementary Material 9*.

Subgroup analyses

There were no significant differences in treatment effects across prespecified subgroups (*Figure 21*).

Secondary outcomes

The rate of reintubation within 48 hours was not significantly different between the groups (HFNC, 13.3%; CPAP, 11.5%; adjusted OR, 1.11, 95% CI 0.7 to 1.9) (see *Table 18*). The time to reintubation was a median of 25 hours (IQR, 8–79) after randomisation for HFNC compared with 11 hours (IQR, 2.5–49) for CPAP (see *Table 18* and *Report Supplementary Material 10*).

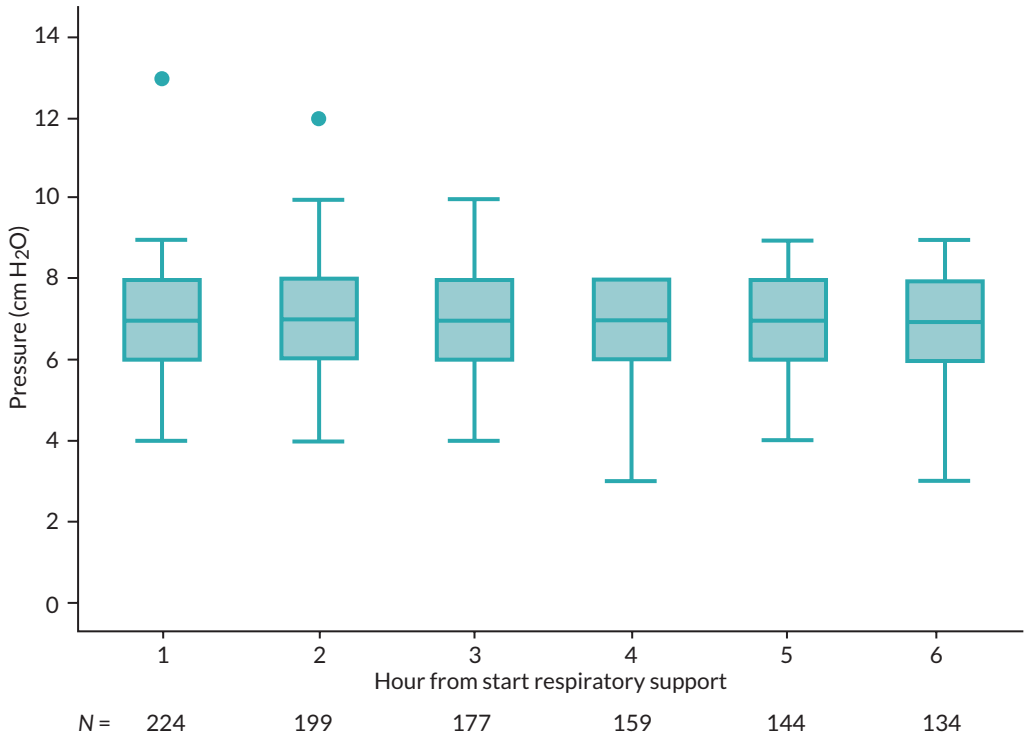

FIGURE 17 Step-down RCT – CPAP pressures during the first 6 hours of treatment. Reproduced with permission from Ramnarayan *et al.*[32] Copyright © 2022 JAMA. All rights reserved.

There was no significant difference in the duration of critical care unit stay or acute hospital stay between the groups. By day 180, there was a higher rate of mortality in the HFNC group (15/268, 5.6%) compared to the CPAP group (6/253, 2.4%) (adjusted OR 2.44, 0.9–6.4) (see *Table 18*). Kaplan–Meier survival plots to day 180 are the shown for primary analysis set in *Figure 22* and for the per-protocol population in *Figure 23*. Characteristics of the patients who died by day 180, by randomised group, are shown in *Report Supplementary Material 11*.

Adverse events

The number of participants with one or more AEs was low in both groups, occurring in 25 out of 281 (8.9%) in the HFNC group and in 28 out of 272 (10.3%) in the CPAP group (*Table 20*). The proportion of patients who experienced one or more SAEs was the same in both groups (1.8%).

Sensitivity analyses

Planned and post hoc sensitivity analyses did not alter interpretation of the primary outcome (*Report Supplementary Material 12*). When repeating the primary analysis in the full ITT population (assigning a nominal 2 hours of respiratory support to patients who did not start any respiratory support following randomisation), the adjusted HR was 0.80 (95% CI 0.68 to 0.96) (*Figure 24*).

Cost-effectiveness analysis

Resource use and costs up to 6 months

Table 21 shows the resource use up to 6 months post randomisation. Patients in the HFNC compared to the CPAP group had, on average, shorter stays in paediatric critical care units (7.43 vs. 7.88 days) but longer stays in general medical ward (11.63 vs. 10.72 days) during the index hospital admission. Up to 6 months post randomisation, re-admissions to critical care units and general medical wards were higher in the HFNC compared to the CPAP group, but the mean lengths of stay in both critical care unit and general medical wards from re-admissions were lower in the HFNC group. The mean total lengths of stay up to 6 months in HFNC and CPAP group were 26.82 days and 28.49, days respectively. Overall, total length of stay up to 6 months was lower in the HFNC group than the CPAP group.

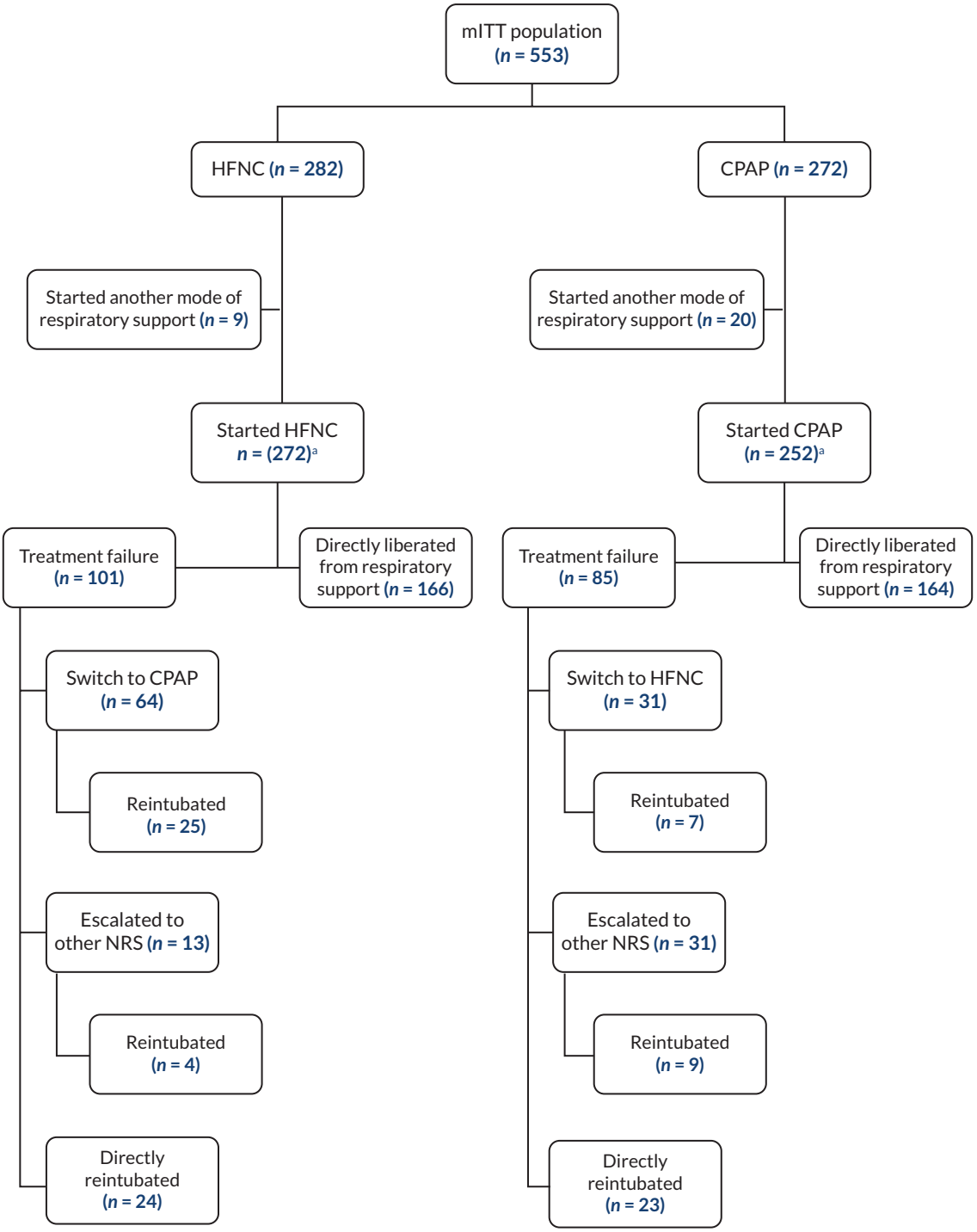

FIGURE 18 Step-down RCT – clinical management of trial patients. a, Time to liberation was censored in five patients started on HFNC and three patients started on CPAP. Reproduced with permission from Ramnarayan *et al.*[32] Copyright © 2022 JAMA. All rights reserved.

Resource use reported from responses to the HSQ is summarised in *Report Supplementary Material 13*. Patients in the HFNC group had on average more outpatient visits and contacts with GP and nurse than the CPAP group. Patients in the CPAP group had higher average number of visits to occupational therapist, physiotherapist and social worker. All other community care contacts up to 6 months were low and similar between the randomised groups.

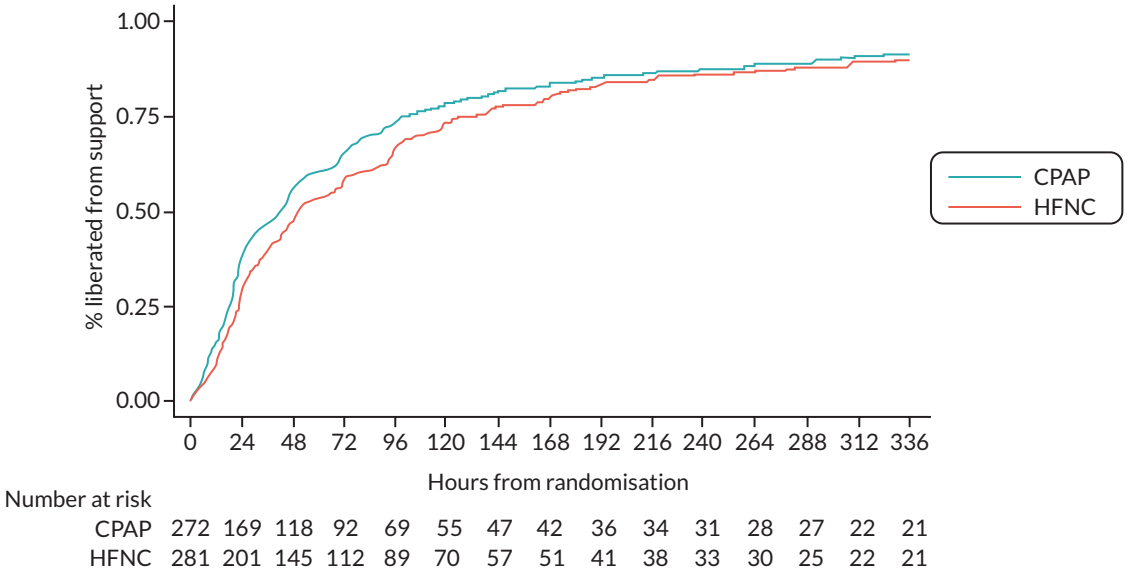

FIGURE 19 Step-down RCT – time to liberation from respiratory support in the primary analysis set. Reproduced with permission from Ramnarayan *et al.*[32] Copyright © 2022 JAMA. All rights reserved.

