Supplemental Online Content

Ramnarayan P, Richards-Belle A, Drikite L, et al; FIRST-ABC Step-Up RCT Investigators and the Paediatric Critical Care Society Study Group. Effect of high-flow nasal cannula therapy vs continuous positive airway pressure therapy on liberation from respiratory support in acutely ill children admitted to pediatric critical care units: a randomized clinical trial. *JAMA*. Published online June 16, 2022. doi:10.1001/jama.2022.9615

This supplemental material has been provided by the authors to give readers additional information about their work.

eAppendix. Supplemental Methods

Patient eligibility criteria

Inclusion criteria

1. Admitted/Accepted for admission to the paediatric intensive care unit/high dependency unit
2. Age >36 weeks corrected gestational age and <16 years
3. Assessed by the treating clinician to require non-invasive respiratory support for an acute illness

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 High Flow Nasal Cannula (HFNC)/Continuous Positive Airway Pressure (CPAP) for >2 hours in the prior 24 hours
4. On home non-invasive ventilation prior to PICU/HDU admission
5. Presence of untreated air-leak (pneumothorax/pneumomediastinum)
6. Midfacial/craniofacial anomalies (unrepaired cleft palate, choanal atresia) or recent craniofacial surgery
7. Agreed ‘not for intubation’ or other limitation of critical care treatment plan in place.
8. Previously recruited to the FIRST-ABC trial
9. Clinician decision to start other form of non-invasive respiratory support (i.e. not HFNC or CPAP)

Trial interventions

High Flow Nasal Cannula (HFNC)

Any approved medical device capable of delivering heated, humidified, high flow through nasal cannulae could be used to provide HFNC at the prescribed gas flow rate during the trial. The study protocol specified clinical criteria and guidance for the initiation, maintenance and weaning of HFNC (see eFigure 1). It was recommended that study participants were assessed for response to the treatment, readiness to wean and readiness for stopping

HFNC, as per the HFNC algorithm, at least twice per day (e.g. at ward rounds).

Staff in all participating units already used HFNC before the study commenced and, therefore, no additional technical training related to the use of HFNC was provided for the study.

Since the medical device and the nasal interface that delivers HFNC is easily distinguishable from the CPAP device and its interface, it was not possible to blind the subject or the clinical staff.

As per current practice, clinicians in the study were able to stop HFNC and switch to CPAP or other forms of respiratory support if clinically deemed necessary. Pre-specified objective criteria to identify non-responders to HFNC were provided (see eFigure 1) as a guide for clinicians considering switching or escalating respiratory support. Reasons for switches and escalations were recorded. Patients who switched or escalated treatments remained in the study and continued to be monitored until they were off respiratory support.

The algorithm was followed until the patient was liberated from all forms of respiratory support for at least 48 continuous hours.

Continuous Positive Airway Pressure (CPAP)

Conventional CPAP was started using an approved medical device at a set expiratory pressure of 7-8 cm H2O. The trial did not specify any particular device or patient interface for the provision of CPAP. In order to standardise treatment, the study protocol specified clinical criteria and guidance for the initiation, maintenance and weaning of CPAP (see eFigure 2). It was recommended that study participants were assessed for response to the treatment, readiness to wean and readiness for stopping CPAP, as per the CPAP algorithm, at least twice per day (e.g. at ward rounds).

Staff in all participating units already used CPAP before the study commenced and, therefore, no additional technical training related to the use of CPAP was provided for the study.

As per current practice, clinicians in the study were able to stop CPAP and switch to HFNC or escalate to other forms of respiratory support if clinically deemed necessary. Pre-specified objective criteria to identify non-responders to CPAP were provided in the study protocol as a guide for clinicians considering switching or escalating respiratory support. Reasons for switches or escalations were recorded. Patients who switched or escalated treatments remained in the study and continued to be monitored until they were off respiratory support.

The protocol was followed until the patient was liberated from all forms of respiratory support for at least 48 continuous hours.

Consent

Consent was sought for the child (patient) from their parent/legal guardian as this is where the responsibility for deciding on medical treatment resides.

FIRST-ABC utilised a deferred ('research without prior consent') consent model. Once a patient was screened and confirmed as eligible for the study (i.e. satisfied inclusion and exclusion criteria), they were randomised and the randomly assigned 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) study guidance,[1] has been found to be acceptable to parents/guardians, as well as to clinicians, in several recent paediatric critical care RCTs,[1-6] including the FIRST-ABC Pilot Study.[2]

Consent prior to hospital discharge - Deferred consent

Once notified of the randomisation of a patient into the study, a trained, delegated member of the site research team approached the parents/legal guardians of the patient as soon as appropriate and practically possible after randomisation to discuss the study. It was anticipated that the first approach would be within 24-48 hours of randomisation, but the specific timing of the approach was determined by the patient's medical situation.

Once approached, a Participant Information Sheet (PIS) for parents/legal guardians was provided. The PIS included information about: the purpose of the study; the consequences of participating or not; participant confidentiality; use of personal data; data security; and the future availability of the results of the study. Parents/legal guardians were given time to read the PIS and to ask any questions that they had about their child's participation in FIRST-ABC. They could also discuss with other family members or friends before confirming their decision. If in agreement, a Consent Form was then provided indicating that: the information given, orally and in writing, had been read and understood; participation was voluntary and could be withdrawn at any time without consequence; and that consent was given for access to medical records to continue data collection, to receive a follow-up questionnaire at six months and for anonymised data to be shared with other researchers in the future. After the person seeking consent had checked that the PIS and Consent Form had been understood, they invited the parent/legal guardians to sign the Consent Form and also countersigned the form themselves, in the presence of the parent/legal guardian.

Due to age and severity of illness in the target population, it was not possible to involve study participants in the consenting process. Instead, assent was obtained prior to hospital discharge if their age/condition allowed (e.g. they regained mental capacity). Where

possible, study participants were provided with an age-appropriate PIS and asked to sign an Assent Form, if appropriate, to confirm that they had been informed and understood the study. Parents/legal guardians were involved in these discussions. If the participant was likely to regain capacity following hospital discharge, then an age-appropriate PIS was provided to parents/legal guardians to discuss with the participant following recovery.

Discharge prior to consent being sought

In the situation where the patient was discharged from hospital prior to the parent/legal guardians confirming their consent decision, a member of the site research team followed the parents/legal guardians up for consent via telephone and then post. Briefly, at least one phone call was attempted to the parents/legal guardians within five working days of hospital discharge and, then, following on from the call (as well as if there was no response to the call), the parents/legal guardians were sent a covering letter, PIS and Consent Form by post. The letter directed the parents/legal guardians to the PIS for detailed information on the study and provided contact details for the local site research team for if the parents/legal guardians wished to discuss the trial further. The letter asked the parents/legal guardians to return the Consent Form to confirm whether they would like their child to continue participation in the study (or not).

If there was no response after four weeks of the postal approach, a second postal approach was made. This second covering letter provided the same information as the first letter but confirmed that if no Consent Form was received within four weeks of the second letter being sent, then the participant would be included in the study unless they notify the site research team otherwise.

If the participant was transferred to another hospital participating in FIRST-ABC before the consent procedures were complete, then the local site research team contacted the research team at the receiving hospital to handover the consenting procedures.

Death prior to consent being sought

In the rare situation where a participant died before consent has been obtained, a site research team member obtained information from colleagues and/or bereavement counsellors to establish the most appropriate research/clinical team member to notify the parents/legal guardians of the involvement in the study. Deferred consent was permitted to be sought from parents/legal guardians following the death of their child and prior to their departure from the hospital; however, it was at the discretion of the site staff to determine if this was appropriate for each individual family.

If deferred consent was not sought prior to the parents'/legal guardians' departure from the hospital, then the parents/legal guardians were approached via post four weeks after

randomisation for informed consent, with trial information adapted for bereaved parents/legal guardians.

If there was no response after four weeks of sending the initial letter, a second approach was made. The second letter provided the same information as the first letter but also confirmed that if no Consent Form was received within four weeks of receipt of the letter, then the participant's data would be included in the study.

Refusal or withdrawals of consent

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 was retained in the trial, unless the parent/legal guardian requested otherwise.

