Great Ormond Street Hospital for Children NHS Foundation Trust

Imperial College London

icnarc intensive care national audit & research centre

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

A master protocol of two pragmatic trials of non-invasive respiratory support in paediatric critical care

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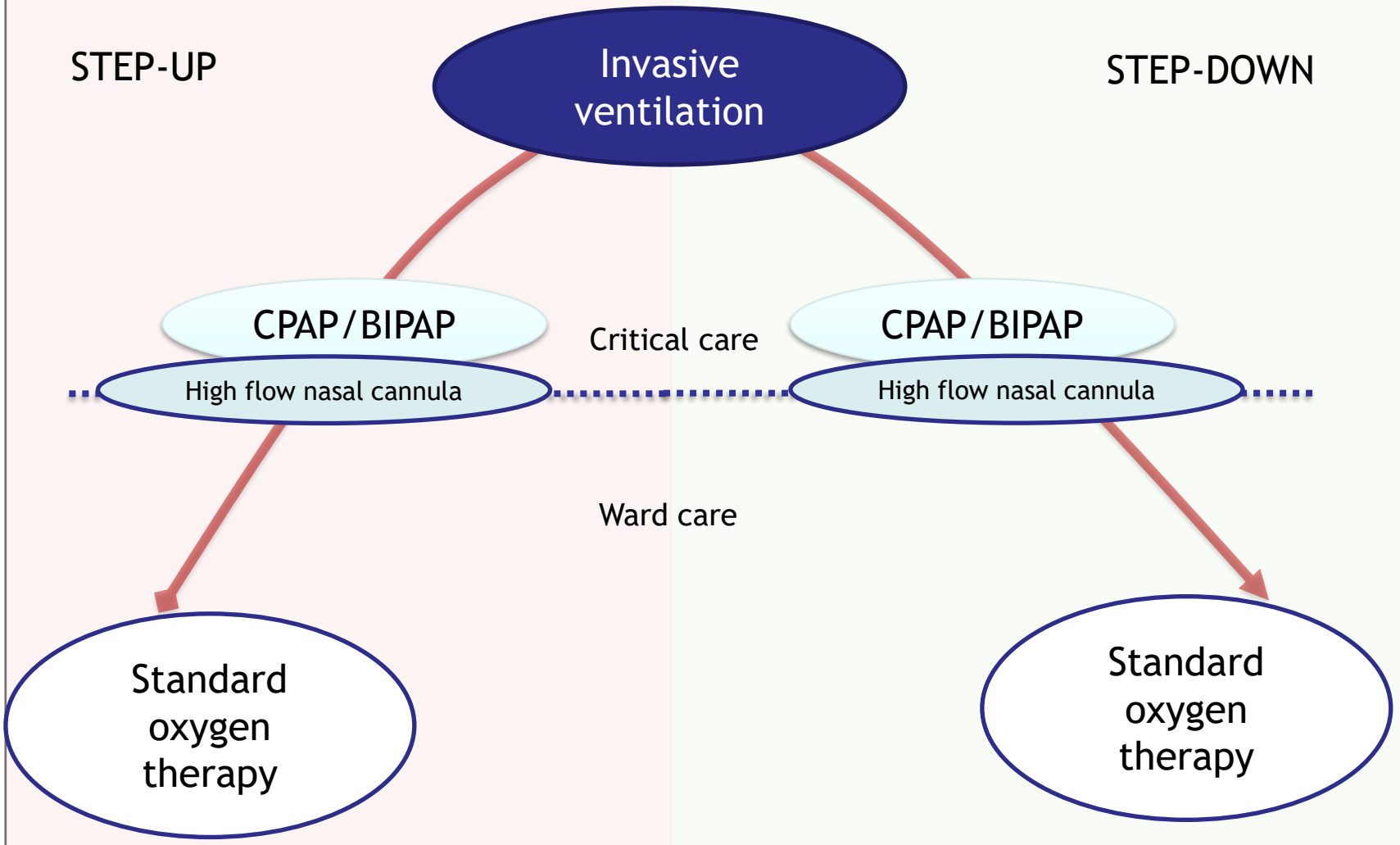
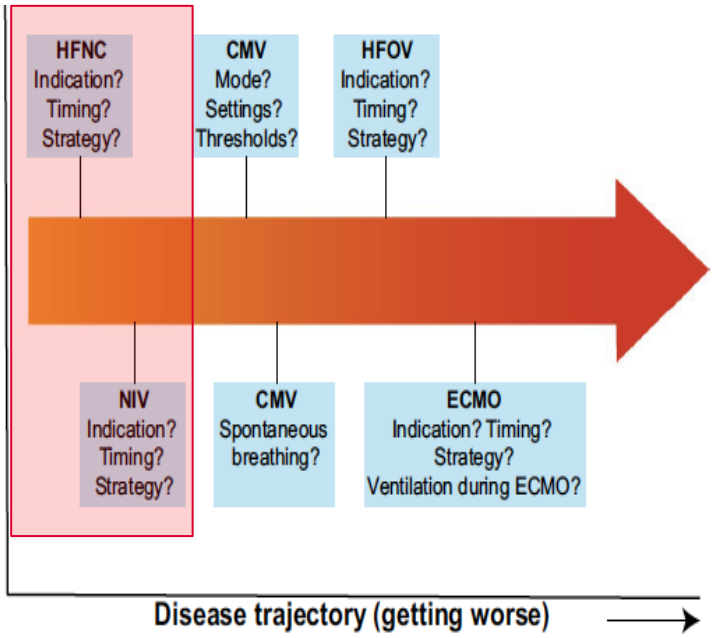
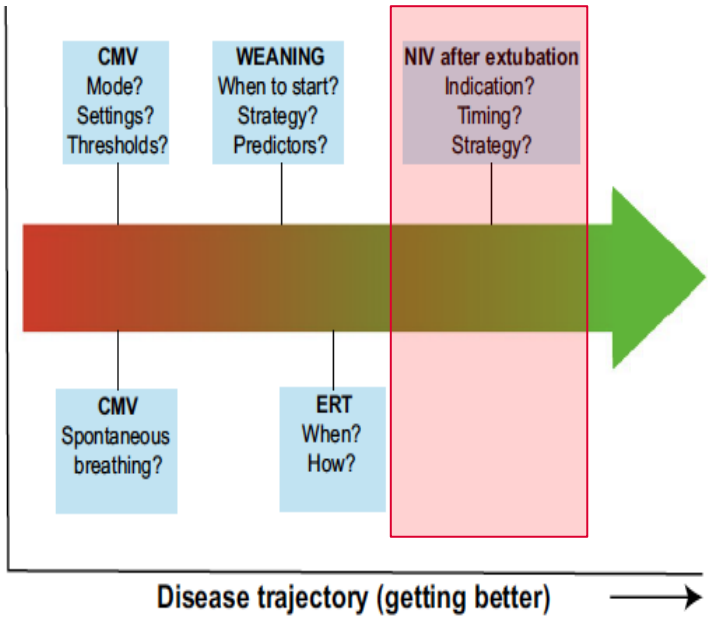
Respiratory support in children



PEMVECC recommendations





Subject	Available data	
	RCT	Observational
Non-invasive support		
Use of HFNC	None	Yes
Use of CPAP	None	Yes
Non-invasive ventilation	Yes ($n = 2$)	Yes