TABLE 18 Step-down RCT – primary and secondary outcomes

	Primary analysis set				Per-protocol population			
Outcome	**HFNC (*N* = 281)**	**CPAP (*N* = 272)**	**Unadjusted effect estimate (95% CI)**	**Adjusted effect estimate (95% CI)[a]**	**HFNC (*N* = 271)**	**CPAP (*N* = 252)**	**Unadjusted effect estimate (95% CI)**	**Adjusted effect estimate (95% CI)[a]**
Primary								
Time from randomisation to liberation from respiratory support, median (IQR), hours	50.5 (43.0–67.9)	42.9 (30.5–48.2)	0.86 (0.72 to 1.02)[b]	0.83 (0.70 to 0.99)[b]	50.5 (42.9–67.9)	39.5 (28.3–45.8)	0.83 (0.69 to 0.99)[b]	0.82 (0.68 to 0.98)[b]
Secondary								
Reintubation at 48 hours, no./total no. (%)	37/279 (13.3)	31/269 (11.5)	1.7 (−3.8 to 7.3)[c] 1.17 (0.7 to 2.0)[d]	– 1.11 (0.7 to 1.9)[d]	35/269 (13.0)	29/250 (11.6)	1.4 (−4.2 to 7.1)[c] 1.14 (0.7 to 1.9)[d]	– 1.07 (0.6 to 1.8)[d]
COMFORT-B score[e] while on randomised treatment, mean ± SD	13.6 ± 2.7 (*n* = 177)	13.2 ± 2.2 (*n* = 165)	0.4 (−0.1 to 0.9)[f]	0.44 (−0.1 to 1.0)[f]	13.6 ± 2.7 (*n* = 176)	13.2 ± 2.2 (*n* = 163)	0.4 (−0.1 to 0.9)[f]	0.41 (−0.1 to 0.9)[f]
COMFORT-B score[e] while on HFNC or CPAP, mean (SD) (*n*)	13.7 (2.7) (*n* = 188)	13.3 (2.1) (*n* = 178)	0.4 (−0.1 to 0.9)	0.38 (−0.1 to 0.9)	13.6 (2.7) (*n* = 185)	13.3 (2.1) (*n* = 1690	0.4 (−0.1 to 0.9)	0.37 (−0.1 to 0.9)
Proportion of patients in whom sedation was used during NRS, no./total no. (%)	168/276 (60.9)	149/264 (56.4)	4.4 (−3.9 to 12.7)[c] 1.20 (0.9 to 1.7)[d]	– 1.14 (0.8 to 1.6)[d]	164/268 (61.2)	141/246 (57.3)	3.9 (−4.6 to 12.4)[c] 1.17 (0.8 to 1.7)[d]	– 1.09 (0.7 to 1.6)[d]
Parental stress (PSS:PICU) score,[g] mean ± SD	1.8 ± 0.7 (*n* = 153)	1.8 ± 0.8 (*n* = 129)	0.0 (−0.1 to 0.2)[f]	0.07 (−0.1 to 0.3)[f]	1.8 ± 0.7 (*n* = 150)	1.8 ± 0.8 (*n* = 121)	0.0 (−0.2 to 0.2)[f]	0.04 (−0.2 to 0.2)[f]

continued

TABLE 18 Step-down RCT – primary and secondary outcomes (*continued*)

Outcome	Primary analysis set				Per-protocol population			
	HFNC (*N* = 281)	CPAP (*N* = 272)	Unadjusted effect estimate (95% CI)	Adjusted effect estimate (95% CI)[a]	HFNC (*N* = 271)	CPAP (*N* = 252)	Unadjusted effect estimate (95% CI)	Adjusted effect estimate (95% CI)[a]
Duration of PICU stay, mean ± SD, days	6.6 ± 13.4 (*n* = 276)	6.9 ± 16.0 (*n* = 265)	−0.2 (−2.7 to 2.2)[f]	−0.56 (−3.0 to 1.9)[f]	6.6 ± 13.4 (*n* = 266)	6.9 ± 16.4 (*n* = 246)	−0.3 (−2.9 to 2.3)[f]	−0.76 (−3.3 to 1.8)[f]
Duration of acute hospital stay, mean ± SD, days	20.6 ± 35.3 (*n* = 275)	20.6 ± 34.5 (*n* = 257)	−0.0 (−5.9 to 5.8)[f]	−1.01 (−6.9 to 4.8)[f]	20.3 ± 35.4 (*n* = 265)	20.9 ± 35.6 (*n* = 239)	−0.6 (−6.5 to 5.4)[f]	−1.95 (−8.0 to 4.2)[f]
Mortality								
At PICU discharge, no./total no. (%)	5/277 (1.8)	3/267 (1.1)	0.7 (−1.3 to 2.7)[c] 1.62 (0.4 to 6.8)[d]	– 2.69 (0.5 to 15.4)[d]	5/267 (1.9)	1/247 (0.4)	1.5 (−0.3 to 3.3)[c] 4.69 (0.5 to 40.5)[d]	– 4.79 (0.5 to 44.4)[d]
At day 60, no./total no. (%)	11/270 (4.1)	3/256 (1.2)	2.9 (0.2 to 5.6)[c] 3.58 (1.0 to 13.0)[d]	– 5.99 (1.2 to 28.7)[d]	11/260 (4.2)	1/239 (0.4)	3.8 (1.2 to 6.4)[c] 10.51 (1.3 to 82.1)	– 10.75 (1.3 to 86.6)
At day 180, no./total no. (%)	15/268 (5.6)	6/253 (2.4)	3.2 (−0.1 to 6.6)[c] 2.44 (0.9 to 6.4)[d]	– 3.07 (1.1 to 8.8)[d]	15/258 (5.8)	4/236 (1.7)	4.1 (0.8 to 7.4)[c] 3.58 (1.2 to 10.9)[d]	– 3.71 (1.2 to 11.7)[d]

a Adjusted for pre-baseline factors of age (< 12 months vs. ≥ 12 months), SpO_2 : FiO_2 ratio, comorbidities (none vs. neurological/neuromuscular vs. other), length of prior IMV (< 5 days vs. ≥ 5 days), reason for IMV (cardiac vs. other) and site (using shared frailty). We did not adjust for severity of respiratory distress (severe vs. mild/moderate), as originally planned, due to low numbers in the 'severe' group.
b Hazard ratio.
c Absolute difference.
d OR.
e COMFORT Behavior Scale Scores range 5–30, scores ≤ 11 indicate oversedation and ≥ 23 undersedation.
f Difference in means.
g PSS:PICU scores range from 1 to 5 (not stressful to extremely stressful).

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TABLE 19 Step-down RCT – breakdown of the duration of invasive and NRS prior to liberation in the primary analysis set

Characteristic	HFNC (*N* = 281)	CPAP (*N* = 272)
Time to liberation from respiratory support, median (95% CI), hours	50.5 (43.0 to 67.9)	42.9 (30.5 to 48.2)
Time to liberation from respiratory support, mean (SD), hours	114 (193)	100 (175)
HFNC		
Duration in those receiving HFNC, median (IQR), hours (*n*)	24 (12–50), (*n* = 274)	36 (18–75), (*n* = 86)
Duration in all patients, mean (SD), hours	50 (116)	21 (64)
CPAP		
Duration in those receiving CPAP, median (IQR), hours (*n*)	29 (8–64), (*n* = 86)	15 (5–36), (*n* = 256)
Duration in all patients, mean (SD), hours	19 (61)	32 (63)

TABLE 19 Step-down RCT – breakdown of the duration of invasive and NRS prior to liberation in the primary analysis set (*continued*)

Characteristic	HFNC (*N* = 281)	CPAP (*N* = 272)
Other NRS		
Duration in those receiving other NRS, median (IQR), hours (*n*)	42 (18–108), (*n* = 39)	29 (8–72), (*n* = 43)
Duration in all patients, mean (SD), hours	10 (45)	10 (45)
IMV		
Duration in those receiving IMV, median (IQR), hours (*n*)	90 (54–216), (*n* = 55)	113 (66–201), (*n* = 42)
Duration in all patients, mean (SD), hours	27 (76)	31 (114)
No respiratory support prior to liberation		
Duration in those receiving a period of no respiratory support, median (IQR), hours (*n*)	6 (6–12), (*n* = 194)	6 (6–12), (*n* = 201)
Duration in all patients, mean (SD), hours	8 (13)	8 (13)

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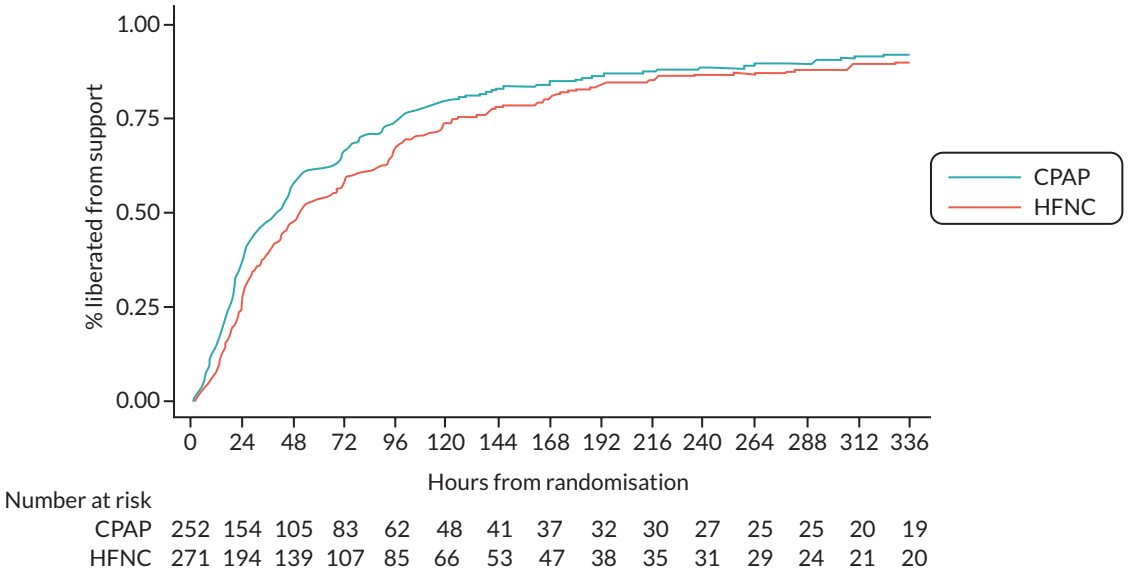

FIGURE 20 Step-down RCT – time to liberation from respiratory support in the per-protocol population. Reproduced with permission from Ramnarayan *et al.*[32] Copyright © 2022 JAMA. All rights reserved.