Outcome Measures

Primary clinical outcome

Time to liberation from respiratory support

The primary outcome was 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. In this definition, respiratory support included HFNC, CPAP, other forms of non-invasive respiratory support (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 zero 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 PICU/HDU 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. HFNC and/or CPAP), measured using the COMFORT-B score

Patient comfort was measured during HFNC or CPAP using the COMFORT-B 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 non-invasive respiratory support. 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 non-invasive respiratory support 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: PICU

Parental stress was measured using the validated Parental Stressor Scale: PICU (PSS: PICU)[7] 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 PICU/HDU 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 day 60 and 180 was calculated as binary endpoints using all patients with known survival status at those times and additionally using time to event methods with surviving patients censored at date last known to be alive (to a maximum of day 180).

Primary economic outcome

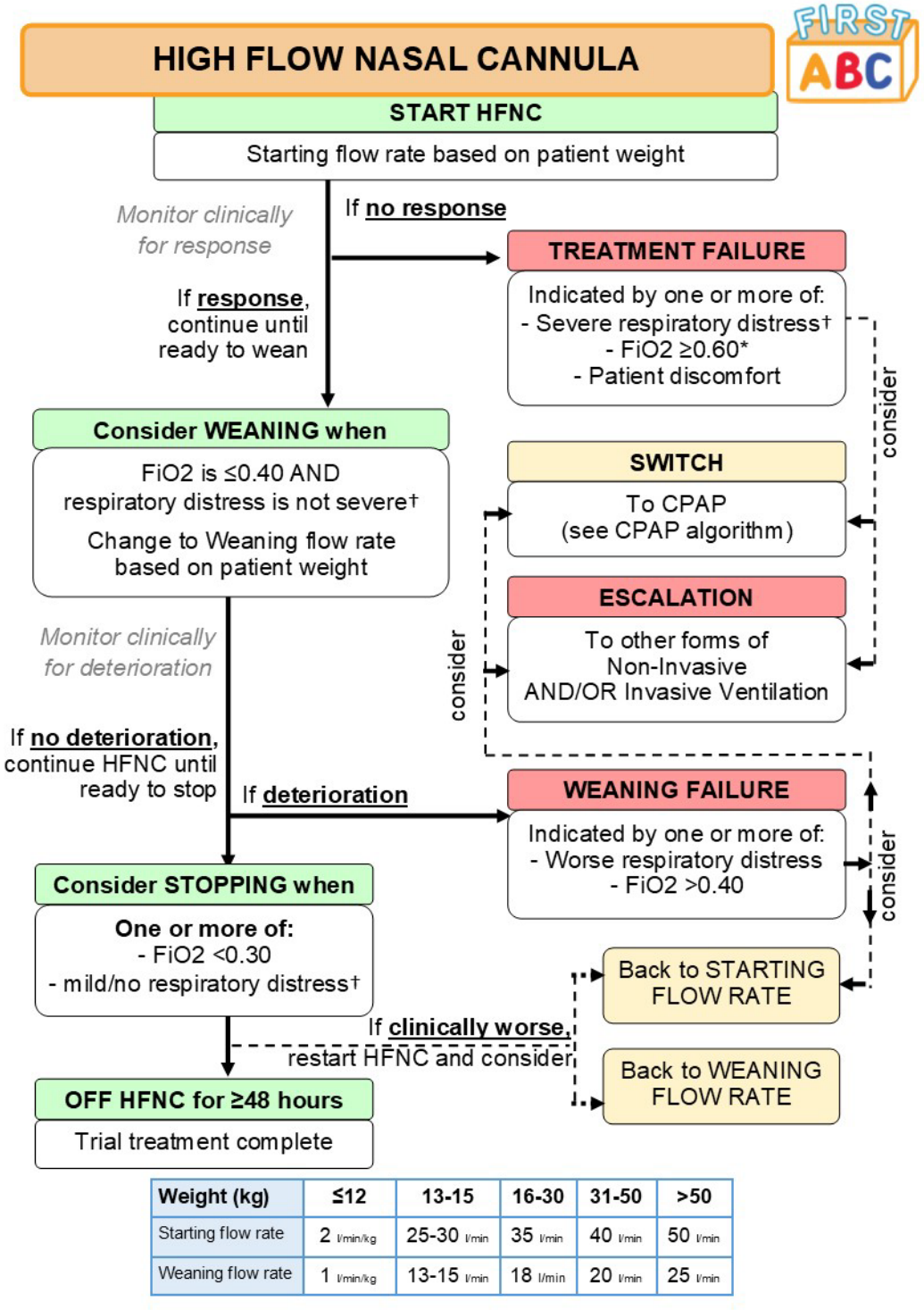
- Incremental net monetary benefit at six months.

Secondary economic outcomes

- Health-related quality of life (HRQoL) at six months assessed using age-appropriate Paediatric Quality of Life Generic Core Scales (PedsQL) and mapped onto the Child Health Utility 9D (CHU-9D) index score.
- Quality-adjusted life years (QALYs) at six months.
- Resource use and costs up to six months.

Note: mortality at day 60, day 180 and economic outcomes are not reported in this article and will be reported separately.

eFigure 1. Trial Algorithm for the Delivery of High Flow Nasal Cannula (HFNC)



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

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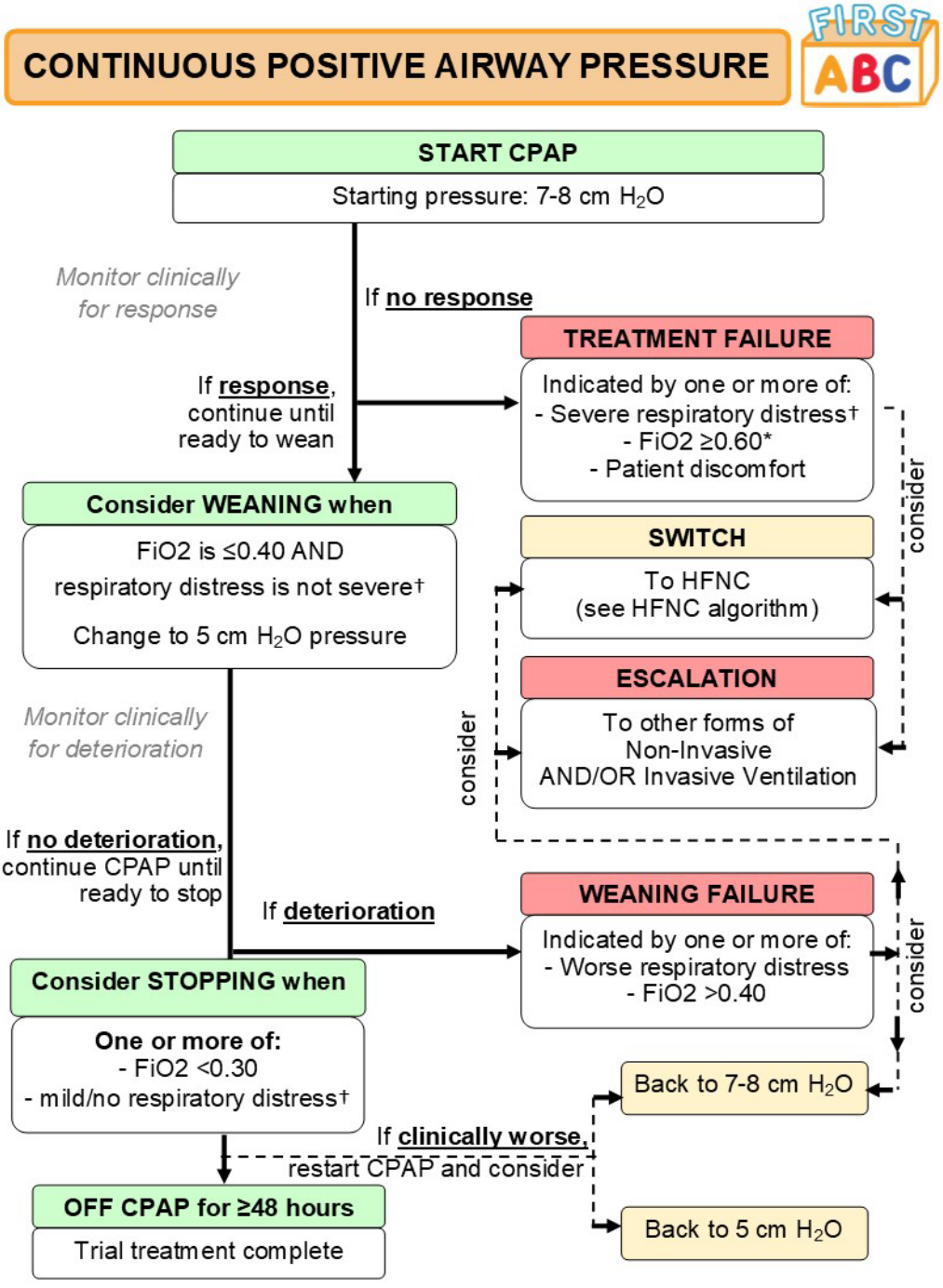
eFigure 2. Trial Algorithm for the Delivery of Continuous Positive Airway Pressure (CPAP)