Kneyber et al. Intensive Care Medicine 2017

Recent systematic review

Recent meta-analysis in *acutely ill children* (7 RCTs, n=547) showed that intubation rate was higher with HFNC compared to CPAP

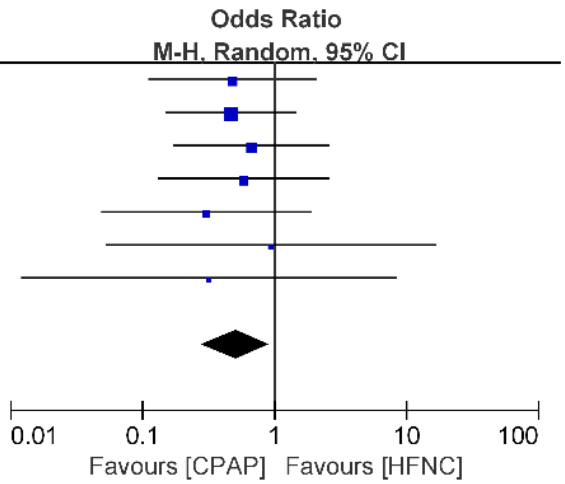
- OR 0.51 (95% CI 0.28, 0.92) but quality of evidence **LOW**[1]

c: CPAP vs. HFNC

Study or Subgroup	CPAP Events	CPAP Total	HFNC Events	HFNC Total	Weight	Odds Ratio M-H, Random, 95% CI
Cesar 2020	3	28	7	35	16.8%	0.48 [0.11, 2.06]
Chisti 2015	5	79	10	79	28.3%	0.47 [0.15, 1.43]
Liu 2020	4	41	6	43	19.8%	0.67 [0.17, 2.56]
Milési 2017	3	71	5	71	16.5%	0.58 [0.13, 2.54]
Ramnarayan 2018	2	13	6	16	10.8%	0.30 [0.05, 1.86]
Sarkar 2018	1	16	1	15	4.3%	0.93 [0.05, 16.39]
Vitaliti 2017	0	20	1	20	3.4%	0.32 [0.01, 8.26]
Total (95% CI)		**268**		**279**	**100.0%**	**0.51 [0.28, 0.92]**
Total events	18		36			

Heterogeneity: Tau² = 0.00; Chi² = 0.78, df = 6 (P = 0.99); I² = 0%

Test for overall effect: Z = 2.23 (P = 0.03)



[1] *Wang et al* (2021). Frontiers in Pediatrics

Pilot RCT (2016)

FIRST-line support for Assistance in Breathing in Children (FIRST-ABC): a multicentre pilot randomised controlled trial of high-flow nasal cannula therapy versus continuous positive airway pressure in paediatric critical care

Padmanabhan Ramnarayan[1,4*], Paula Lister[2], Troy Dominguez[3], Parviz Habibi[4], Naomi Edmonds[5], Ruth R. Canter[6], Jerome Wulff[6], David A. Harrison[6], Paul M. Mouncey[6], and Mark J. Peters[2,7] on behalf of the United Kingdom Paediatric Intensive Care Society Study Group (PICS-SG)

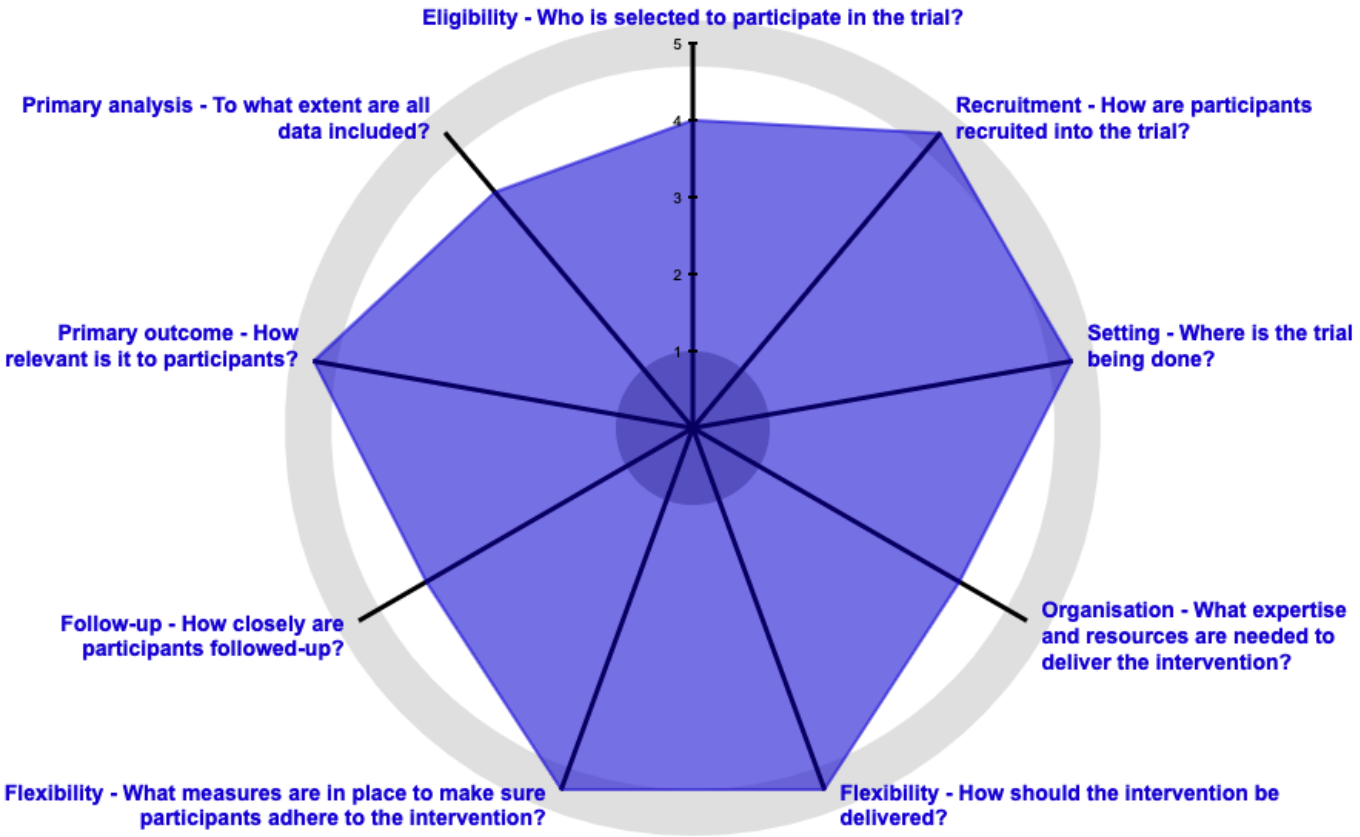
- Two distinct populations (step-up, step-down)
- Feasible to randomise ~50% of eligible patients
- Deferred consent acceptable to parents/professionals
- Reintubation rate and length of respiratory support potential outcomes

FIRST-ABC Master Protocol

- Master protocol to compare HFNC with CPAP
  - Step-up pragmatic RCT (acute illness)
  - Step-down pragmatic RCT (post-extubation)
- Shared infrastructure and integrated health economic evaluation
- Internal pilot phase (6 months)