Total costs (GB£)

Table 22 reports total costs per patient up to 6 months post randomisation. For both randomised groups, costs of the index hospital stay account for a major share of total costs associated with the provision of HFNC and CPAP in this population, accounting for up to 75% and 71%, respectively, of the total cost at 6 months. Within the index admission, costs in the critical care unit were lower in the HFNC compared to CPAP group (£11,755 vs. £12,592), and higher that than those of general medical ward costs. The re-admission costs were lower in the HFNC group than in the CPAP group. The re-admission costs of stays in general medical wards were higher than the costs of stays in critical care units for both randomised groups. The costs of outpatient visits and community healthcare services were lower in the HFNC group than in the CPAP group (£984 vs. £1013). The mean total costs per patient were lower in the HFNC group (£28,275) compared to the CPAP group (£30,303).

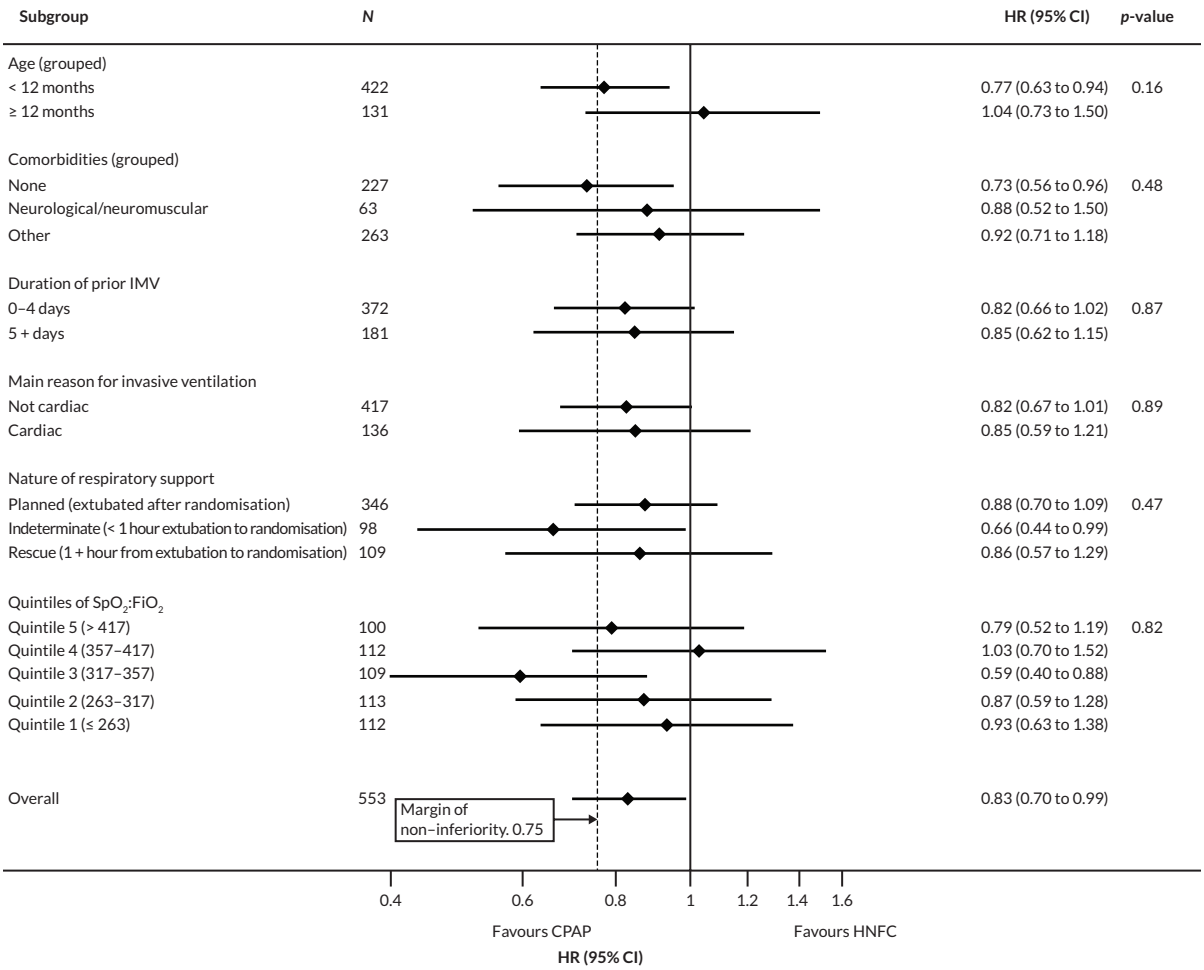

FIGURE 21 Step-down RCT – subgroup analyses of the primary outcome in the primary analysis set. Reproduced with permission from Ramnarayan *et al.*[32] Copyright © 2022 JAMA. All rights reserved.

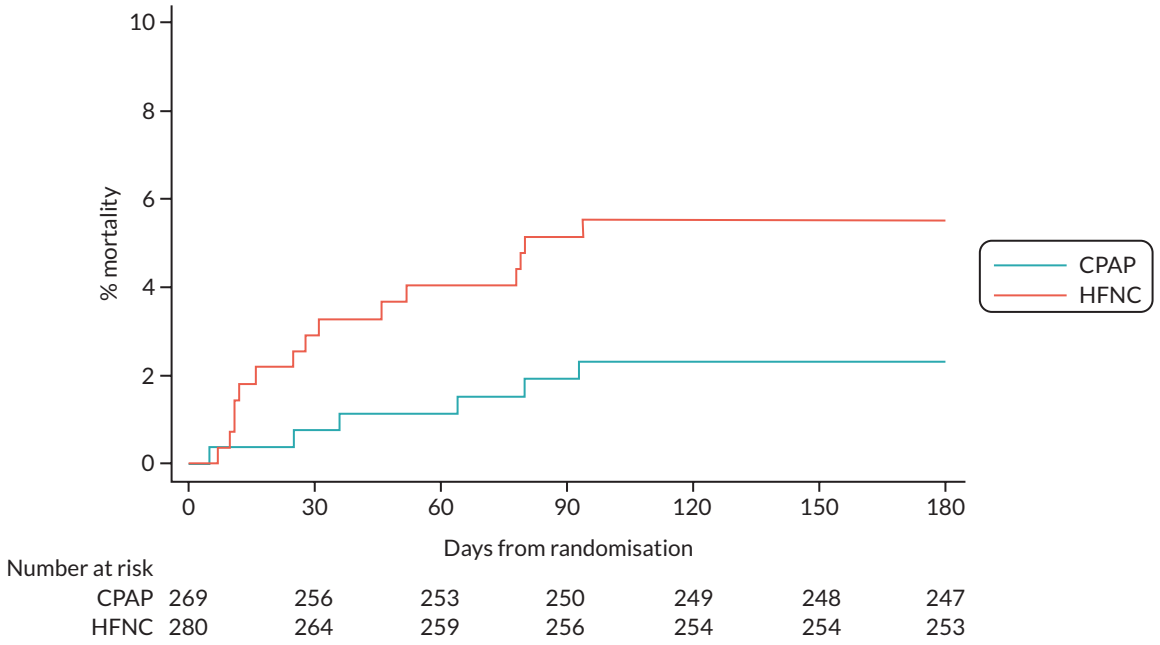

FIGURE 22 Step-down RCT – Kaplan–Meier survival curve in the primary analysis set. Reproduced with permission from Ramnarayan *et al.*[32] Copyright © 2022 JAMA. All rights reserved.

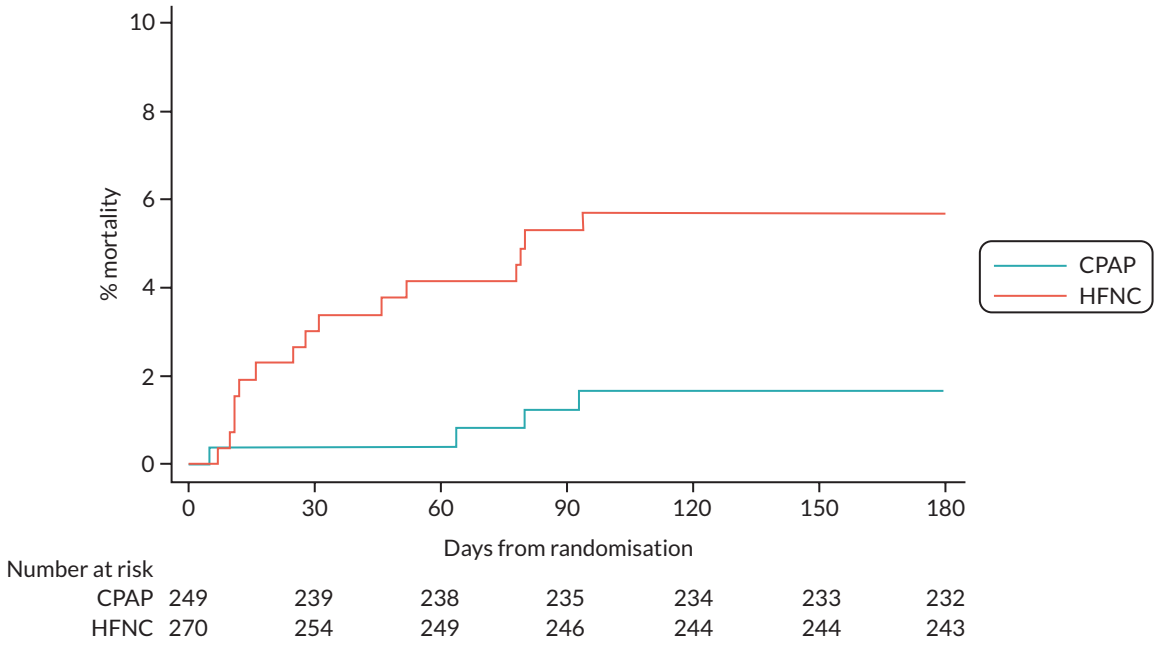

FIGURE 23 Step-down RCT – Kaplan–Meier survival curve in the per-protocol population. Reproduced with permission from Ramnarayan *et al.*[32] Copyright © 2022 JAMA. All rights reserved.