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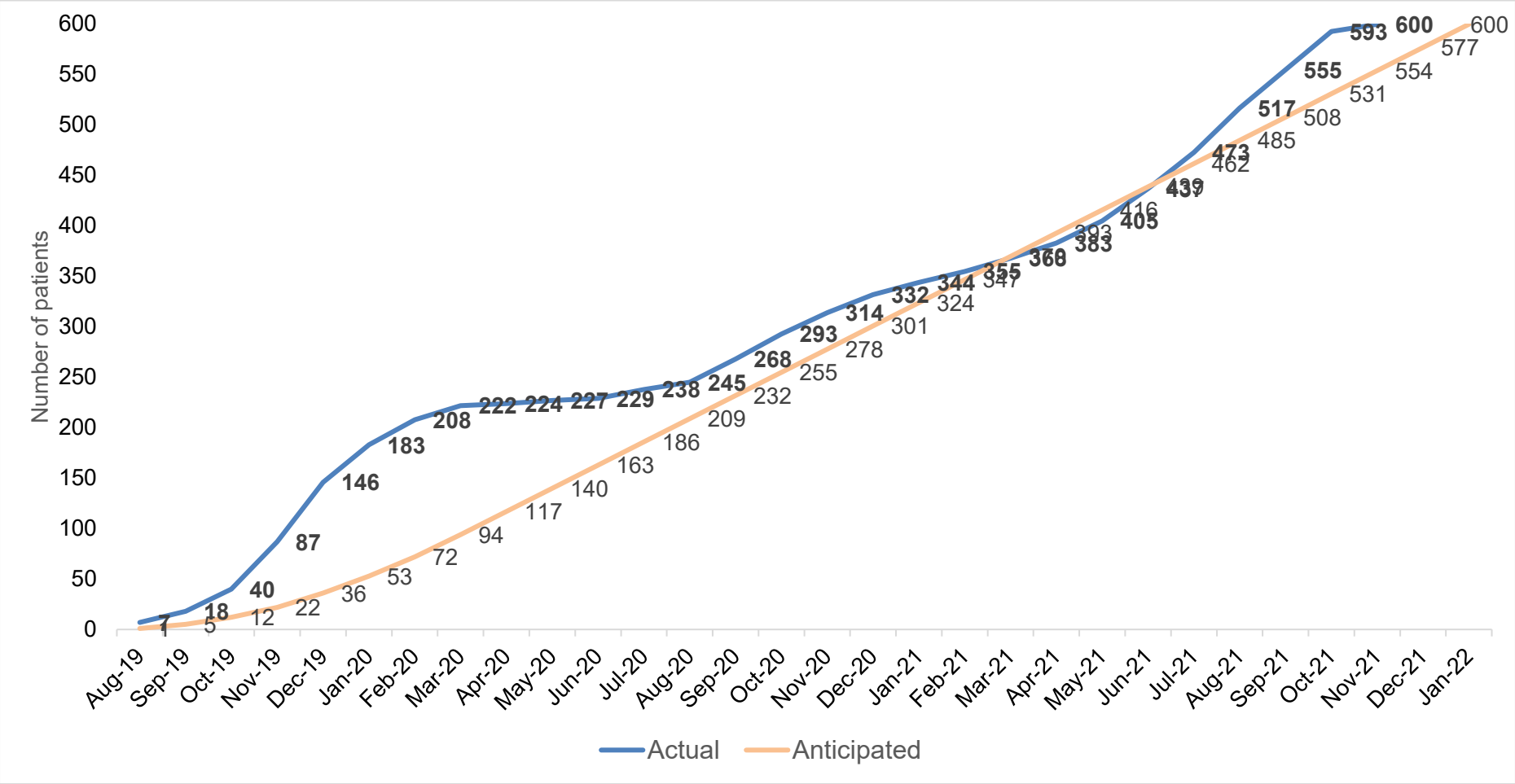
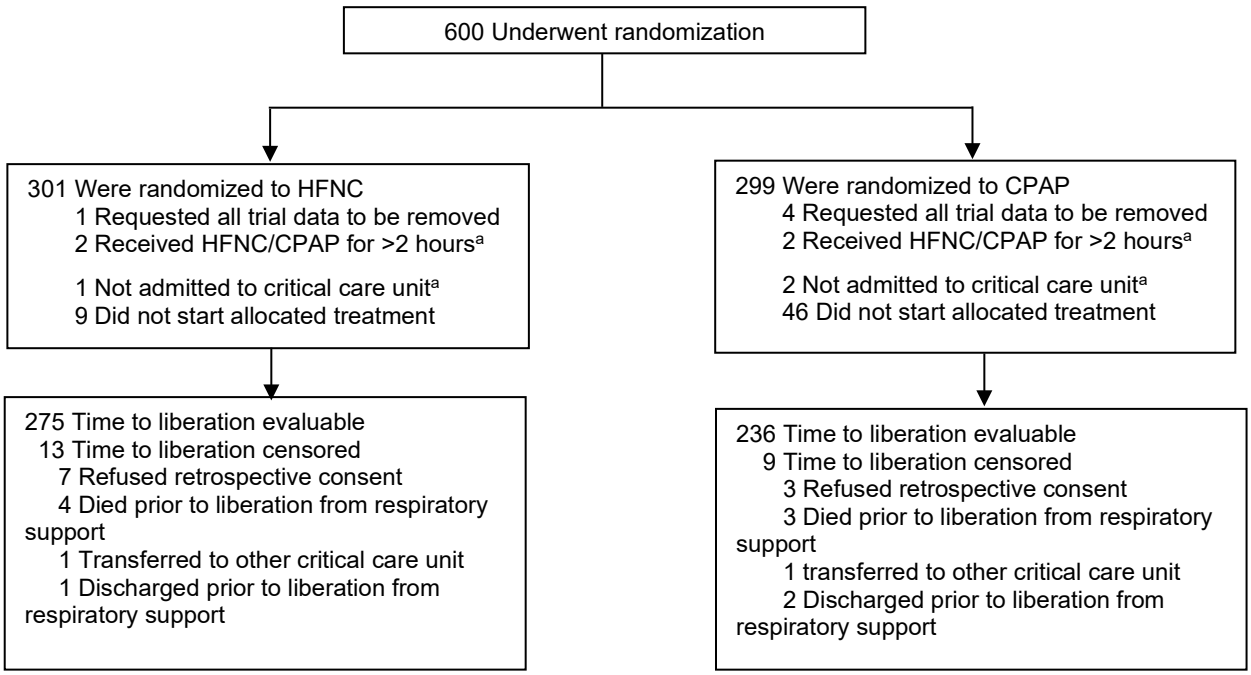
eFigure 3. Actual Versus Anticipated Patient Randomization



Comparison of actual versus anticipated cumulative randomization of patients into the FIRST-ABC step-up RCT.