Pragmatic design

- Balance between pragmatic (‘real-world’) and explanatory (‘ideal-world’) trial



The PRagmatic-Explanatory Continuum Indicator Summary 2 (PRECIS-2) wheel

Population Intervention Control Outcome

- Homogenous (disease-specific) versus heterogenous (all-comers) cohort
  - Indication to start NRS based on physiological criteria
  - Results applicable to all situations where HFNC is started
- Clinical decision to start NRS versus objective Physiological criteria
  - Wide variation in when HFNC is started within and between clinicians
  - No evidence to indicate the optimal timing and patient status to start NRS

Inclusion criteria

✓ Admitted/Accepted for admission to PICU/HDU

+

✓ Age >36 weeks corrected gestational age and <16 years

+

✓ Assessed by the treating clinician to require non-invasive respiratory support, **EITHER**

✓ For an acute illness (*step-up RCT*)

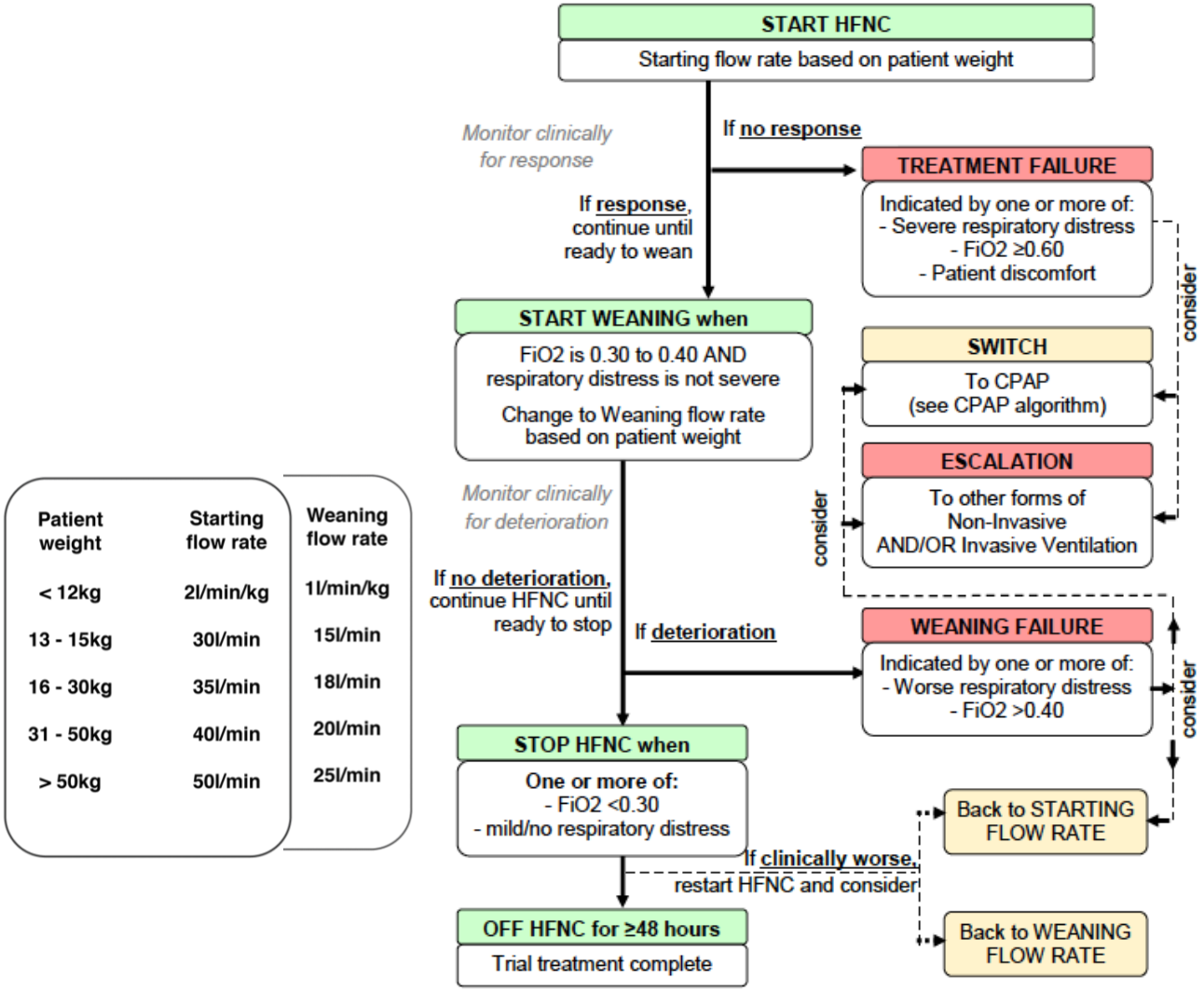
OR

✓ Within 72 hours of extubation following a period of invasive ventilation (*step-down RCT*)

Population Intervention Control Outcome

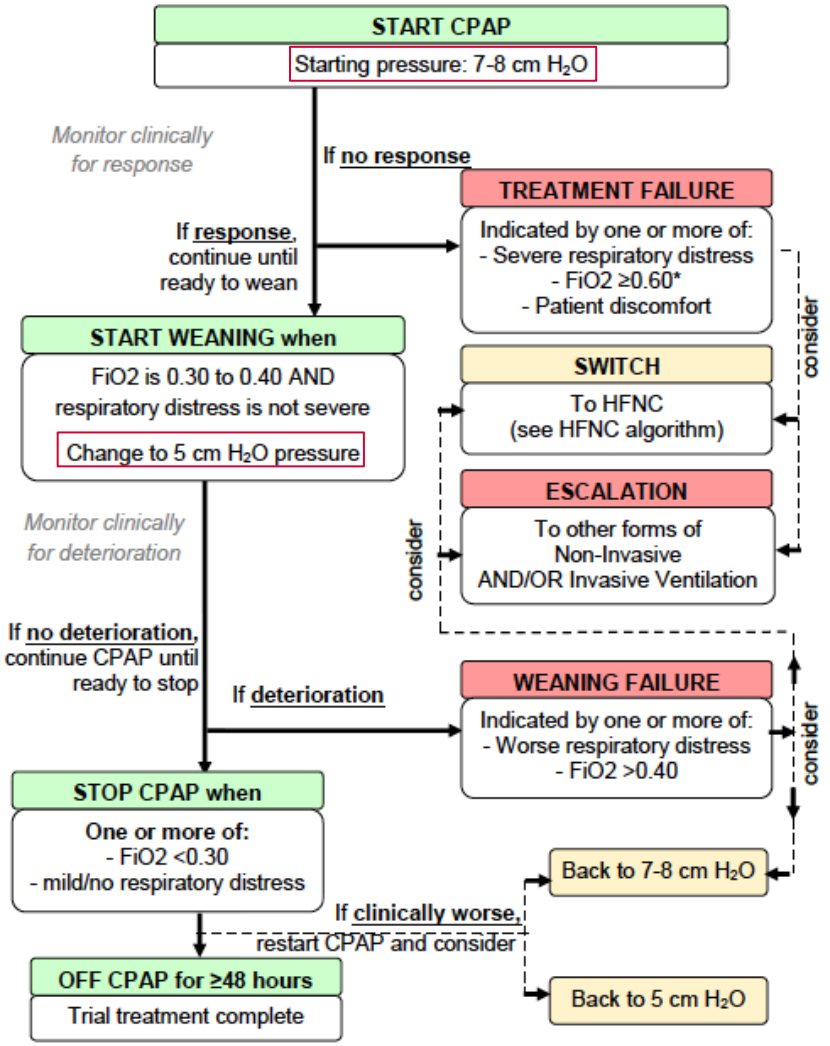
- Switch between HFNC and CPAP (and vice versa)
  - Ethically justifiable
  - Prevalent clinical practice
  - Consistent with previous RCTs
  - Unblinded nature = potential for bias
- Non-inferiority
  - Ease of use, patient comfort
  - Clinicians willing to tolerate some inferiority of HFNC
  - Consistent with previous RCTs