TABLE 20 Step-down RCT – summary of AEs and SAEs

Event	HFNC (*N* = 281)	CPAP (*N* = 272)	*p*-value
AE			
Nasal trauma	6 (2.1)	7 (2.6)	
Facial/neck trauma	8 (2.8)	8 (2.9)	
Abdominal distension	8 (2.8)	7 (2.6)	
Pneumothorax	2 (0.7)	2 (0.7)	
Respiratory arrest	2 (0.7)	2 (0.7)	
Cardiac arrest	1 (0.4)	3 (1.1)	
Aspiration	3 (1.1)	2 (0.7)	
Other	2 (0.7)	2 (0.7)	
Any one or more event	25 (8.9)	28 (10.3)	0.665
SAE			
Nasal trauma	0 (0.0)	0 (0.0)	
Facial/neck trauma	0 (0.0)	0 (0.0)	
Abdominal distension	0 (0.0)	0 (0.0)	
Pneumothorax	1 (0.4)	0 (0.0)	
Respiratory arrest	2 (0.7)	2 (0.7)	
Cardiac arrest	1 (0.4)	3 (1.1)	
Aspiration	2 (0.7)	1 (0.4)	
Other	1 (0.4)	1 (0.4)	
Any one or more event	5 (1.8)	5 (1.8)	

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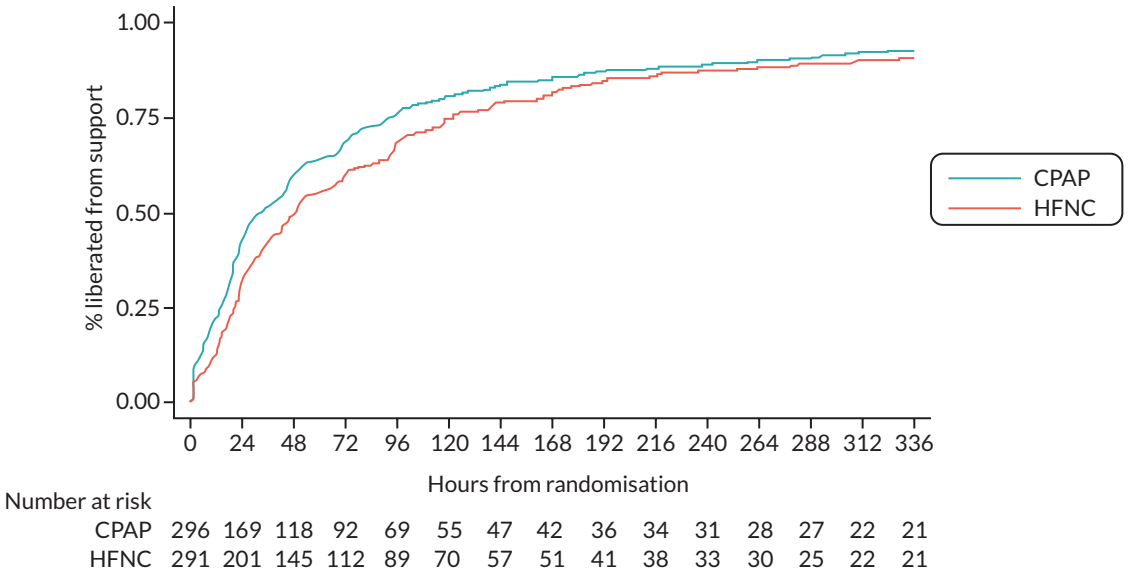

FIGURE 24 Step-down RCT – time to liberation from respiratory support – post hoc sensitivity analysis in all randomised children including those who were not started on respiratory support. a, To enable the inclusion of all randomised patients we assigned a minimal time to liberation of 2 hours in those who did not start any respiratory support following randomiation, and repeated the primary analysis. Reproduced with permission from Ramnarayan *et al.*[32] Copyright © 2022 JAMA. All rights reserved.

TABLE 21 Step-down RCT – resource use up to 6 months

	HFNC (*n* = 254)	CPAP (*n* = 228)
Index admission		
Days in PICU/HDU[a,b]	7.43 (13.73)	7.88 (16.38)
Days in general medical ward[a]	11.63 (23.77)	10.72 (22.86)
Re-admission		
N (%) re-admission to PICU/HDU	18 (7.09)	11 (4.82)
N (%) to general medical ward	100 (39.37)	84 (36.84)
Days in PICU/HDU[a]	0.65 (3.08)	1.32 (8.85)
Days in general medical[a,c]	7.11 (12.11)	8.57 (17.06)
Total length of stay up to 6 months[a,c]	26.82 (33.08)	28.49 (37.30)

a Data censored at 180 days.
b Including admissions to PICU/HDU following initial discharge to the ward.
c Following multiple imputation to handle missing resource use data.

Note
All numbers are mean (SD) unless stated otherwise.

TABLE 22 Step-down RCT – costs (GB£) up to 6 months, mean (SD)

	HFNC (*n* = 254)	CPAP (*n* = 228)
Hospital costs		
Index admission		
PICU/HDU	11,755 (24,766)	12,592 (30,808)
General medical ward	9352 (19,112)	8799 (18,706)
Re-admission[a]		

TABLE 22 Step-down RCT – costs (GB£) up to 6 months, mean (SD) (*continued*)

	HFNC (*n* = 254)	CPAP (*n* = 228)
PICU/HDU	735 (4951)	1335 (11,342)
General medical ward	5449 (9273)	6565 (13,068)
Outpatient and community costs[b]	984 (897)	1013 (1012)
Total costs up to 6 months[a,b]	**28,275 (36,668)**	**30,303 (42,710)**

a Following multiple imputation to handle missing resource use data: FIRST-ABC Study and PICANet database.
b Following multiple imputation to handle missing resource use data: HSQ.

Health-related quality of life

The health status profiles reported from responses to the PedsQL questionnaires administered at 6 months post randomisation are summarised by randomised group in *Table 23*. The mean overall scores across the four PedsQL dimensions were similar between HFNC and CPAP patients (79 vs. 81 in the physical dimension, 71 vs. 73 in the emotional dimension, 89 vs. 89 in the social dimension, and 79 vs. 77 in the school functioning dimension). The mean total PedsQL scores at 6 months were high in both randomised groups (77 and 79 in HFNC and CPAP group, respectively).

The mean mapped CHU-9D utility scores at 6 months were similar between the randomised groups (*Table 24*). At 6 months, HFNC compared to CPAP group had lower life-years. The resultant mean QALYs at 6 months were slightly lower in the HFNC (0.218) compared to CPAP (0.227) group.

Cost-effectiveness

The unadjusted incremental cost of HFNC compared to CPAC was −£2028, and this estimate was surrounded by a wide 95% CI that included zero (*Table 25*). After adjustment for baseline characteristics, the estimated incremental cost of HFNC compared to CPAP was −£4565, but the 95% CI around it was wide. HFNC compared to CPAP results in fewer life-years and QALYs at 6 months, but the magnitude of the effect on both end points was small. The cost-effectiveness plane shows that the majority of points representing mean incremental costs and mean incremental QALYs are in the third (south-west) quadrant of the cost-effectiveness plane, indicating that HFNC had lower mean QALYs and lower costs (*Figure 25*). The INB for HFNC versus CPAP was positive, but there is considerable statistical uncertainty around INB; at £20,000 per QALY, the INB from adjusted analysis was £4388 (95% CI −£2551 to £11,307).

The results of the subgroup analyses presented in *Report Supplementary Material 14* show that the INBs were similar across all subgroups. For the neurological/neuromuscular, cardiac and SF ratio (quintile 2) subgroups, mean INB associated with HFNC versus CPAP was positive. For all subgroups, as for the overall results, the 95% CIs around the INB included zero.

Report Supplementary Material 15 reports the mean INB and 95% CI around it (at £20,000 per QALY gain) according to alternative assumptions, compared with the base case (first row). The INB estimates remain around the base-case INB (£4388), whether analysis sample is ITT, or alternative assumption for costs (intervention costs irrespective of location, follow-up costs from HES database, 10% increase or decrease in unit costs), alternative mapping algorithm for CHU-9D, and alternative analysis model is considered (complete case analysis, gamma distribution for costs and QALYs, and multilevel model). These sensitivity analyses showed that the results were robust to alternative scenarios.

TABLE 23 Step-down RCT – PedsQL score at 6 months, mean (SD)

	HFNC (*n* = 114)	CPAP (*n* = 75)
PedsQL dimension		
Physical score[a]	79 (14)	81 (16)
Emotional score[a]	71 (18)	74 (17)
Social score[a]	89 (15)	89 (18)
School score[a]	79 (22)	77 (23)
CHU-9D utility score[a]	77 (13)	79 (14)

a Only reported for patients who were alive and completed the follow-up questionnaires at 6 months post randomisation.

TABLE 24 Step-down RCT – CHU-9D utility score, life-years and QALYs up to 6 months, mean (SD)[a]

	HFNC (*n* = 254)	CPAP (*n* = 228)
CHU-9D utility score (survivors)	0.920 (0.045)	0.919 (0.053)
Life-years	0.473 (0.086)	0.490 (0.030)
QALY	0.218 (0.052)	0.227 (0.027)

a The CHU-9D, life-years and QALY results are all reported after applying multiple imputation to handle missing data.

TABLE 25 Step-down RCT – cost-effectiveness at 6 months: total costs (£ GB), CHU-9D utility score, life-years, QALYs and INB

	HFNC (*n* = 254)	CPAP (*n* = 228)	Incremental effect (unadjusted) mean (95% CI)	Incremental effect (adjusted)[a] mean (95% CI)
Costs (£)	28,275 (36,668)	30,303 (42,710)	−2028 (−9223 to 5166)	−4565 (−11,499 to 2368)
CHU-9D utility score (survivors)	0.920 (0.045)	0.919 (0.053)	0.002 (−0.011 to 0.015)	0.002 (−0.011 to 0.015)
Life-years	0.473 (0.086)	0.490 (0.030)	−0.017 (−0.029 to −0.005)	−0.017 (−0.029 to −0.005)
QALY	0.218 (0.052)	0.227 (0.027)	−0.009 (−0.017 to −0.001)	−0.009 (−0.017 to −0.001)
INB (GBP)[b]			1845 (−5362 to 9052)	4388 (−2551 to 11,327)

a The incremental effects are reported after applying case-mix adjustment.
b The INB is calculated according to NICE methods guidance, by multiplying the mean QALY gain (or loss) by £20,000, and subtracting from this the incremental cost.

Note
The cost, CHU-9D, life-years, QALY and INB results are all reported after applying multiple imputation to handle missing data.
All numbers are mean (SD), unless stated otherwise.