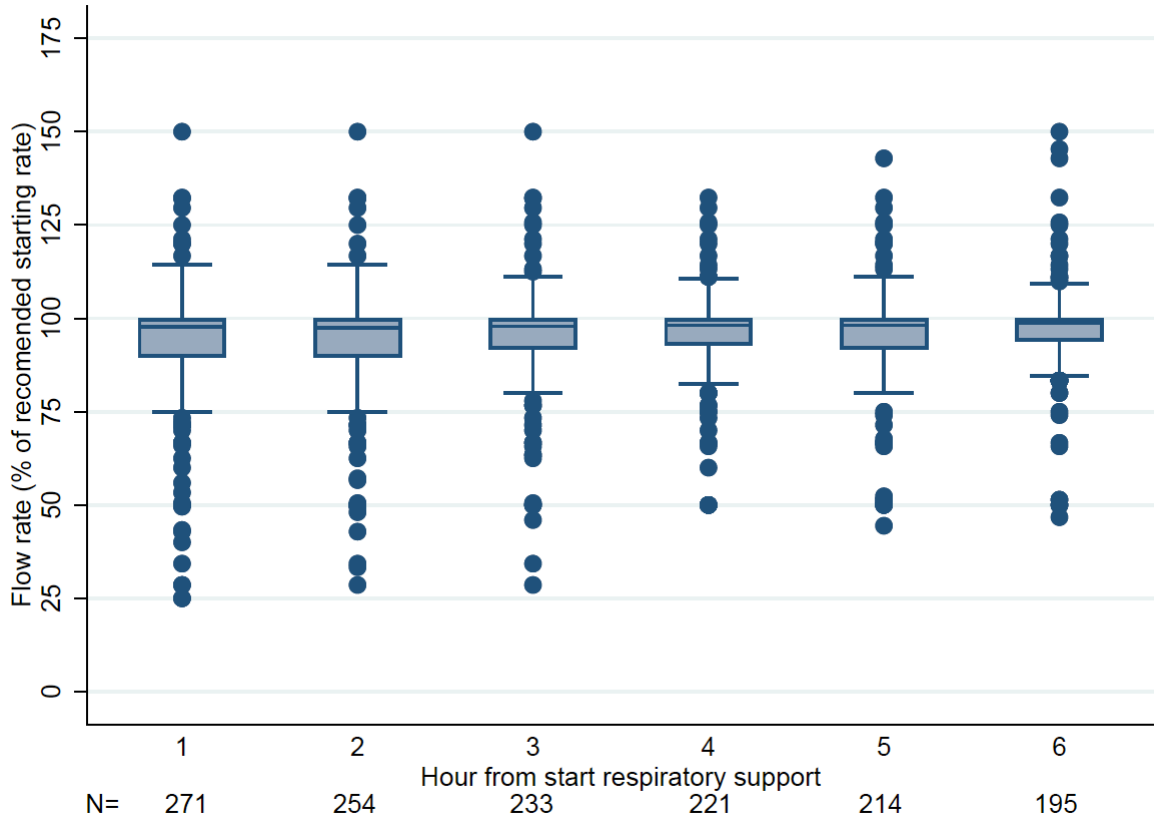
During the first wave of the COVID-19 epidemic in the UK, 17 (of 24) sites suspended recruitment for an average of 4.8 months. During the second wave, 5 sites suspended recruitment for an average of 2.6 months.

eFigure 4. Screening, Randomization and Follow-up in the Per-Protocol Population

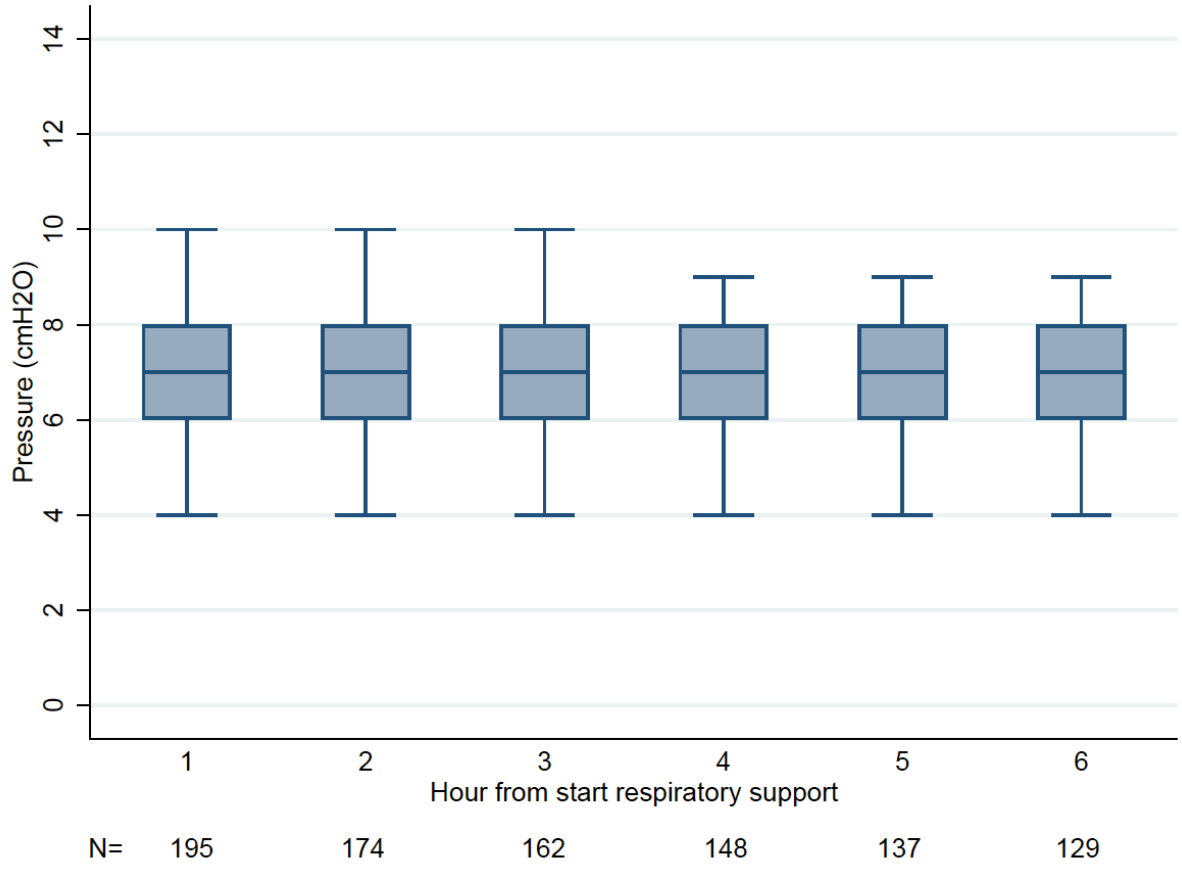


[a] Found to have met an exclusion criterion after randomization.

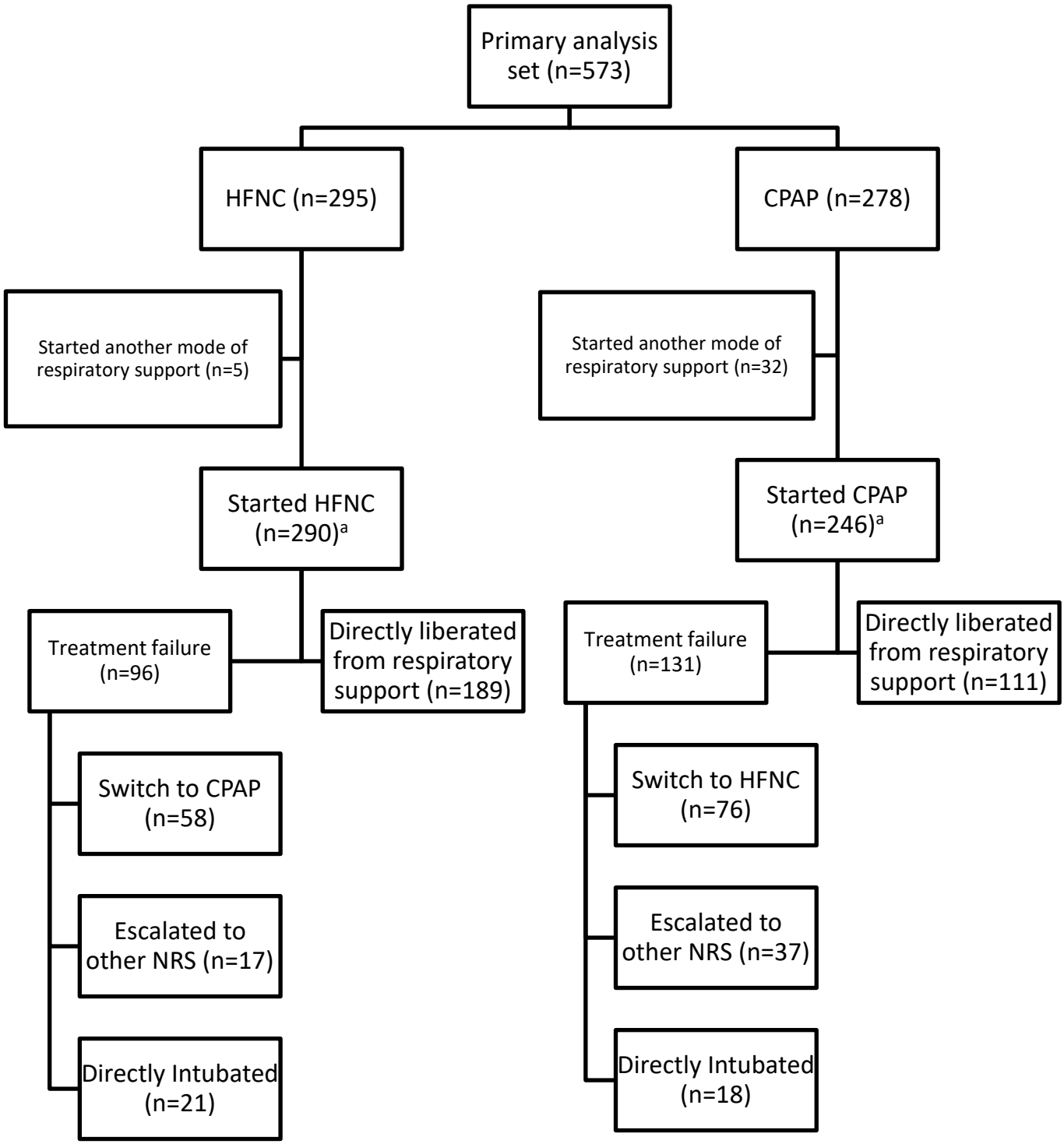
eFigure 5. HFNC Flow Rates During the First Six Hours of Treatment