HFNC



Patient weight	Starting flow rate	Weaning flow rate
< 12kg	2l/min/kg	1l/min/kg
13 - 15kg	30l/min	15l/min
16 - 30kg	35l/min	18l/min
31 - 50kg	40l/min	20l/min
> 50kg	50l/min	25l/min

CPAP


START CPAP
Starting pressure: 7-8 cm H_2O
Monitor clinically for response
If no response
TREATMENT FAILURE
Indicated by one or more of:
- Severe respiratory distress
- FiO2 ≥0.60*
- Patient discomfort
If response, continue until ready to wean
START WEANING when
FiO2 is 0.30 to 0.40 AND respiratory distress is not severe
Change to 5 cm H_2O pressure
SWITCH
To HFNC
(see HFNC algorithm)
ESCALATION
To other forms of Non-Invasive AND/OR Invasive Ventilation
consider
consider
Monitor clinically for deterioration
If no deterioration, continue CPAP until ready to stop
If deterioration
WEANING FAILURE
Indicated by one or more of:
- Worse respiratory distress
- FiO2 >0.40
consider
STOP CPAP when
One or more of:
- FiO2 <0.30
- mild/no respiratory distress
Back to 7-8 cm H_2O
If clinically worse, restart CPAP and consider
Back to 5 cm H_2O
OFF CPAP for ≥48 hours
Trial treatment complete

Superiority versus Noninferiority

Trial Design		Interpretation
Superiority	HFNC > CPAP	Intervention > Control
Equivalence	HFNC = CPAP	Intervention = Control Eg a new drug is not "unacceptably different" compared to the standard
Non-inferiority	HFNC < CPAP Reasonable alternative with a trade-off *Hazard ratio 0.75*	Intervention is not "unacceptably worse" than control The new drug may be meaningfully less efficacious compared to the standard but that lost efficacy is acceptable to us!

Population Intervention Control Outcome

- Choice between (re)intubation and duration of respiratory support

- Intubation
  - Simple, dichotomous measure
  - Anticipated 15-20% event rate
  - Large sample size for non-inferiority

- Duration of respiratory support
  - Include data from patients not re-intubated
  - Time-to-event outcome provides more power
  - Smaller sample size for non-inferiority
  - **Prioritised by parents/public members**

Primary outcome

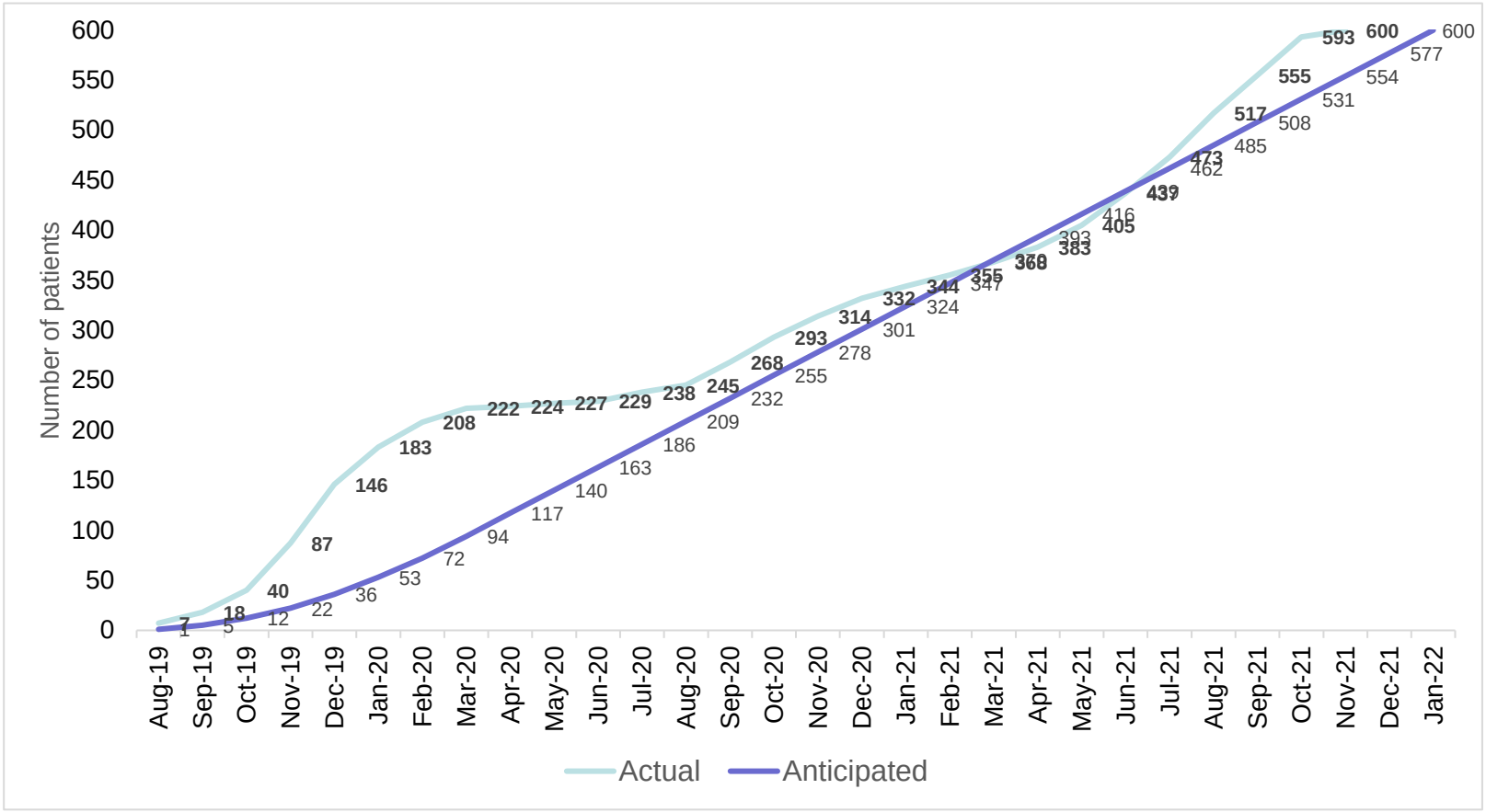
- Time to liberation from respiratory support
  - defined as the start of a 48-hour period during which the child was free of all forms of respiratory support (excluding supplemental oxygen).