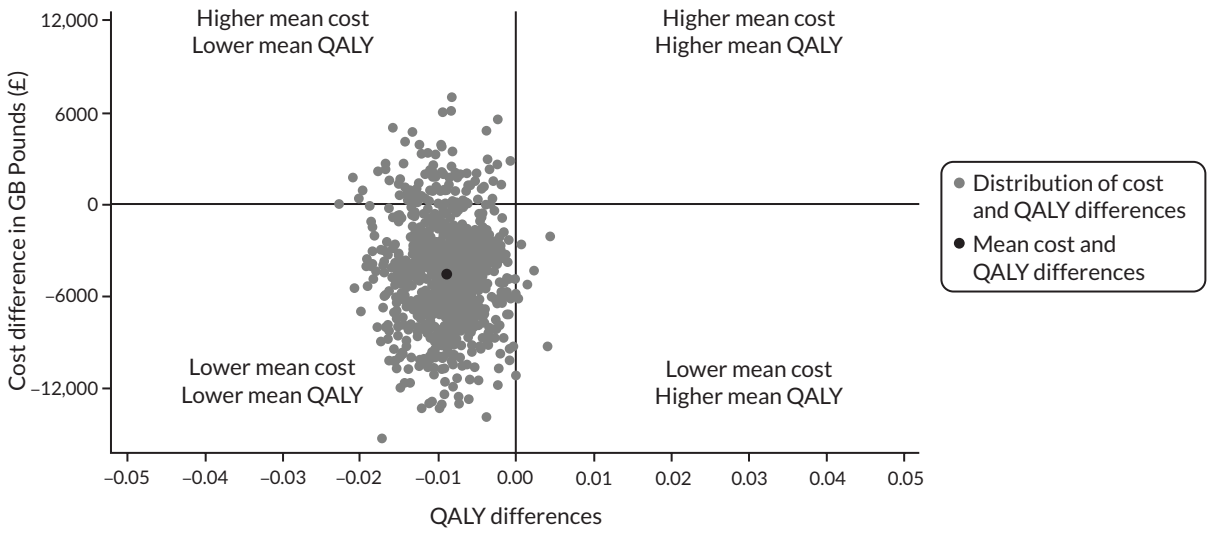

FIGURE 25 Step-down RCT – uncertainty in the mean costs (GB£) and QALY differences and their distribution for HFNC vs. CPAP (within 6 months post randomisation).

Chapter 5 Discussion

Key findings and interpretation

Each of the FIRST-ABC trials in the master protocol recruited 600 children. There was minimal loss to follow-up – the primary analysis in each of the trials included over 92% of randomised children.

Step-up randomised controlled trial

In the step-up RCT, HFNC was shown to be non-inferior to CPAP (i.e. it was not worse than the preset non-inferiority margin) in acutely ill children in whom the treating clinician had decided to start NRS. The median time to liberation from all forms of respiratory support (primary outcome) was 5 hours longer for HFNC compared with CPAP (CIs ranged from 10 hours longer to 17 hours shorter). However, sedation use was lower with HFNC (28% vs. 37%), mean PICU length of stay was shorter (5 days vs. 7.4 days) and mean hospital length of stay was also shorter (13.8 days vs. 19.5 days). The main findings were robust to sensitivity analyses.

In subgroup analyses, HFNC appeared to be non-inferior in all subgroups classified by age (< 12 months vs. ≥ 12 months), diagnosis (bronchiolitis vs. other respiratory illness vs. cardiac vs. other diagnosis), severity of oxygenation defect (SpO_2 : FiO_2 ratio) and degree of respiratory distress (severe vs. not severe), although these remain exploratory findings since the trial was not designed to detect subgroup effects. In children already receiving NRS at randomisation, however, the non-inferiority of HFNC was unable to be demonstrated (the lower CI of the HR was 0.73, lower than the preset non-inferiority margin). This may reflect the higher severity of illness in children already started on NRS prior to randomisation, suggesting that HFNC may not be non-inferior to CPAP in the subgroup of sicker children.

A third of children started on HFNC required rescue treatment(s), which occurred at a median of 6 hours after starting HFNC. A switch to CPAP was the most common rescue treatment, mainly for clinical deterioration on HFNC.

Step-down randomised controlled trial

In the step-down RCT, in children receiving NRS within 72 hours of extubation, the non-inferiority of HFNC was not demonstrated compared to CPAP (i.e. it was worse than the preset non-inferiority margin). The median time to liberation from all forms of respiratory support (primary outcome) was 8 hours longer for HFNC, with CIs ranging from 20 hours longer to 4 hours shorter. Reintubation rate was similar for HFNC versus CPAP (13.3% vs. 11.5%), as was use of sedation (60.9% vs. 56.4%) and duration of PICU stay (6.6 days vs. 6.9 days). However, there was higher mortality at 180 days in the HFNC group (5.6% vs. 2.4%), which was not explained by differences in patient characteristics. Although this was a secondary outcome, and the trial was not powered to detect differences in secondary outcomes, this finding requires further research. Potential explanations for this finding include the fact that deteriorating children may be supported for longer on HFNC outside the critical care unit, resulting in more physiological derangement and that there might have been a differential impact of previous physiological derangement associated with invasive ventilation. The main findings were robust to sensitivity analyses.

Non-inferiority of HFNC could not be demonstrated in any subgroups classified by age (< 12 months vs. ≥ 12 months), reason for ventilation (non-cardiac vs. cardiac), severity of oxygenation defect (SpO_2 : FiO_2 ratio) and duration of prior ventilation (0–4 days vs. > 4 days). There was a suggestion of non-inferiority of HFNC in older children (age ≥ 12 months), with the lower confidence limit of a HR of 0.73 close to the preset non-inferiority margin of 0.75 (although a HR of 0.73 still represented at least 16 hours longer for time to liberation from HFNC compared with CPAP); however, these remain exploratory findings since the trial was not designed to detect subgroup effects.

One-third of children started on CPAP required rescue treatment(s) after a median of 8 hours of treatment, mainly a switch to HFNC due to discomfort.

Cost-effectiveness analyses

The main finding from the CEA of both step-up and step-down RCTs is that on average HFNC compared to CPAP reduces costs and improves QALYs by a small magnitude, which leads to positive INB, but there is considerable statistical uncertainty surrounding the cost-effectiveness results. The results of the cost-effectiveness analyses should be interpreted carefully, taking the small QALY gains and uncertainty around the cost-effectiveness analyses into account. The CEA results for the prespecified subgroups are similar to the overall results. The sensitivity analysis finds that this conclusion is robust to alternative assumptions to those made in the base-case analysis.

Findings in context

Other than the FIRST-ABC step-down RCT, there are no other clinical trials comparing modes of post-extubation respiratory support. In acutely ill children, a few small RCTs were published during the time the FIRST-ABC step-up RCT comparing HFNC with CPAP was recruiting – these RCTs were included in a systematic review published in 2021[61] (prior to the publication of the FIRST-ABC trial findings in 2022). Compared to CPAP, HFNC had a significantly higher risk of treatment failure [relative risk (RR) 1.45, 95% CI 1.06 to 1.99; I^2 = 0.0%, n = 6 RCTs]. The need for intubation was similar (RR 1.69, 95% CI 0.97 to 2.94; I^2 = 0.0%, n = 5 RCTs). In contrast, we found a higher rate of treatment failure for CPAP, although this was mainly for patient discomfort reasons rather than clinical deterioration. This may also relate to the fact that the systematic review only included children under the age of 2 years, whereas patient discomfort with CPAP is greater in older children.

The baseline characteristics of the children included in the FIRST-ABC step-up RCT were similar to those in other previous RCTs, especially in the subgroup of children with bronchiolitis. In FIRST-ABC, almost 65% of the children had a respiratory rate greater than the 90th centile value for their age; in infants under the age of 1, the 90th centile value ranged from 50 to 55 breaths per minute. In contrast, the mean respiratory rate in the TRAMONTANE trial comparing HFNC with CPAP in infants aged < 6 months with severe bronchiolitis was 53 breaths per minute.[62] Similarly, in a large observational data set of infants with bronchiolitis from the USA, 75% of the respiratory rate values at initiation of HFNC or CPAP were > 50 per minute.[63] Participants in the FIRST-ABC step-up RCT were also sick even though inclusion criteria were pragmatic and based on clinical decision to start some form of respiratory support: just over 40% of children in both groups had significant hypoxaemia (pulse oximetry oxyhaemoglobin saturation to fractional inspired oxygen ratio < 265, corresponding to the definition of acute lung injury).

In the step-down RCT, the Consolidated Standards of Reporting Trials diagram shows that out of 3121 children extubated in the participating PICUs during the trial, 1421 (45%) were started on some form of NRS. In comparison, in a multicentre cohort of extubated infants with bronchiolitis from the USA, post-extubation NRS was started in 783/1765 infants (43.7%),[64] and in a single-centre study of 514 postcardiac surgery infants after extubation, 260 (50%) were started on NRS, reflecting that practice during the FIRST-ABC step-down RCT was comparable to practice in other settings.

Previous systematic reviews had shown that patients receiving HFNC had a lower risk of AEs, mainly nasal trauma.[61] These findings were corroborated in the FIRST-ABC step-up RCT, where nasal trauma occurred in 2% of patients started on HFNC and 6.5% of patients started on CPAP.

The main finding when the two trials were compared side by side was that they showed different results. The population of acutely ill children requiring NRS was different from the children requiring post-extubation NRS, and the effect of HFNC versus CPAP treatment was also different. This was shown in the FIRST-ABC pilot RCT,[40] which is one of the main reasons why we chose to run the two trials separately within a master protocol. For example, compared with acutely ill children, extubated children were younger (many of whom were post-surgical infants), had received several days of invasive ventilation, and were still weaning off their sedative agents, all factors that might be expected to alter the balance of risks and benefits of HFNC and CPAP.

Reporting equality, diversity and inclusion

The population of patients that are seen in UK PICUs is diverse, and we sought to ensure that this diversity was reflected in the FIRST-ABC trials. The eligibility criteria for the trials were designed to be inclusive and pragmatic, only excluding patients where there was a clear contra-indication or indication for either HFNC or CPAP (e.g. patients with midfacial/craniofacial anomalies).

We monitored the representativeness of the study population by reviewing data on key characteristics, including age, sex, geographic region and ethnicity. With regard to ethnicity, both RCTs had good representation of patients from an ethnic minority background, in line with the ethnic distribution seen in clinical practice. However, ethnicity data were sourced via data linkage to HES and, accordingly, were missing for 26% (step-up RCT) and 32% (step-down RCT) of patients. Future studies might improve on this by collecting ethnicity data via multiple data sources to ensure completeness. Across the FIRST-ABC RCTs, the vast majority of PICUs across the UK were included; however, we note that we had no sites based in Northern Ireland and therefore this region of the UK was not represented.

Language barriers are a potential factor that can limit participation in research at the outset. This barrier was reduced in FIRST-ABC through use of a deferred consent model. This model allowed research teams to aim to enrol all eligible patients, regardless of language spoken, and then follow up at a later appropriate time, with the assistance of locally available translation services. However, it must be noted that availability of translation services varied significantly across sites. Future studies could improve on these efforts by offering a range of translated study documents to participants (noting additional cost and difficulty in predicting which languages will be required). Obtaining consent also appeared more challenging in situations where patients were under the care of local authorities – further guidance on deferred consent for research in these circumstances would be useful to ensure such patients can be included in research.

Strengths and limitations

Strengths

FIRST-line support for Assistance in Breathing in Children was a set of two pragmatic trials, set in a real-world context. They represent the largest RCTs on the topic of paediatric non-invasive breathing support, where the pre-existing evidence base was poor. The master protocol included children receiving NRS in two important clinical scenarios, during step-up treatment in acutely ill children and during step-down treatment in children following extubation from invasive ventilation. This provided an efficient way to answer the research question in two key populations within a common trial infrastructure.