eFigure 6. CPAP Pressures During the First Six Hours of Treatment

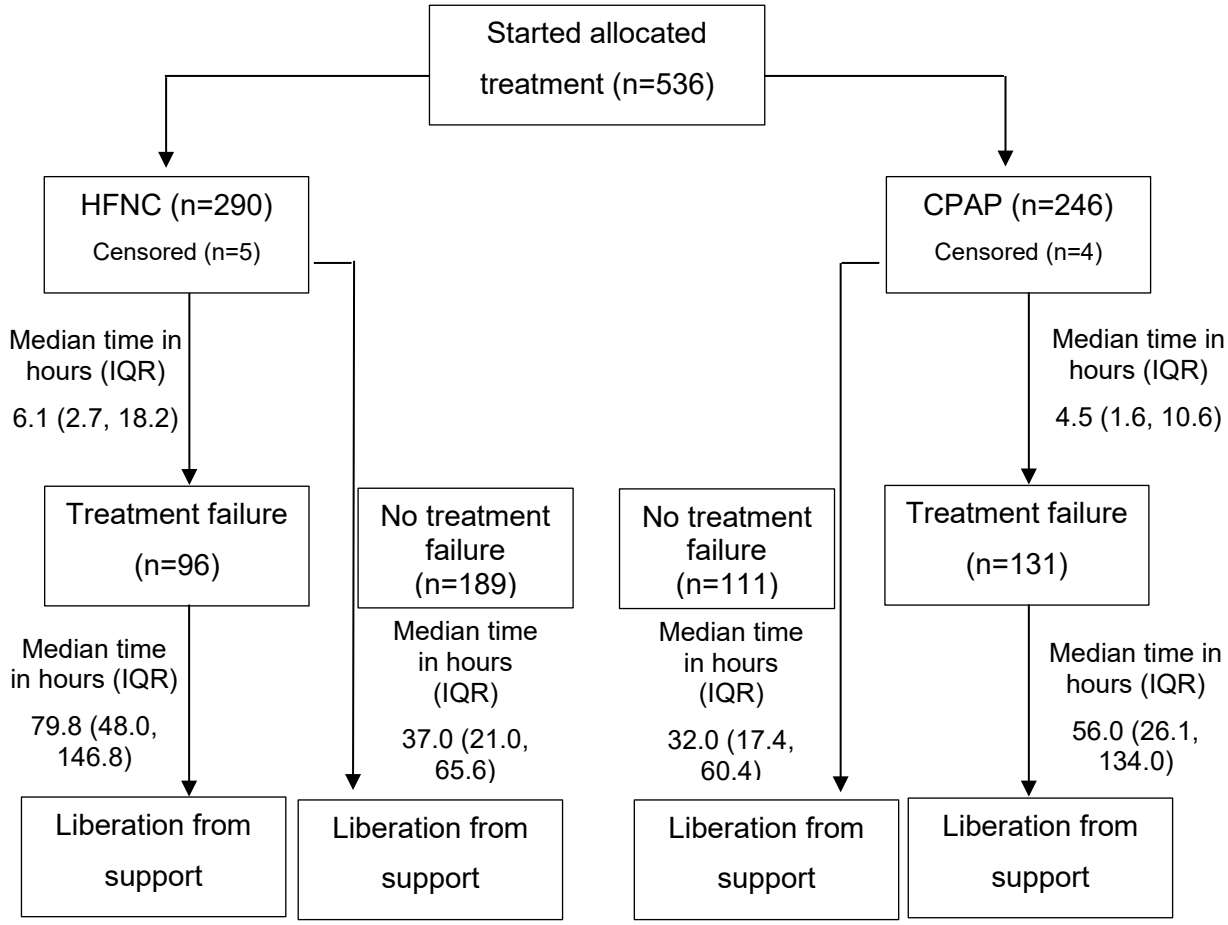


eFigure 7. Clinical Management of Trial Patients

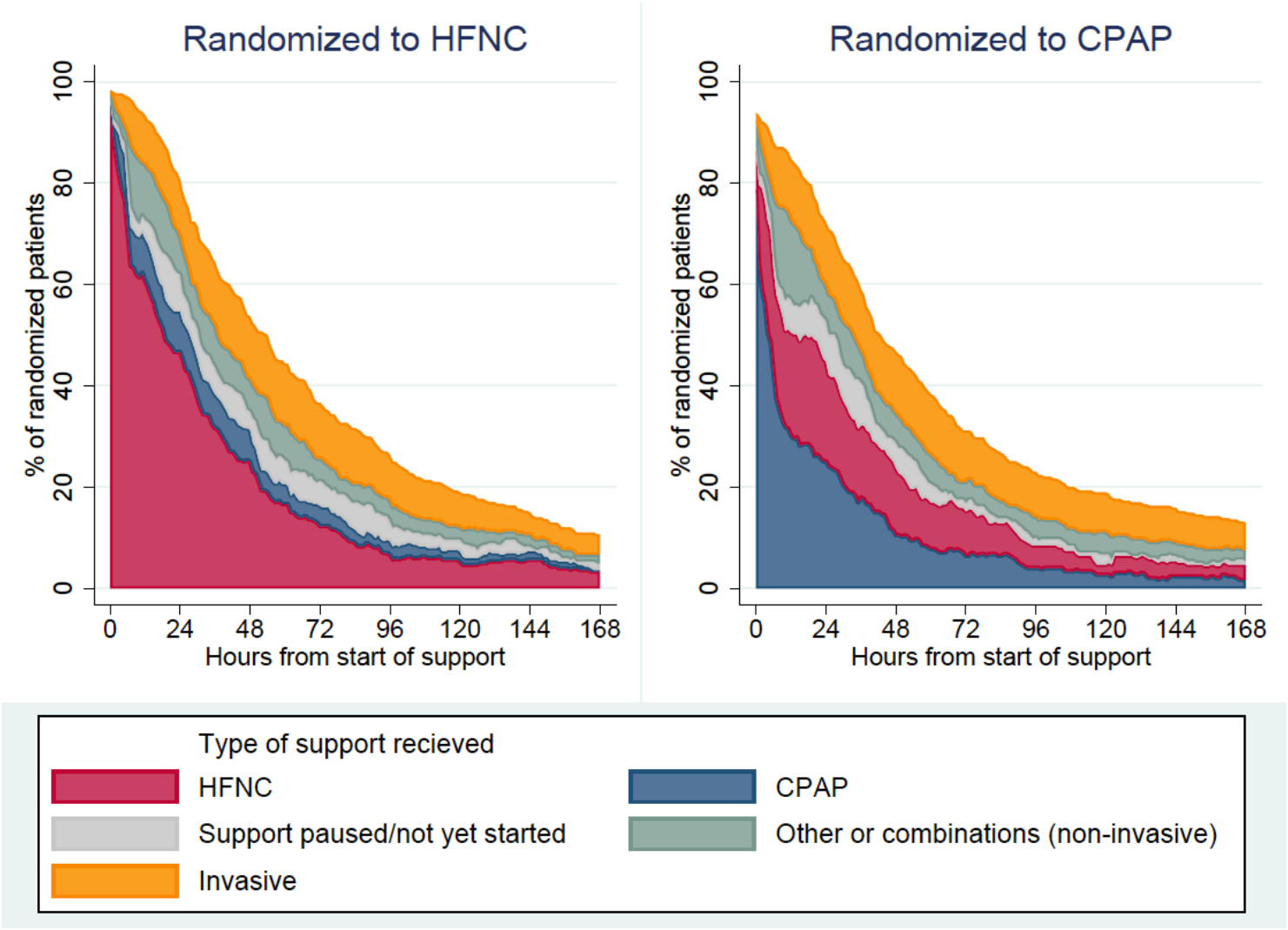


[a] Time to liberation was censored in 5 patients started on HFNC and 4 patients started on CPAP.

eFigure 8. Breakdown of the Time to Liberation From Respiratory Support by Occurrence of Treatment Failure in Children Who Started the Allocated Treatment

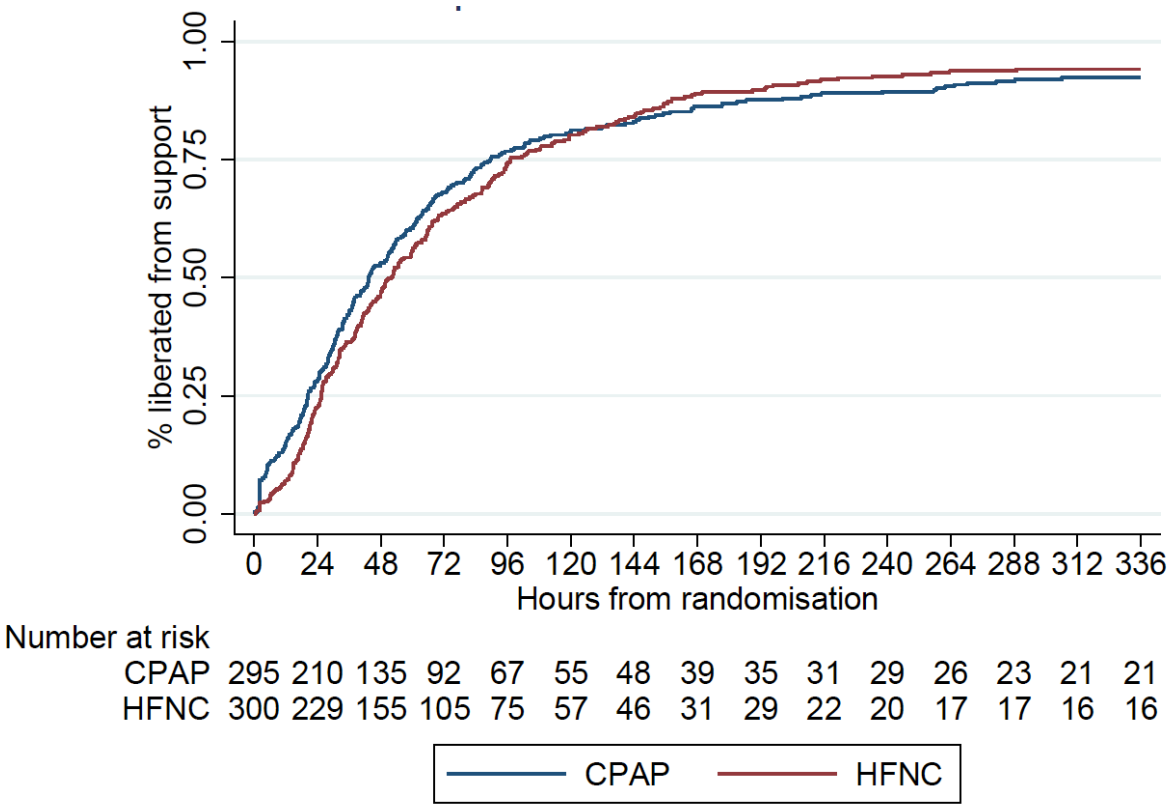


eFigure 9. Respiratory Support Treatments Provided Over Time to Children in the Primary Analysis Set



The colored areas represent the percentage of patients by type of support being received, by time since start of support

eFigure 10. Time to Liberation From Respiratory Support – Post-Hoc Sensitivity Analysis in All Randomized Children Including Those Who Were Not Started on Respiratory Support[a]



[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 randomisation, and repeated the primary analysis.

eTable 1. Patient Data Collection Schedule

	Baseline	At time of consent	During respiratory support[a]		End of PICU stay	End of hospital stay	At six months
			Hourly (first six hours)	Six-hourly until liberation			
In-hospital							
Clinical/baseline data	✓						
Patient/parent details		✓					
Types of respiratory support received	✓		✓	✓			
Patient comfort[b] and sedation use			✓	✓			
Parental stress		✓					
Discharge data					✓	✓	
Safety monitoring data			✓	✓			
At follow-up[c]							
PedsQL and CHU-9D							✓
Health services/resource use							✓

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

[a] Type of respiratory support and, when receiving HFNC or CPAP, physiology and sedation use, were recorded hourly for the first six hours of respiratory support after randomization, followed by six-hourly, until liberation from respiratory support, discharge from hospital or death (whichever came first). Attempts to wean, switches between, and escalations (e.g., to other forms of non-invasive or invasive ventilation) from, HFNC or CPAP were recorded.