Start HFNC	**Switch to CPAP**	**Intubation**	**Extubation**	**HFNC**	**Off HFNC for 48 hrs**

Start HFNC	**Intubation**	**Extubation**	**NC oxygen for 12 hrs**	**HFNC**	**Intubation**

Step up RCT

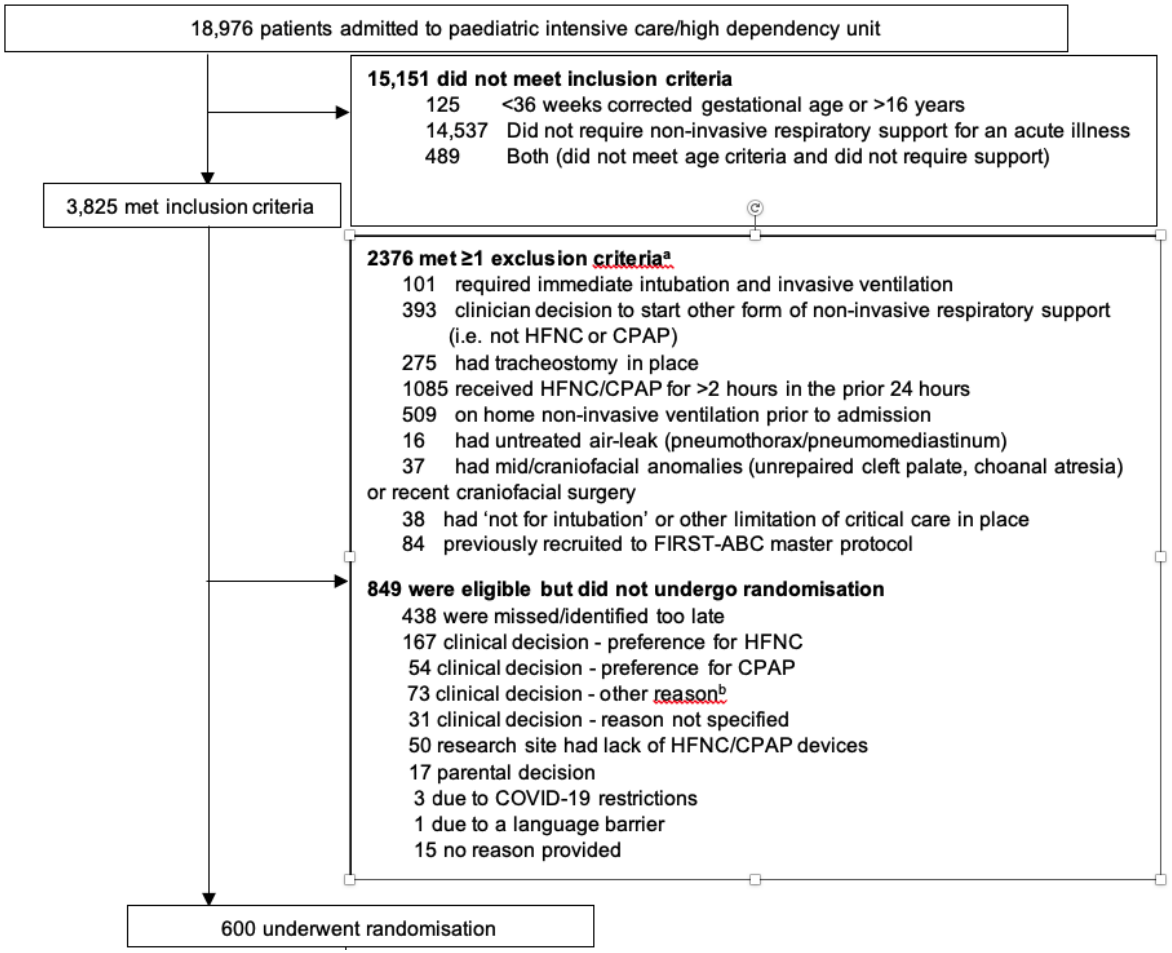
Patient recruitment



10 Aug 2019 – 7 Nov 2021 (27 months) in 24 PICU/HDUs

Interim analysis planned when 300 patients reached 60-day follow-up: continue trial

Step up RCT: CONSORT diagram

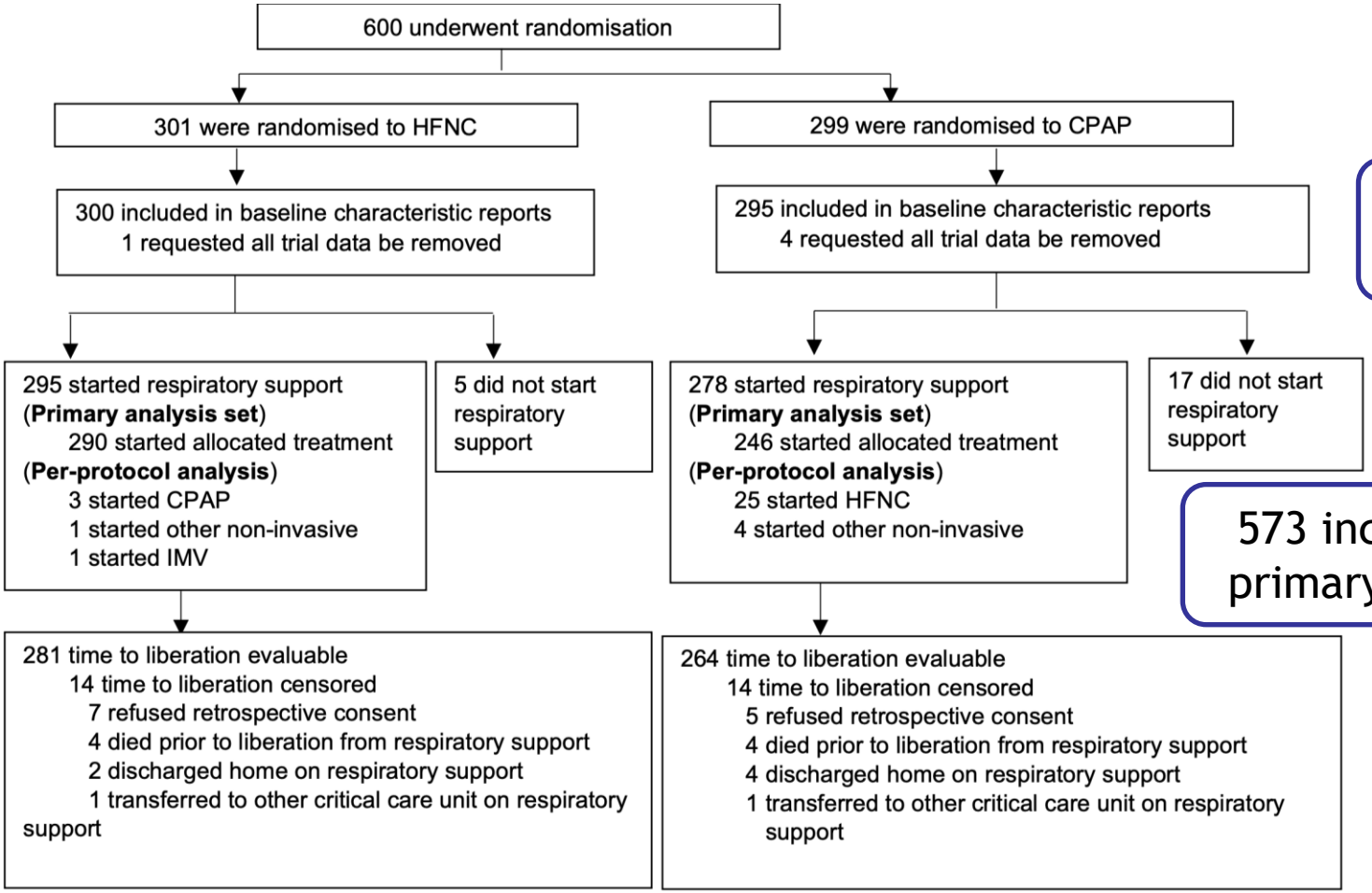


20% of admissions received non-invasive support

1449 eligible children

600 children were randomized

Step up RCT: CONSORT diagram



Baseline characteristics

Characteristic	HFNC (N=295)	CPAP (N=278)
Age, median (IQR), months	10 (2-31)	9 (1-27)
Sex - Female, no. (%)	116 (39.3)	110 (39.6)
At least one comorbidity, no. (%)	143 (48.5)	128 (46.2)
Main reason for admission, no. (%)		
Bronchiolitis	143 (48.5)	138 (49.6)
Cardiac	17 (5.8)	12 (4.3)
Other respiratory condition	55 (18.6)	57 (20.5)
Sepsis/infection	24 (8.1)	23 (8.3)
Upper airway problem	15 (5.1)	12 (4.3)
Neurological	4 (1.4)	2 (0.7)
Asthma/Wheeze	31 (10.5)	20 (7.2)
Other	6 (2.0)	13 (4.7)
Receiving noninvasive support at randomization, no. (%)	66 (22.4)	65 (23.4)