The findings from the trials are generalisable to the NHS, since the vast majority of PICUs in the UK participated (24 critical care units in the step-up RCT and 22 PICUs in the step-down RCT). The age, sex and ethnic distribution of FIRST-ABC trial participants are similar to that of the overall UK PICU population reported by the PICANet national audit report,[2] providing confidence that there were no sex/ethnic/racial barriers to being included in the trial. For example, in 2018, 50.5% of patients admitted to UK PICUs receiving respiratory support were infants younger than 1 year (compared to 56% in the step-up trial).

In addition, practice during the FIRST-ABC trial was similar to previous audits of clinical practice, attesting to the generalisability of the trial findings to routine practice. Observational data from UK PICUs in 2015–6 had shown that nearly 20% of admissions received HFNC or CPAP as first-line NRS;[65] in the FIRST-ABC step-up trial, out of 18,976 admissions to participating PICUs during the study period, 3825 (20%) met inclusion criteria and were started on some form of NRS.

Patient recruitment was rapid and followed target timelines, especially in the step-down RCT, in which the 600 participants were recruited in < 9 months (as opposed to projected 15-month recruitment). The step-down RCT completed recruitment in May 2020, just after the first COVID-19 lockdown. On the other hand, the step-up RCT recruited through the COVID-19 pandemic, and despite the loss of nearly 6 months of recruitment time on average across sites, managed to complete recruitment in 27 months (as opposed to projected 30 months). This was enabled through good clinical buy-in and the ability of participating sites to embed delivery of the trial into routine clinical practice, allowing randomisation to be carried out 24 hours per day, 7 days per week. The simplicity of the web/telephone randomisation process, with only minimal information needed at the point of randomisation, the use of a research without prior consent model which meant that recruitment could be undertaken in an emergency, and the pragmatic nature of the trial, with trial procedures reflecting clinical practice as far as possible, were other factors contributing to rapid patient recruitment.

Both the protocol and statistical analysis plan were published during the recruitment period to ensure transparency, and all analyses were conducted following the analysis plan. Planned sensitivity analyses were also conducted, which evaluated different definitions of time to liberation, and a post hoc sensitivity analysis to include all randomised patients irrespective of whether they started respiratory support or not was carried out.

From the point of view of the economic evaluation, this study included prospectively designed economic evaluation integrated with well-designed step-up and step-down RCTs, which ensured that detailed resource use and health economic outcome data were collected for each patient randomised. The resource use measurement harnessed information from four linked sources – data from trial CRFs linked to the PICANet database, responses to follow-up health service questionnaires and HES database. The cost measurement utilised the detailed patient-level information from PICANet database on the intensity of resource use for each day in the paediatric critical unit. The CEA also measured HRQoL with the age-appropriate PedsQL instruments.

Paediatric Quality of Life Inventory is a widely used measure of HRQoL among children and adolescents, but the PedsQL scores cannot be directly used to calculate QALYs for the application in economic evaluation because it produces summary scores which are not preference-based. We have mapped the PedsQL to CHU-9D utility score using appropriate mapping algorithms, which provides a preference-based HRQoL score for calculating QALYs that can be used in the application of economic evaluation. The CEA followed the mITT principle and reported results for all patients randomised in the RCT. There were some missing data in the 6 months follow-up of HRQoL and costs, which were imputed using the recommended MICE approach. The study followed a harmonised and prespecified statistical and economic analysis plan, allowing for consistent approach for analysis of clinical and health economic end points. Detailed subgroup analysis was performed, and the cost-effectiveness results were similar across all subgroups. Extensive sensitivity analyses were performed, and the base-case results were not sensitive to alternative assumptions.

Limitations

The main limitation of the trials was the fact the intervention and control treatments could not be blinded. This lack of blinding may have influenced decisions to switch or escalate treatment or to start respiratory support at all. This was highlighted in the step-up RCT in the high rate of switching from CPAP to HFNC for perceived patient discomfort, and a larger than anticipated number of patients in the CPAP group who did not start any respiratory support after randomisation.

The pragmatic inclusion criteria resulted in a heterogeneous population of acutely ill children, mostly younger than 2 years, and although prespecified subgroup analyses based on age, diagnosis and receipt of prior NRS were performed, there may be other unidentified subgroups (e.g. children aged ≥ 10 years) for whom one treatment was more effective over another.

Clinician preference also meant that several children who were eligible for the trials were not randomised, and some children (especially older children randomised to CPAP in the step-up RCT) did not start any respiratory support after randomisation, which created an imbalance between the groups. Changes in clinical practice resulting in greater use of HFNC outside the critical care setting also meant that in the step-up RCT, nearly 1000 children who had received more than 2 hours of prior NRS outside critical care had to be excluded from the trial. Data related to feeding were not collected as part of the trial; therefore, it was not possible to assess the effect of feeding on patient comfort in either of the trials.

In the post-extubation setting, there was a low threshold for starting non-invasive support, with nearly 50% of extubated children receiving some form of support. It was not possible to understand the reasons for this practice; specifically, we did not collect ventilation data, such as mean airway pressure at randomisation, which might have indicated why clinicians chose to start NRS in some patients and not others.

Cost-effectiveness analysis can be challenging in young children who are unable to respond to questionnaires themselves; in addition, the questionnaires used commonly (such as PedsQL) need mapping to CHU-9D. Our CEA presented results for the same prespecified subgroups as for the analysis of clinical effectiveness. The results of these

subgroup analyses suggested that the point estimate of the INB was positive for some subgroups and negative for others, but that the CIs around each of these estimates were wide and included zero. In interpreting these findings, it should be recognised that this study was not powered to detect subgroup effect for either clinical effectiveness or cost-effectiveness end points, and hence the subgroup results should be regarded as exploratory.

Implications for practice

Acutely ill children

Other than a handful of small RCTs, mainly from low-middle income settings, there has been a paucity of research to guide clinical practice regarding breathing support in acutely ill children. Previous RCTs have focused on short-term outcomes, such as treatment failure rather than on patient-centred outcomes, such as time to liberation from respiratory support.

Findings from the FIRST-ABC step-up trial indicate that starting an acutely ill child on NRS using HFNC is a reasonable first-line option. It should be expected however that around one in three children will fail HFNC, mainly due to clinical deterioration, and require a switch to CPAP or escalation to other forms of respiratory support, including invasive ventilation (which occurred in one in seven children). Clinicians should expect treatment failure to occur on average 6 hours after starting HFNC treatment.

Following extubation

There have been no previous randomised trials comparing different modes of NRS following extubation.

Results of the step-down trial indicate that in the post-extubation setting, starting CPAP as the first-line mode of NRS is a reasonable option, especially in infants under the age of 1. In children over the age of one, either HFNC or CPAP is a suitable first-line option. Similar to the step-up scenario, clinicians should expect that one in three children started on CPAP will fail, mainly due to patient discomfort with CPAP. Treatment failure in this situation occurred on average 8 hours after starting CPAP.

Recommendations for research

Recommendation 1

Since the trials enrolled a heterogeneous population of children and their trajectory after starting the first-line mode of NRS was variable, further analyses exploring which baseline patient characteristics and patterns of evolving physiological parameters can predict treatment failure, intubation and prolonged time to liberation from respiratory support constitute important areas of future research.

Recommendation 2

The relatively high proportion of extubated children in whom clinicians started NRS following extubation (45%) highlights that developing and testing the utility of protocolised approaches regarding when and which children to start post-extubation respiratory support in future clinical trials is an important area of further research.

Recommendation 3

The results from the prespecified subgroup analyses raise the hypothesis that there may be some subgroups (e.g. cardiac patient subgroup in both step-up and step-down RCTs) for whom HFNC intervention is cost-effective, compared to CPAP. Further research could evaluate clinical and cost-effectiveness of targeted interventions to subgroups who are admitted to paediatric critical care unit for cardiac reasons.

Recommendation 4

Reasons for the unexpected finding of higher mortality at 180 days in the HFNC group in the step-down RCT need to be explored further in future research.

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Patient data statement

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that they are stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Please note exclusive use will be retained until the publication of major outputs. Access to anonymised data may be granted following review.

Ethics statement

FIRST-line support for Assistance in Breathing in Children was granted ethical approval by the East of England – Cambridge South Research Ethics Committee (reference: 19/EE/0185) and approval from the Health Research Authority (reference: 260536) on 26 July 2019.

Information governance statement

Intensive Care National Audit & Research Centre is committed to handling all personal information in line with the UK Data Protection Act (2018) and the General Data Protection Regulation (EU GDPR) 2016/679.

Under the Data Protection legislation Intensive Care National Audit & Research Centre is Joint Data Controller with Great Ormond Street Hospital for Children NHS Foundation Trust, who are the sponsor. You can find out more about how ICNARC handles personal data, including how to exercise your individual rights and the contact details for our Data Protection Officer here: www.icnarc.org/About/Information-Standards/Information-Security/Data-Protection

Disclosure of interests

Full disclosure of interests: Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at https://doi.org/10.3310/PDBG1495.

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Publications

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continuous positive airway pressure following extubation on liberation from respiratory support in critically ill children: a randomized clinical trial. *JAMA* 2022;**327**:1555–1565. https://doi.org/10.1001/jama.2022.3367. PMID: 35390113; PMCID: PMC8990361.

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Appendix 1 Unit costs (£)

Items	Unit costs	Source
Hospital costs (bed-day)		
Enhanced care	766	NHS National Benchmark price
Basic critical care	1149	NHS National Benchmark price
Intermediate critical care	1437	NHS National Benchmark price
Advanced critical care 1	1916	NHS National Benchmark price
Advanced critical care 2	2395	NHS National Benchmark price
Advanced critical care 3	2874	NHS National Benchmark price
Advanced critical care 4	3832	NHS National Benchmark price
Advanced critical care 5	5747	NHS National Benchmark price
General medical bed-day	766	NHS National Benchmark price
Outpatient and community health services		
Hospital outpatient	135	PSSRU
GP practice visit (per visit)	39	PSSRU
GP home visit (per visit)	90	PSSRU
GP nurse visit[a]	11	PSSRU
GP nurse home visit[a]	19	PSSRU
Hospital nurse[a]	10	PSSRU
Health visitor[a]	8	PSSRU
Health visitor home visit[a]	14	PSSRU
Occupational therapist[a]	9	PSSRU
Physiotherapist[a]	9	PSSRU
Psychiatrist[a]	29	PSSRU
Paediatric nurse[a]	9	PSSRU
School nurse[a]	12	PSSRU
Social worker[a]	13	PSSRU
Counsellor[a]	9	PSSRU
Speech and language therapist[a]	9	PSSRU
Dietitian[a]	9	PSSRU
Midwife[a]	9	PSSRU

a 15 minutes of consultation time.