[b] COMFORT-B scores were recorded at least six hourly whilst patients were receiving CPAP or HFNC.

[c] These outcomes are not reported in this article.

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eTable 2. Characteristics of Participating UK National Health Service Critical Care Units

Characteristic	Critical care units n=24
Country/Region	
England	
London	7 (29.2)
Northeast 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)

PICU: paediatric intensive care unit, HDU: high dependency unit.

eTable 3. Additional Baseline Characteristics, Including Physiological Variables Split by Child on/Not on Non-invasive Respiratory Support at Randomization in the Primary Analysis Set

Characteristic	HFNC (N=295)	CPAP (N=278)
Geographical location of patient residence, no. (%)		
Urban	235 (79.7)	222 (79.9)
Rural	25 (8.5)	24 (8.6)
Missing	35 (11.9)	32 (11.5)
Comorbidities, no. (%)		
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. (%)		
Planned, following surgery	8 (2.7)	7 (2.5)
Unplanned, following surgery	6 (2.0)	3 (1.1)
Planned, not following surgery	5 (1.7)	13 (4.7)
Unplanned, not following surgery	226 (76.6)	211 (75.9)
Missing	50 (16.9)	44 (15.8)
Source of admission, no. (%)		
Same hospital	215 (72.9)	209 (75.2)
Other hospital	11 (3.7)	10 (3.6)
Home	19 (6.4)	14 (5.0)

Characteristic	HFNC (N=295)	CPAP (N=278)
Missing	50 (16.9)	45 (16.2)
SpO_2/FiO_2 ratio, no. (%)		
>350	117 (39.7)	121 (43.5)
301-350	29 (9.8)	24 (8.6)
266-300	16 (5.4)	12 (4.3)
220-265	38 (12.9)	40 (14.4)
<220	87 (29.5)	74 (26.6)
Missing	8 (2.7)	7 (2.5)
Comfort-B score,[a] no. (%)		
<10	5 (1.7)	6 (2.2)
10-12	17 (5.8)	18 (6.5)
13-17	25 (8.5)	17 (6.1)
>17	32 (10.8)	19 (6.8)
Missing	216 (73.2)	218 (78.4)