Baseline characteristics

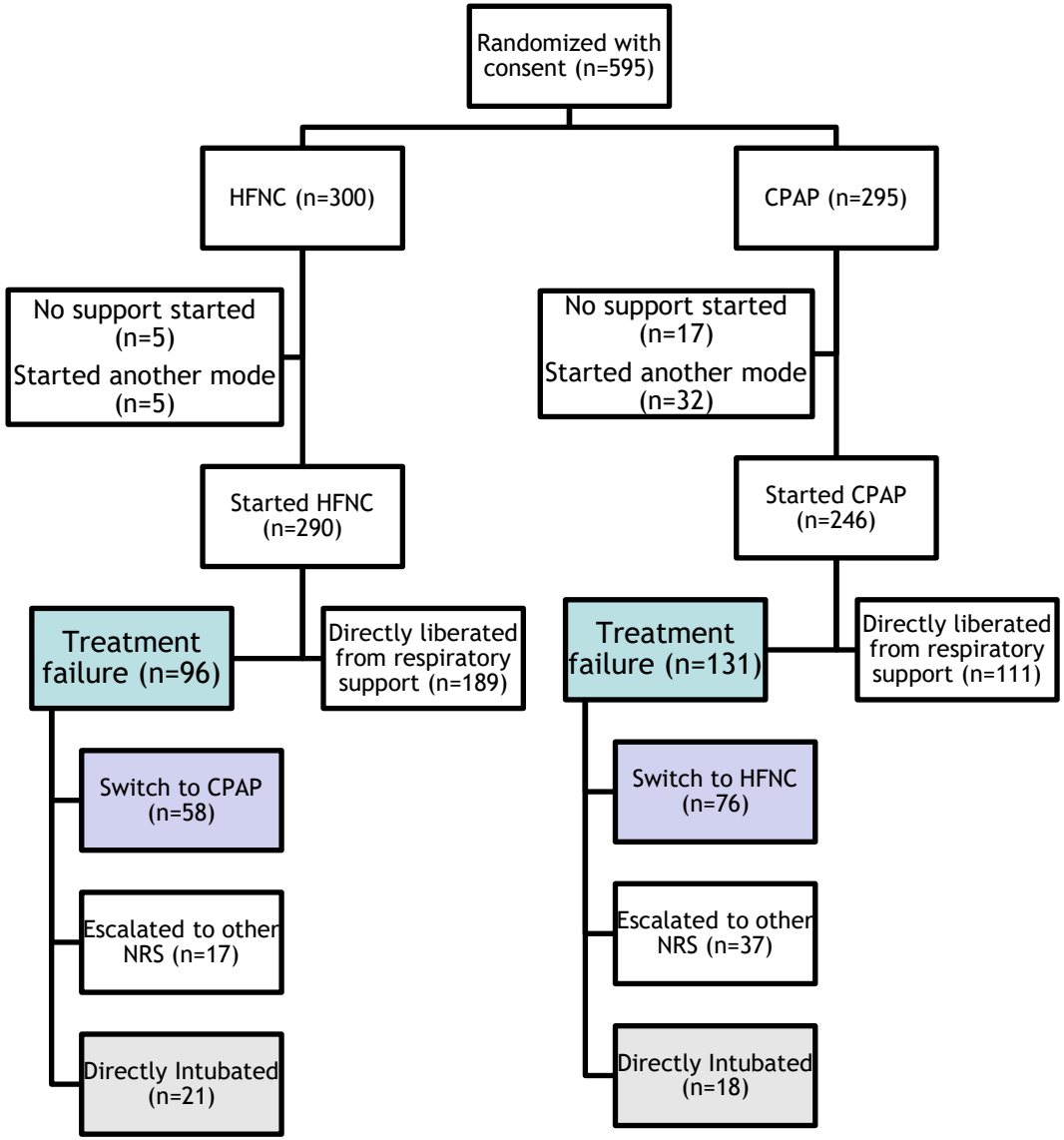
Clinical characteristics at randomization	HFNC (N=295)	CPAP (N=278)
Respiratory distress, no. (%)	N=244	N=227
None	14 (4.7)	12 (4.3)
Mild	47 (15.9)	39 (14.0)
Moderate	140 (47.5)	136 (48.9)
Severe	43 (14.6)	40 (14.4)
Respiratory rate, median (IQR), breaths/min	48 (38-60)	49 (39-60)
>90th centile for age	*186 (63.0)*	*165 (59.3)*
SpO2/FiO2 ratio, median (IQR)	313 (198-424)	330 (218-438)
</=265 (ALI threshold)	*125 (42.4)*	*114 (41.0)*
Heart rate, median (IQR), beats/minute	155 (140-171)	154 (140-173)
>90th centile for age	*163 (55.3)*	*157 (56.5)*