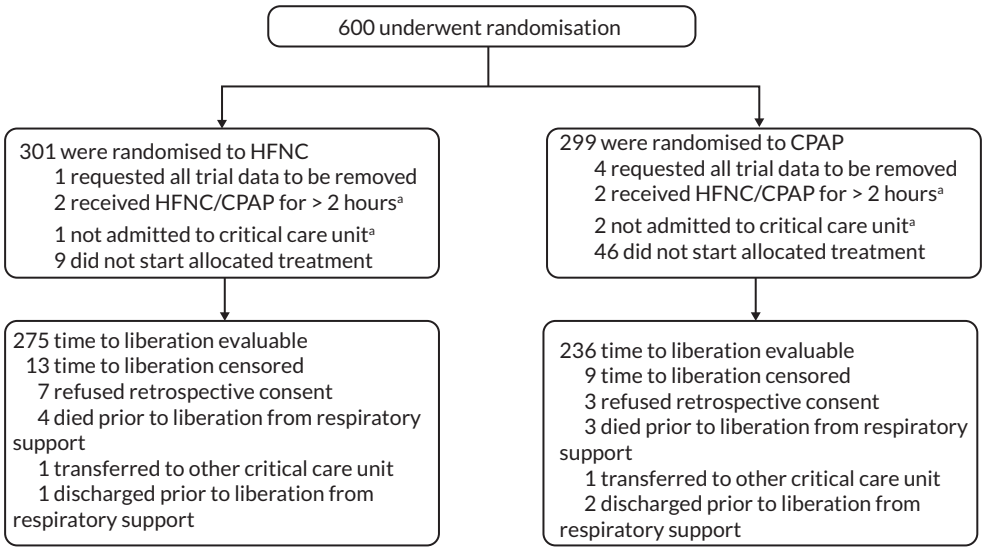
Appendix 2 Step-up randomised controlled trial – variables considered for multiple imputation and form of imputation model

Variable	Missing values, *n* (%)	Imputation model
Baseline covariates		
Allocated treatment group	0 (0)	None required
Age	0 (0)	None required
On support at randomisation	0 (0)	None required
Main reason for admission	1 (0.20)	Multinomial logit
Comorbidities	1 (0.20)	Multinomial logistic regression
SpO_2/FiO_2 ratio	12 (2.37)	Predictive mean matching
Severe respiratory distress at baseline	87 (17.19)	Logistic regression
Resource use		
Index hospital admission		
Duration of stay in the PICU/HDU	0 (0)	None required
Duration of stay in general medical ward	0 (0)	None required
Re-admissions up to 6 months		
Duration of stay in the PICU/HDU	0 (0)	None required
Duration of stay in general medical ward	315 (62.25)	Predictive mean matching
Outcomes		
Mortality	3 (0.59)	Logistic regression
CHU-9D utility score	344 (67.98)	Predictive mean matching
HSQ costs	315 (62.25)	Predictive mean matching

Appendix 3 Step-down randomised controlled trial – variables considered for multiple imputation and form of imputation model

Variable	Missing values, *n* (%)	Imputation model
Baseline covariates		
Allocated treatment group	0 (0)	None required
Age	0 (0)	None required
Reason for IMV	0 (0)	None required
Duration of prior IMV	0 (0)	None required
Comorbidities	0 (0)	None required
Planned respiratory support	0 (0)	None required
SpO_2/FiO_2 ratio	4 (< 0.1)	Predictive mean matching
Resource use		
Index hospital admission		
Duration of stay in the PICU/HDU	0 (0)	None required
Duration of stay in general medical ward	0 (0)	None required
Re-admissions up to 6 months		
Duration of stay in the PICU/HDU	0 (0)	None required
Duration of stay in general medical ward	158 (34.4)	Predictive mean matching
Outcomes		
Mortality	8 (1.7)	Logistic regression
CHU-9D utility score	270 (58.8)	Predictive mean matching
HSQ costs	230 (50.1)	Predictive mean matching

Appendix 4 Step-up randomised controlled trial – screening, randomisation and follow-up in the per-protocol population



a, Found to have met an exclusion criterion after randomisation. Reproduced with permission from Ramnarayan *et al.*[31] Copyright © 2022 JAMA. All rights reserved.

Appendix 5 Step-up randomised controlled trial – baseline characteristics in all randomised and consented children irrespective of whether respiratory support was started or not

Characteristic	HFNC (*N* = 300)		CPAP (*N* = 295)	
	Started respiratory support *n* = 295	Did not start respiratory support *n* = 5	Started respiratory support *n* = 278	Did not start respiratory support *n* = 17
Age, months				
Median (IQR)	10 (2–31)	13 (11–25)	9 (1–27)	41 (8–57)
Age (categories), no. (%)				
≤ 28 days	31 (10.5)	0 (0.0)	37 (13.3)	1 (5.9)
29–180 days	87 (29.5)	1 (20.0)	80 (28.8)	3 (17.6)
181–364 days	49 (16.6)	1 (20.0)	43 (15.5)	1 (5.9)
1 year	41 (13.9)	1 (20.0)	44 (15.8)	3 (17.6)
2 years	24 (8.1)	2 (40.0)	15 (5.4)	0 (0.0)
3 years	13 (4.4)	0 (0.0)	9 (3.2)	2 (11.8)
4 years	3 (1.0)	0 (0.0)	3 (1.1)	3 (17.6)
5–10 years	29 (9.8)	0 (0.0)	26 (7.6)	3 (17.6)
11–15 years	18 (6.1)	0 (0.0)	21 (7.6)	1 (5.9)
Sex, no. (%)				
Female	116 (39.3)	2 (40.0)	110 (39.6)	8 (47.1)
Male	179 (60.7)	3 (60.0)	168 (60.4)	9 (52.9)
Comorbidities, no. (%)				
None	152 (51.5)	3 (75.0)	149 (53.8)	6 (35.3)
At least one	143 (48.5)	1 (25.0)	128 (46.2)	11 (64.7)
Airway/respiratory	59 (20.0)	0 (0.0)	48 (17.3)	4 (23.5)
Cardiac/vascular	40 (13.6)	0 (0.0)	33 (11.9)	4 (23.5)
Neurological/neuromuscular	46 (15.6)	0 (0.0)	39 (14.0)	1 (5.9)
Congenital/genetic/syndrome	33 (11.2)	0 (0.0)	39 (14.0)	1 (5.9)
Gastro/surgical	24 (8.1)	0 (0.0)	30 (10.8)	0 (0.0)
Haematology/oncology	20 (6.8)	1 (20.0)	21 (7.6)	1 (5.9)
Metabolic/endocrine	9 (3.1)	0 (0.0)	14 (5.0)	1 (5.9)
Immunodeficiency	10 (3.4)	0 (0.0)	9 (3.2)	0 (0.0)
Prematurity	8 (2.7)	0 (0.0)	7 (2.5)	0 (0.0)
Other	17 (5.8)	0 (0.0)	11 (4.0)	2 (11.8)
Missing	0 (0.0)	1 (25.0)	1 (0.4)	0 (0.0)

continued

Characteristic	HFNC (*N* = 300)		CPAP (*N* = 295)	
	Started respiratory support *n* = 295	Did not start respiratory support *n* = 5	Started respiratory support *n* = 278	Did not start respiratory support *n* = 17
Type of admission, no. (%)	*n = 245*	*n = 4*	*n = 234*	*n = 16*
Planned, following surgery	8 (3.3)	0 (0.0)	7 (3.0)	3 (18.8)
Unplanned, following surgery	6 (2.4)	0 (0.0)	3 (1.3)	0 (0.0)
Planned, not following surgery	5 (2.0)	0 (0.0)	12 (5.1)	2 (12.5)
Unplanned, not following surgery	226 (92.2)	4 (100)	212 (90.6)	11 (68.8)
Source of admission, no. (%)	*n = 245*	*n = 4*	*n = 233*	*n = 16*
Same hospital	215 (87.8)	4 (100)	211 (90.6)	13 (81.3)
Other hospital	11 (4.5)	0 (0.0)	8 (3.4)	1 (6.3)
Home	19 (7.8)	0 (0.0)	14 (6.0)	2 (12.5)
Main reason for admission, no. (%)			*n = 277*	
Upper airway problem	15 (5.1)	0 (0.0)	12 (4.3)	0 (0.0)
Bronchiolitis	143 (48.5)	1 (20.0)	138 (49.8)	4 (23.5)
Asthma/wheeze	31 (10.5)	1 (20.0)	20 (7.2)	5 (29.5)
Other respiratory	55 (18.6)	2 (40.0)	57 (20.6)	2 (11.8)
Cardiac	17 (5.8)	0 (0.0)	12 (4.3)	3 (17.6)
Neurological	4 (1.4)	0 (0.0)	2 (0.7)	0 (0.0)
Sepsis/infection	24 (8.1)	0 (0.0)	23 (8.3)	2 (11.8)
Other	6 (2.0)	1 (20.0)	13 (4.7)	1 (5.9)
Time (minutes) on non-invasive respiratory support at randomisation, no. (%)			*n = 276*	
0	229 (77.6)	-	213 (77.2)	-
1–30	24 (8.1)	-	13 (4.7)	-
31–60	21 (7.1)	-	20 (7.2)	-
61–90	9 (3.1)	-	16 (5.8)	-
91–120	10 (3.4)	-	10 (3.6)	-
> 120	2 (0.7)	-	4 (1.4)	-
Clinical characteristics at randomisation[a]				
Respiratory distress[b]	*n = 244*	*n = 2*	*n = 227*	*n = 15*
None	14 (5.7)	0 (0.0)	12 (5.3)	6 (40.0)
Mild	47 (19.3)	1 (50.0)	39 (17.2)	3 (20.0)
Moderate	140 (57.4)	1 (50.0)	136 (59.9)	6 (40.0)
Severe	43 (17.6)	0 (0.0)	40 (17.6)	0 (0.0)
Respiratory rate, median (IQR), (*N*), breaths per minute	48 (38–60), (*N* = 286)	44 (40–58), (*N* = 3)	49 (39–60), (*N* = 272)	42 (26–53), (*N* = 15)
SpO_2 (%), median (IQR), (*N*)	97 (94–99), (*N* = 290)	92 (89–95), (*N* = 4)	97 (94–99), (*N* = 275)	96 (95–100), (*N* = 17)