	HFNC		CPAP	
Characteristic	On NRS N=66	Not on NRS N=234	On NRS N=65	Not on NRS N=230
Respiratory distress,[b] no. (%)				
None	2 (3.0)	12 (5.1)	2 (3.1)	16 (7.0)
Mild	14 (21.2)	34 (14.5)	6 (9.2)	36 (15.7)
Moderate	27 (40.9)	114 (48.7)	34 (52.3)	108 (47.0)
Severe	14 (21.2)	29 (12.4)	14 (21.5)	26 (11.3)
Missing	9 (13.6)	45 (19.2)	9 (13.8)	44 (19.1)
Respiratory rate				
Median (IQR)	51 (36, 64)	46 (40, 60)	52 (43, 60)	48 (36, 58)
Missing	2 (3.0)	9 (3.8)	0 (0.0)	8 (3.5)
SpO2 (%)				

Characteristic	HFNC (N=295)		CPAP (N=278)	
Median (IQR)	98 (96, 99)	96 (94, 99)	98 (96, 100)	96 (94, 99)
Missing	1 (1.5)	5 (2.1)	0 (0.0)	3 (1.3)
FiO2				
Median (IQR)	0.40 (0.28, 0.50)	0.28 (0.21, 0.44)	0.40 (0.28, 0.45)	0.28 (0.21, 0.44)
Missing	3 (4.5)	5 (2.1)	1 (1.5)	6 (2.6)
SpO2/FiO2 ratio				
Median (IQR)	250 (192, 354)	336 (209, 445)	250 (211, 350)	357 (218, 448)
>350	16 (24.2)	104 (44.4)	16 (24.6)	116 (50.4)
301-350	8 (12.1)	21 (9.0)	7 (10.8)	17 (7.4)
266-300	5 (7.6)	11 (4.7)	4 (6.2)	10 (4.3)
220-265	11 (16.7)	27 (11.5)	19 (29.2)	22 (9.6)
<220	23 (34.8)	65 (27.8)	18 (27.7)	59 (25.7)
Missing	3 (4.5)	6 (2.6)	1 (1.5)	6 (2.6)
Heart rate				
Median (IQR)	160 (148, 172)	154 (136, 170)	162 (146, 177)	152 (137, 171)
Missing	1 (1.5)	4 (1.7)	0 (0.0)	6 (2.6)
Comfort-B score[a]				
Median (IQR)	17.0 (16.0, 20.0)	15.0 (11.0, 20.0)	17.5 (11.0, 21.0)	13.0 (11.0, 18.0)
<10	1 (1.5)	4 (1.7)	0 (0.0)	7 (3.0)
10-12	1 (1.5)	16 (6.8)	4 (6.2)	15 (6.5)
13-17	8 (12.1)	17 (7.3)	3 (4.6)	16 (7.0)
>17	9 (13.6)	24 (10.3)	7 (10.8)	13 (5.7)
Missing	47 (71.2)	173 (73.9)	51 (78.5)	179 (77.8)

HFNC: high flow nasal cannula; CPAP: continuous positive airway pressure; NRS: non-invasive respiratory support.

[a] COMFORT Behavior (COMFORT-B) scale scores range from 5 to 30 (most sedated to least sedated).

[b] Respiratory distress was defined as Mild: one accessory muscle used, mild indrawing of subcostal and intercostal muscles, mild tachypnea, no grunting. Moderate: two accessory muscles used, moderate indrawing of subcostal and intercostal muscles, moderate tachypnea, occasional grunting. Severe: use of all accessory muscles, severe indrawing of subcostal and intercostal muscles, severe tachypnea, regular grunting.

eTable 4. 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)
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)
Geographical location of patient residence, no. (%)		
Urban	228 (79.2)	193 (78.8)
Rural	25 (8.7)	22 (9.0)
Missing	35 (12.2)	30 (12.2)
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)

Characteristic	HFNC (N=288)	CPAP (N=245)
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. (%)		
Planned, following surgery	8 (2.8)	4 (1.6)
Unplanned, following surgery	5 (1.7)	3 (1.2)
Planned, not following surgery	5 (1.7)	13 (5.3)
Unplanned, not following surgery	222 (77.1)	190 (77.6)
Missing	48 (16.7)	35 (14.3)
Source of admission, no. (%)		
Same hospital	210 (72.9)	188 (76.7)
Other hospital	11 (3.8)	10 (4.1)
Home	19 (6.6)	12 (4.9)
Missing	48 (16.7)	35 (14.3)
Respiratory distress[a], no. (%)		
None	13 (4.5)	9 (3.7)
Mild	46 (16.0)	37 (15.1)
Moderate	138 (47.9)	119 (48.6)
Severe	41 (14.2)	37 (15.1)
Missing	50 (17.4)	43 (17.6)
Respiratory rate		
Median (IQR)	48 (38, 60)	50 (40, 60)
Missing	8 (2.8)	5 (2.0)
SpO2 (%)		

Characteristic	HFNC (N=288)	CPAP (N=245)
Median (IQR)	97 (94, 99)	97 (94, 99)
Missing	5 (1.7)	2 (0.8)
FiO2		
Median (IQR)	0.30 (0.21, 0.48)	0.30 (0.21, 0.44)
Missing	7 (2.4)	4 (1.6)
SpO2/FiO2 ratio		
Median (IQR)	308 (198, 424)	333 (218, 443)
>350	114 (39.6)	109 (44.5)
301-350	28 (9.7)	22 (9.0)
266-300	16 (5.6)	8 (3.3)
220-265	38 (13.2)	34 (13.9)
<220	84 (29.2)	68 (27.8)
Missing	8 (2.8)	4 (1.6)
Heart rate		
Median (IQR)	155 (140, 171)	154 (140, 172)
Missing	4 (1.4)	5 (2.0)
Comfort-B score[b]		
Median (IQR)	16.0 (12.0, 20.0)	14.0 (11.0, 18.5)
<10	5 (1.7)	5 (2.0)
10-12	17 (5.9)	17 (6.9)
13-17	25 (8.7)	17 (6.9)
>17	32 (11.1)	17 (6.9)
Missing	209 (72.6)	189 (77.1)

HFNC: high flow nasal cannula; CPAP: continuous positive airway pressure.

[a] Respiratory distress was defined as Mild: one accessory muscle used, mild indrawing of subcostal and intercostal muscles, mild tachypnea, no grunting. Moderate: two accessory muscles used, moderate indrawing of subcostal and intercostal muscles, moderate tachypnea, occasional grunting. Severe: use of all accessory muscles, severe indrawing of subcostal and intercostal muscles, severe tachypnea, regular grunting.

[b] COMFORT Behavior (COMFORT-B) scale scores range from 5 to 30 (most sedated to least sedated).

eTable 5. Adherence With Trial Algorithms in Children Who Started the Allocated Treatment

Characteristic	HFNC (N=290)	CPAP (N=246)
Starting noninvasive respiratory support		
Time from randomization 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 H2O, no./total (%)	NA	170 (69.1)
Started on pressure of ≥6 cm H_2O, no./total (%)	NA	196 (79.7)
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)

Characteristic	HFNC (N=290)	CPAP (N=246)
Clinical deterioration, criteria not met	32 (26.4)	35 (30.7)
Non-adherent	5 (4.1)	2 (1.8)
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)

HFNC: high flow nasal cannula; CPAP: continuous positive airway pressure.

[a] More than one reason could be selected.

eTable 6. 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)

HFNC: high flow nasal cannula; CPAP: continuous positive airway pressure.

eTable 7. 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 noninvasive support	17 (5.9)	37 (15.0)
Directly escalated to invasive ventilation	21 (7.2)	18 (7.3)
Time from randomization 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 randomization 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)
FiO2 >=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 randomization 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)
FiO2 >=0.60	14 (36.8)	8 (14.5)
Patient discomfort	6 (15.8)	4 (7.3)
Other reason	12 (31.6)	17 (30.9)

HFNC: high flow nasal cannula; CPAP: continuous positive airway pressure.