Switch and escalation

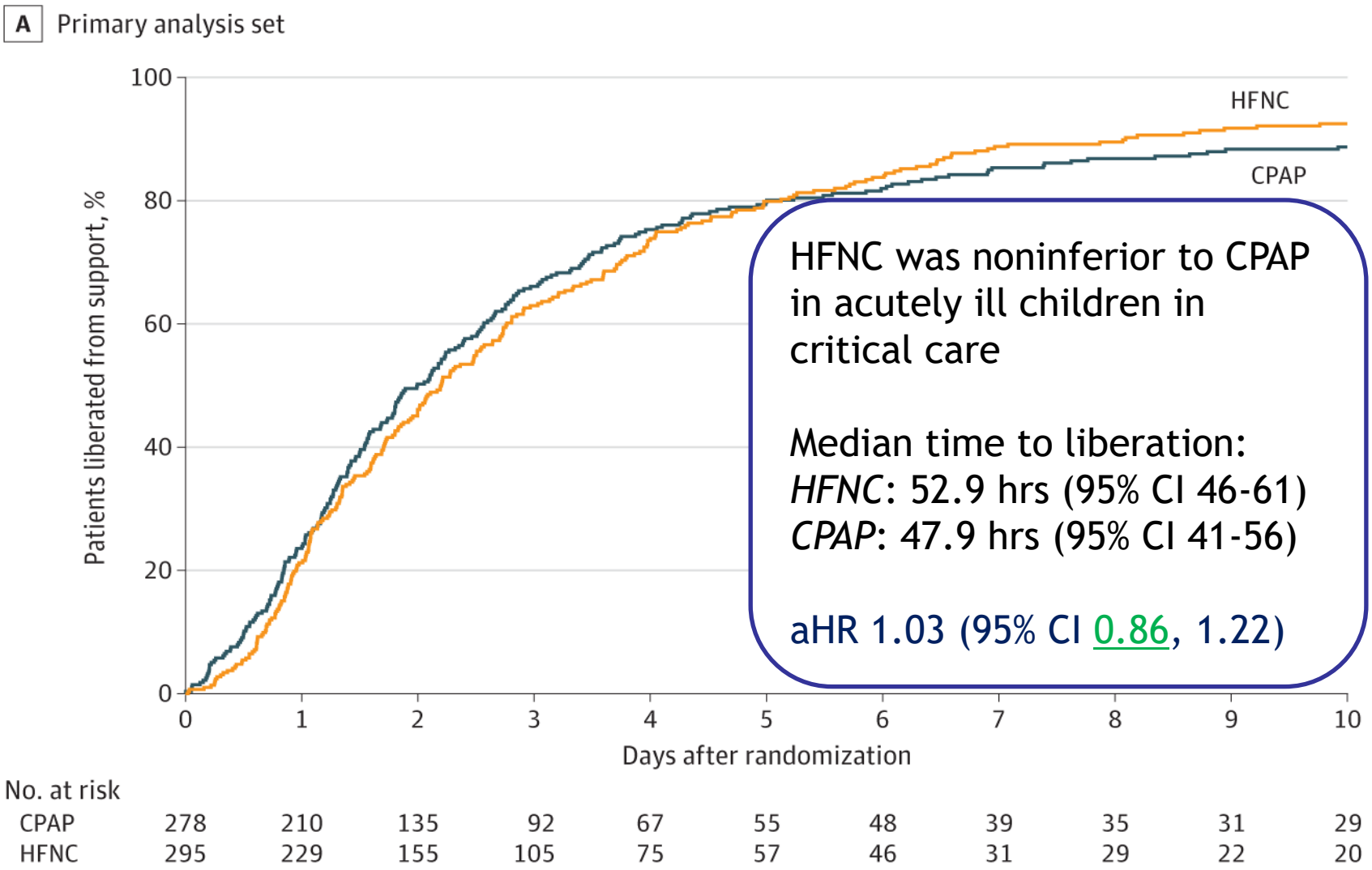
Treatment ‘failure’
HFNC: 96/290 (**33.1%**)
CPAP: 131/246 (**53.3%**)

Switch
HFNC to CPAP: 58/290 (**20.0%**)
(mainly clinical deterioration)

CPAP to HFNC: 76/246 (**30.9%**)
(mainly patient discomfort)



Step up RCT



HFNC was noninferior to CPAP in acutely ill children in critical care

Median time to liberation:
HFNC: 52.9 hrs (95% CI 46-61)
CPAP: 47.9 hrs (95% CI 41-56)

aHR 1.03 (95% CI 0.86, 1.22)

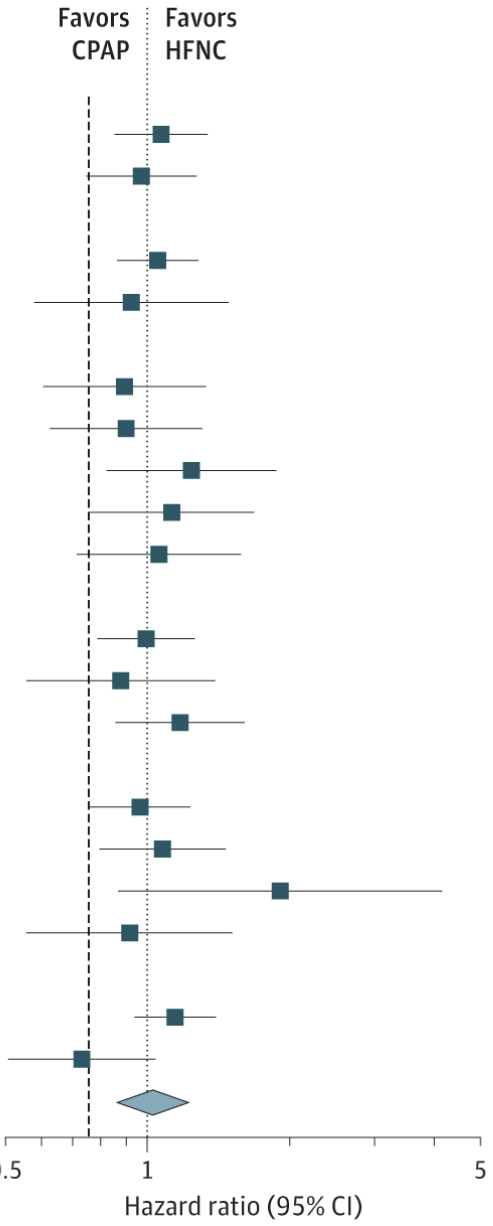
Secondary outcomes

Outcome	HFNC (N=281)	CPAP (N=272)	Adjusted effect estimate
Intubation at 48 hours, no./N (%)	45/292 (15.4)	44/276 (15.9)	OR 0.99 (0.61, 1.6)
Bronchiolitis subgroup only**	15/143 (10.5)	10/138 (7.2)	
Mean (SD) COMFORT-B score while on randomized treatment	14.1 (3.6)	14.4 (4.8)	MD -0.6 (-1.4, 0.2)
Sedation used during non-invasive support, no./N (%)	81/292 (27.7))	97/262 (37.0)	OR 0.59 (0.4, 0.9)
Mean (SD) duration of PICU/HDU stay	5.0 (8.2)	7.4 (18.9)	MD -0.3 (-5.1, -1.0)
Mean (SD) duration of acute hospital stay	13.8 (26.8)	19.5 (47.7)	MD -7.6 (-13.2, -1.9)
Mortality			
At PICU discharge	5/292 (1.7)	4/274 (1.5)	OR 1.22 (0.3, 4.6)