Characteristic	HFNC (*N* = 300)		CPAP (*N* = 295)	
	Started respiratory support *n* = 295	Did not start respiratory support *n* = 5	Started respiratory support *n* = 278	Did not start respiratory support *n* = 17
FiO_2, median (IQR), (*N*)	0.30 (0.21–0.48), (*N* = 288)	0.22 (0.21–0.34), (*N* = 4)	0.30 (0.21–0.44) (*N* = 271)	0.24 (0.21–0.35), (*N* = 17)
SpO_2/FiO_2 ratio	*n = 287*	*n = 4*	*n = 271*	*n = 17*
Median (IQR)	313 (198–424)	407 (300–433)	330 (218–438)	383 (286–457)
> 350	117 (40.8)	3 (75.0)	121 (44.6)	11 (64.7)
301–350	29 (10.1)	0 (0.0)	24 (8.9)	2 (11.8)
266–300	16 (5.6)	0 (0.0)	12 (4.4)	1 (5.9)
220–265	38 (13.2)	0 (0.0)	40 (14.8)	3 (17.6)
< 220	87 (30.3)	1 (25.0)	74 (27.3)	0 (0.0)
Heart rate, median (IQR), (*N*), beats per minute	155 (140–171), (*N* = 291)	149 (121–193), (*N* = 4)	154 (140–173), (*N* = 272)	142 (131–161), (*N* = 17)
COMFORT-B score[c]	*n = 79*	*n = 1*	*n = 60*	*n = 5*
Median (IQR)	16.0 (12.0–20.0)	-[d]	14.0 (11.0–18.5)	15.0 (12.0–17.0)
< 10	5 (6.3)	-[d]	6 (10.0)	1 (5.9)
10–12	17 (21.5)	-[d]	18 (30.0)	1 (5.9)
13–17	25 (31.6)	-[d]	17 (28.3)	2 (11.8)
> 17	32 (40.5)	-[d]	19 (31.7)	1 (5.9)

a Data were recorded at or withinone1 hour prior to randomisation, except for COMFORT Behavior Scale score, which was the last recorded value prior to randomisation.
b Respiratory distress was defined as Mild: one accessory muscle used, mild indrawing of subcostal and intercostal muscles, mild tachypnoea, no grunting. Moderate: two accessory muscles used, moderate indrawing of subcostal and intercostal muscles, moderate tachypnoea, occasional grunting. Severe: use of all accessory muscles, severe indrawing of subcostal and intercostal muscles, severe tachypnoea, regular grunting.
c COMFORT Behavior Scale Scores range from 5 to 30 (most sedated to least sedated).
d Not reported as only available for one participant.

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Appendix 6 Step-up randomised controlled trial – devices and interfaces used in children who started the allocated treatment

Characteristic	HFNC (*N* = 290)	CPAP (*N* = 246)
Devices used, no. (%)		
Airvo™	142 (49.0)	NA
Optiflow™ MR850	60 (20.7)	NA
Vapotherm™	16 (5.5)	NA
PICU ventilator (closed circuit)	68 (23.4)	100 (40.7)
Infant Flow™ SiPAP	NA	56 (22.8)
Bubble CPAP	NA	14 (5.7)
Portable/home ventilator (vented circuit)	NA	55 (22.4)
Missing	4 (1.4)	21 (8.5)
CPAP interface used, no./total (%)		
Binasal prongs	NA	46 (18.7)
Nasal mask	NA	62 (25.2)
Oronasal mask	NA	15 (6.1)
Full face mask	NA	48 (19.5)
Helmet/hood	NA	5 (2.0)
Other	NA	6 (2.4)
Missing	NA	64 (26.0)

Note

Appendix 7 Step-up randomised controlled trial – timing and reasons for treatment failure (switch/escalation events) in children who started the allocated treatment

Characteristic	HFNC (*N* = 290)	CPAP (*N* = 246)
Treatment failure (switch/escalation for clinical reason)		
Occurrence of treatment failure, no. (%)	96 (33.1)	131 (53.3)
Switch	58 (20.0)	76 (30.9)
Escalated to other mode of non-invasive support	17 (5.9)	37 (15.0)
Directly escalated to invasive ventilation	21 (7.2)	18 (7.3)
Time from randomisation to treatment failure, median (IQR), hours	6.1 (2.7–18.2)	4.5 (1.6–10.6)
First switch		
First switch, no. (%)	58 (20.0)	76 (30.9)
Time from randomisation to switch, median (IQR), hours	6.3 (2.9–22.6)	2.8 (1.5–8.8)
Reason for switch, no. (% of those switched)[a]		
Severe respiratory distress	37 (63.8)	11 (14.5)
FiO_2 ≥ 0.60	9 (15.5)	3 (3.9)
Patient discomfort	8 (13.8)	61 (80.3)
Other reason	16 (27.6)	12 (15.8)
First escalation		
First escalation, no. (%)	38 (13.1)	55 (22.4)
Time from randomisation to escalation, median (IQR), hours	6.0 (2.6–17.8)	5.8 (2.5–18.6)
Reason for escalation, no. (% of those escalated)[a]		
Severe respiratory distress	22 (57.9)	32 (58.2)
FiO_2 ≥ 0.60	14 (36.8)	8 (14.5)
Patient discomfort	6 (15.8)	4 (7.3)
Other reason	12 (31.6)	17 (30.9)

a More than one reason could be selected.

Note

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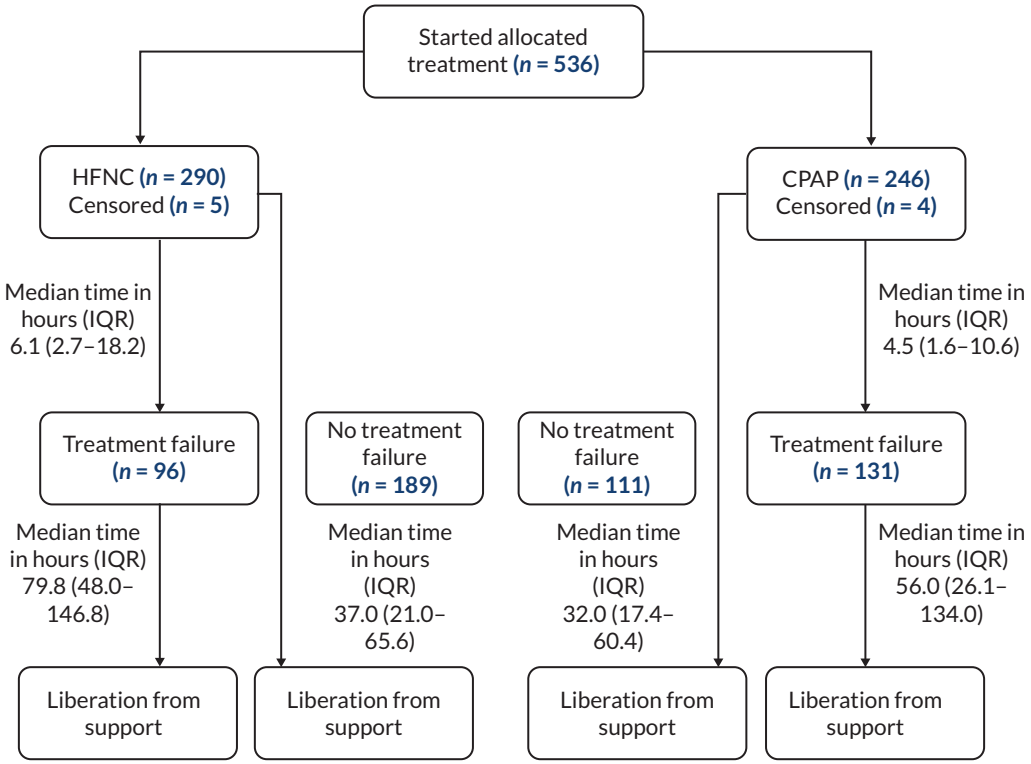
Appendix 8 Step-up randomised controlled trial – breakdown of the time to liberation from respiratory support by occurrence of treatment failure in children who started the allocated treatment



Appendix 9 Step-up randomised controlled trial – sensitivity analyses

Outcome	Primary analysis set				Per-protocol analysis			
	HFNC	CPAP	Unadjusted HR	Adjusted HR[a]	HFNC	CPAP	Unadjusted HR	Adjusted HR[a]
Planned sensitivity analyses								
Hours from randomisation to first weaning attempt, median (95% CI), (*N*)	38.0 (30.0 to 43.7), (*n* = 277)	39.2 (33.0 to 48.1), (*n* = 260)	1.11 (0.90 to 1.38)	1.13 (0.90 to 1.40)	38.0 (30.0 to 43.7), (*n* = 271)	40.0 (34.5 to 50.0), (*n* = 231)	1.16 (0.93 to 1.45)	1.19 (0.95 to 1.5)
Hours from randomisation to first meeting weaning criteria, median (95% CI), (*N*)	1.4 (1.3 to 1.6), (*n* = 259)	1.6 (1.4 to 1.8), (*n* = 266)	1.04 (0.88 to 1.25)	1.27 (1.03 to 1.57)	1.4 (1.3 to 1.6), (*n* = 255)	1.5 (1.3 to 1.8), (*n* = 2410	1.03 (0.86 to 1.23)	1.20 (1.00 to 1.45)
Hours from starting support to liberation from respiratory support, median (95% CI), (*N*)	52.5 (44.1 to 60.0), (*n* = 295)	44.5 (38.1 to 52.3), (*n* = 277)	1.02 (0.86 to 1.21)	1.01 (0.85 to 1.20)	52.4 (43.3 to 59.5), (*n* = 288)	44.0 (37.4 to 52.0), (*n* = 245)	1.04 (0.87 to 1.24)	1.02 (0.85 to 1.22)
Post hoc sensitivity analysis								
	All randomised patients							
Hours from randomisation to liberation from respiratory support, median (95% CI), (*N*)	52.0 (44.0 to 59.6), (*n* = 300)	43.4 (37.2 to 52.2), (*n* = 295)	0.99 (0.84 to 1.16)	0.98 (0.83 to 1.16)				

a Adjusted for prespecified baseline factors of age (< 12 months vs. ≥ 12 months), SpO_2 : FiO_2 ratio, comorbidities (none vs. neurological/neuromuscular vs. other), severity of respiratory distress, on respiratory support at randomisation (yes/no), reason for admission (bronchiolitis vs. other respiratory vs. cardiac vs. other) and site (using shared frailty).

Note

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Appendix 10 Step-up randomised controlled trial – mean (standard deviation) resource use from Health Services Questionnaire between discharge from hospital and 6 months following initial critical care episode for patients who were alive and completed the questionnaire at 6 months post randomisation[a]

	HFNC (*n* = 99)	CPAP (*n* = 81)
Outpatient visits	2.37 (4.10)	2.75 (7.85)
GP contacts	1.61 (3.00)	1.14 (1.66)
Nurse contacts	0.47 (1.64)	0.30 (0.97)
Health visitor contacts	2.59 (7.47)	1.91 (5.48)
Counsellor contacts	0.20 (2.02)	0.00 (0.00)
Dietitian contacts	0.33 (1.00)	0.70 (2.75)
Midwife visits	0.00 (0.00)	0.00 (0.00)
Occupational therapist contacts	0.31 (1.30)	0.65 (3.40)
Psychiatric nurse contacts	0.08 (0.55)	0.22 (1.89)
Physiotherapist contacts	0.69 (2.47)	1.20 (2.72)
School nurse visits	0.03 (0.17)	0.09 (0.60)
Social worker visits	0.04 (0.25)	0.14 (0.82)
Paediatric nurse visits	0.70 (2.45)	0.33 (1.75)
Speech therapist contacts	0.30 (1.34)	0.22 (0.79)

a Only reported for patients who were alive and completed the HSQ at 6 months post randomisation.

EME
HSDR
HTA
PGfAR
PHR

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