[a] More than one reason could be selected.

eTable 8. Sensitivity Analyses

	Primary analysis set				Per-protocol analysis			
Outcome	**HFNC**	**CPAP**	**Unadjusted effect estimate**	**Adjusted effect estimate[a]**	**HFNC**	**CPAP**	**Unadjusted effect estimate**	**Adjusted effect estimate[a]**
Planned sensitivity analyses								
Hours from randomization to first weaning attempt, median (95% CI) [N]	38.0 (30.0, 43.7), [n=277]	39.2 (33.0, 48.1), [n=260]	HR 1.11 (0.90, 1.38)	HR 1.13 (0.90, 1.40)	38.0 (30.0, 43.7), [n=271]	40.0 (34.5, 50.0), [n=231]	HR 1.16 (0.93, 1.45)	HR 1.19 (0.95, 1.5)
Hours from randomization to first meeting weaning criteria, median (95% CI) [N]	1.4 (1.3, 1.6), [n=259]	1.6 (1.4, 1.8), [n=266]	HR 1.04 (0.88, 1.25)	HR 1.27 (1.03, 1.57)	1.4 (1.3, 1.6), [n=255]	1.5 (1.3, 1.8), [n=241]	HR 1.03 (0.86, 1.23)	HR 1.20 (1.00, 1.45)
Hours from starting support to liberation from respiratory support, median (95% CI) [N]	52.5 (44.1, 60.0), [n=295]	44.5 (38.1, 52.3), [n=277]	HR 1.02 (0.86, 1.21)	HR 1.01 (0.85, 1.20)	52.4 (43.3, 59.5), [n=288]	44.0 (37.4, 52.0), [n=245]	HR 1.04 (0.87, 1.24)	HR 1.02 (0.85, 1.22)
Post-hoc sensitivity analysis								
	All randomized patients							
Hours from randomization to liberation from respiratory support, median (95% CI) [N]	52.0 (44.0, 59.6), [n=300]	43.4 (37.2, 52.2), [n=295]	HR 0.99 (0.84, 1.16)	HR 0.98 (0.83, 1.16)				

Mortality at critical care discharge, no./total no. (%)	5/297 (1.7)	4/291 (1.4)	OR 1.23 (0.33, 4.62)	OR 1.22 (0.32, 4.63)	
Intubation at 48 hours, no./total no. (%)	45/296 (15.2)	44/291 (15.1)	OR 1.01 (0.64, 1.58)	OR 0.98 (0.60, 1.60)	
Duration of critical care unit stay, mean (SD), [N], days	4.9 (8.1) [292]	7.1 (18.4) [287]	MD -2.1(-4.4, 0.2)	MD -2.4 (-4.5, -0.3)	
Duration of acute hospital stay, mean (SD), [N], days	13.7 (26.6) [284]	18.5 (46.4) [277]	MD -4.8(-11.0, 1.4)	MD -5.9 (-11.4, -0.4)	
Parental stress (PSS:PICU) score at the time of consent, mean (sd), [N]	1.5 (0.8) [183]	1.6 (0.7) [194]	MD -0.0(-0.2, 0.1)	MD -0.0 (-0.2, 0.1)	

HFNC: high flow nasal cannula; CPAP: continuous positive airway pressure HR: hazard ratio, OR: odds ratio, MD: mean difference, CI: confidence interval

[a] Adjusted for pre-specified 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 randomization (yes/no), reason for admission (bronchiolitis vs other respiratory vs cardiac vs other) and site (using shared frailty)

eTable 9. Baseline Characteristics in All Randomized 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)

	Started respiratory support n=295	Did not start respiratory support n=5	Started respiratory support n=278	Did not start respiratory support n=17
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)
Type of admission, no. (%)				
Planned, following surgery	8 (2.7)	0 (0.0)	7 (2.5)	3 (17.6)
Unplanned, following surgery	6 (2.0)	0 (0.0)	3 (1.1)	0 (0.0)
Planned, not following surgery	5 (1.7)	0 (0.0)	12 (4.3)	2 (11.8)
Unplanned, not following surgery	226 (76.6)	4 (80.0)	212 (76.3)	11 (64.7)
Missing	50 (16.9)	1 (20.0)	44 (15.8)	1 (5.9)
Source of admission, no. (%)				
Same hospital	215 (72.9)	4 (80.0)	211 (75.9)	13 (76.5)
Other hospital	11 (3.7)	0 (0.0)	8 (2.9)	1 (5.9)
Home	19 (6.4)	0 (0.0)	14 (5.0)	2 (11.8)
Missing	50 (16.9)	1 (20.0)	45 (16.2)	1 (5.9)
Main reason for admission, no. (%)				
Upper airway problem	15 (5.1)	0 (0.0)	12 (4.3)	0 (0.0)
Bronchiolitis	143 (48.5)	1 (20.0)	138 (49.6)	4 (23.5)

	Started respiratory support n=295	Did not start respiratory support n=5	Started respiratory support n=278	Did not start respiratory support n=17
Asthma/Wheeze	31 (10.5)	1 (20.0)	20 (7.2)	5 (29.5)
Other respiratory	55 (18.6)	2 (40.0)	57 (20.5)	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)
Missing	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Time (minutes) on non-invasive respiratory support at randomization, no. (%)				
0	229 (77.6)	-	213 (76.6)	-
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)	-
Missing	0 (0.0)	-	2 (0.7)	-
Respiratory distress[a]				
None	14 (4.7)	0 (0.0)	12 (4.3)	6 (35.3)
Mild	47 (15.9)	1 (20.0)	39 (14.0)	3 (17.6)
Moderate	140 (47.5)	1 (20.0)	136 (48.9)	6 (35.3)
Severe	43 (14.6)	0 (0.0)	40 (14.4)	0 (0.0)
Missing	51 (17.3)	3 (60.0)	51 (18.3)	2 (11.8)
Respiratory rate				
Median (IQR)	48 (38, 60)	44 (40, 58)	49 (39, 60)	42 (26, 53)
Missing	9 (3.1)	2 (40.0)	6 (2.2)	2 (11.8)

	Started respiratory support n=295	Did not start respiratory support n=5	Started respiratory support n=278	Did not start respiratory support n=17
SpO2 (%)				
Median (IQR)	97 (94, 99)	92 (89, 95)	97 (94, 99)	96 (95, 100)
Missing	5 (1.7)	1 (20.0)	3 (1.1)	0 (0.0)
FiO2				
Median (IQR)	0.30 (0.21, 0.48)	0.22 (0.21, 0.34)	0.30 (0.21, 0.44)	0.24 (0.21, 0.35)
Missing	7 (2.4)	1 (20.0)	7 (2.5)	0 (0.0)
SpO2/FiO2 ratio				
Median (IQR)	313 (198, 424)	407 (300, 433)	330 (218, 438)	383 (286, 457)
>350	117 (40.8)	3 (60.0)	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 (20.0)	74 (27.3)	0 (0.0)
Missing	8 (2.8)	1 (20.0)	7 (2.6)	11 (64.7)
Heart rate				
Median (IQR)	155 (140, 171)	149 (121, 193)	154 (140, 173)	142 (131, 161)
Missing	4 (1.4)	1 (20.0)	6 (2.2)	0 (0.0)
Comfort-B score [b]				
Median (IQR)	16.0 (12.0, 20.0)	-[c]	14.0 (11.0, 18.5)	15.0 (12.0, 17.0)
<10	5 (6.3)	-[c]	6 (10.0)	1 (5.9)
10-12	17 (21.5)	-[c]	18 (30.0)	1 (5.9)
13-17	25 (31.6)	-[c]	17 (28.3)	2 (11.8)
>17	32 (40.5)	-[c]	19 (31.7)	1 (5.9)
Missing	216 (273.4)	4 (80.0)	218 (363.3)	12 (70.6)

HFNC: high flow nasal cannula; CPAP: continuous positive airway pressure.

[a] Respiratory distress was defined as Mild: one accessory muscle used, mild indrawing of subcostal and intercostal muscles, mild tachypnea, no grunting. Moderate: two accessory muscles used, moderate indrawing of subcostal and intercostal muscles, moderate tachypnea, occasional grunting. Severe: use of all accessory muscles, severe indrawing of subcostal and intercostal muscles, severe tachypnea, regular grunting.

[b] COMFORT Behavior (COMFORT-B) scale scores range from 5 to 30 (most sedated to least sedated).

[c] Not reported as only available for one participant.

eTable 10. Summary of Adverse Events and Serious Adverse Events

Event	HFNC (N=295)	CPAP (N=278)	*P* value
Adverse Event			
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)	p=0.03
Serious Adverse Event			
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	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)	-

HFNC: high flow nasal cannula; CPAP: continuous positive airway pressure.

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