OR, odds ratio; MD, mean difference

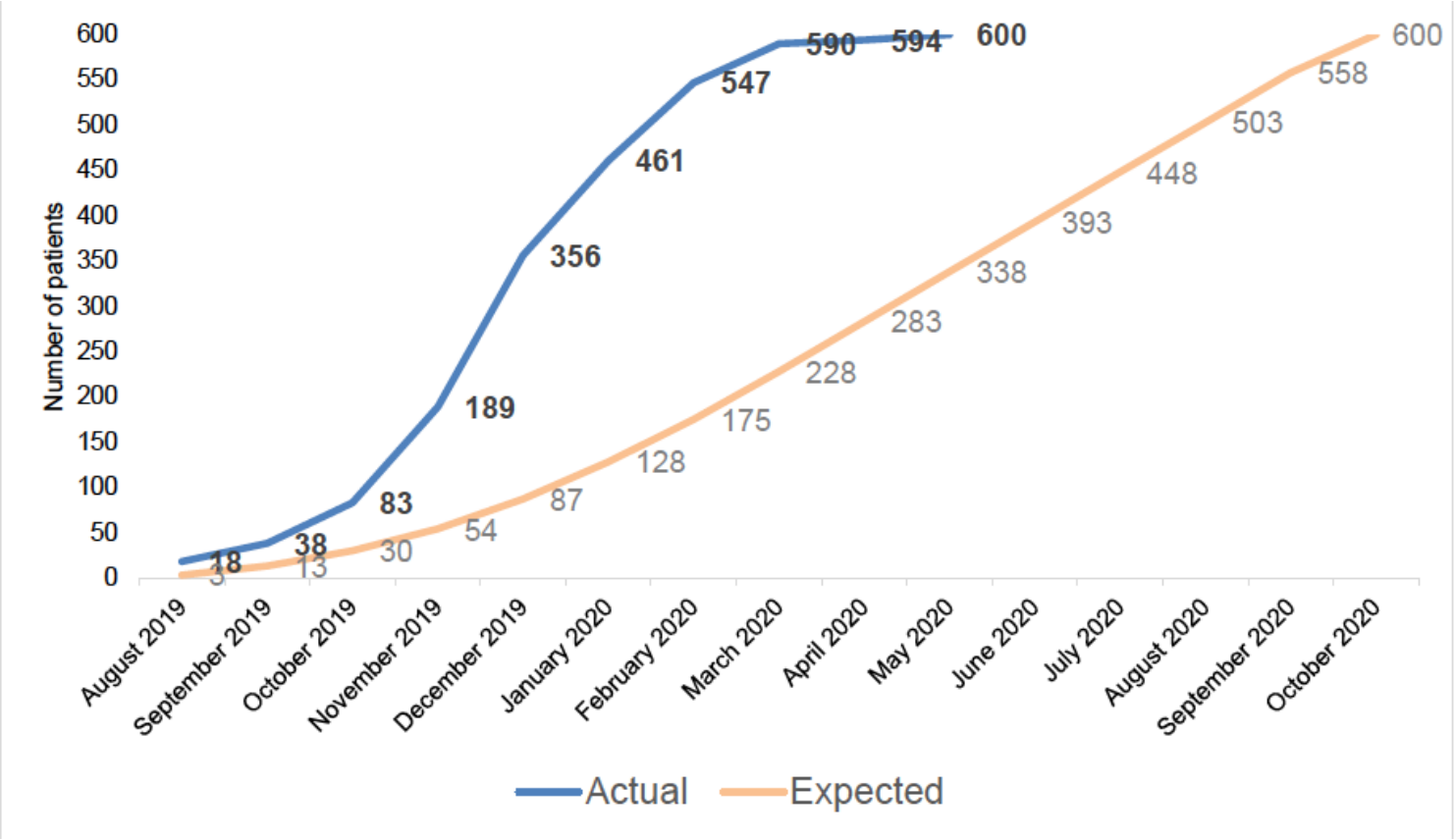
Subgroup analyses

Subgroup	Events/ person-days	Hazard ratio (95% CI)	*P* value
Age, mo			.59
<12	317/1560	1.07 (0.85-1.34)	
≥12	228/1357	0.97 (0.74-1.27)	
Respiratory distress			.63
Not severe	372/1700	1.05 (0.86-1.28)	
Severe	81/379	0.92 (0.58-1.48)	
Spo_2:FIo_2 ratio by quintile			.50
≤184	104/666	0.89 (0.60-1.33)	
>184 to ≤250	122/396	0.90 (0.62-1.31)	
>250 to ≤366	100/764	1.24 (0.82-1.87)	
>366 to ≤452	106/431	1.13 (0.75-1.68)	
>452	102/570	1.06 (0.71-1.58)	
Comorbidities			.55
None	297/712	0.99 (0.78-1.26)	
Neurological/neuromuscular	77/411	0.88 (0.55-1.39)	
Other	170/1794	1.17 (0.86-1.61)	
Reason for admission			.41
Bronchiolitis	275/793	0.96 (0.76-1.23)	
Other respiratory	180/1245	1.08 (0.79-1.46)	
Cardiac	26/569	1.91 (0.87-4.21)	
Other reason	63/311	0.91 (0.55-1.51)	
Receiving support at randomization			.03
No	417/2535	1.14 (0.94-1.40)	
Yes	128/382	0.73 (0.51-1.04)	
Overall	545/2918	1.03 (0.86-1.22)	



Step-down RCT

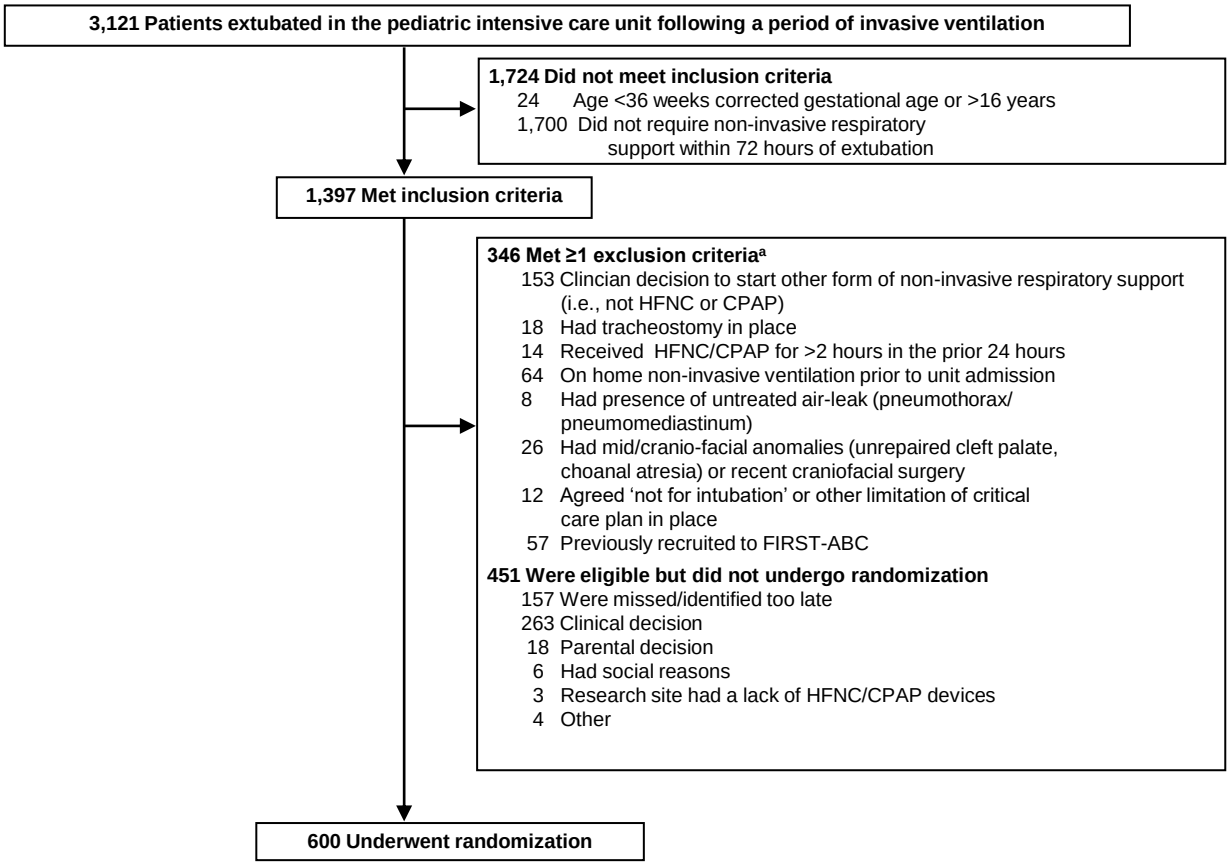
Patient recruitment



8 Aug 2019 – 18 May 2020 (9 months) in 22 PICUs

Interim analysis planned when 300 patients reached 60-day follow-up - deemed redundant

Step down RCT: CONSORT diagram



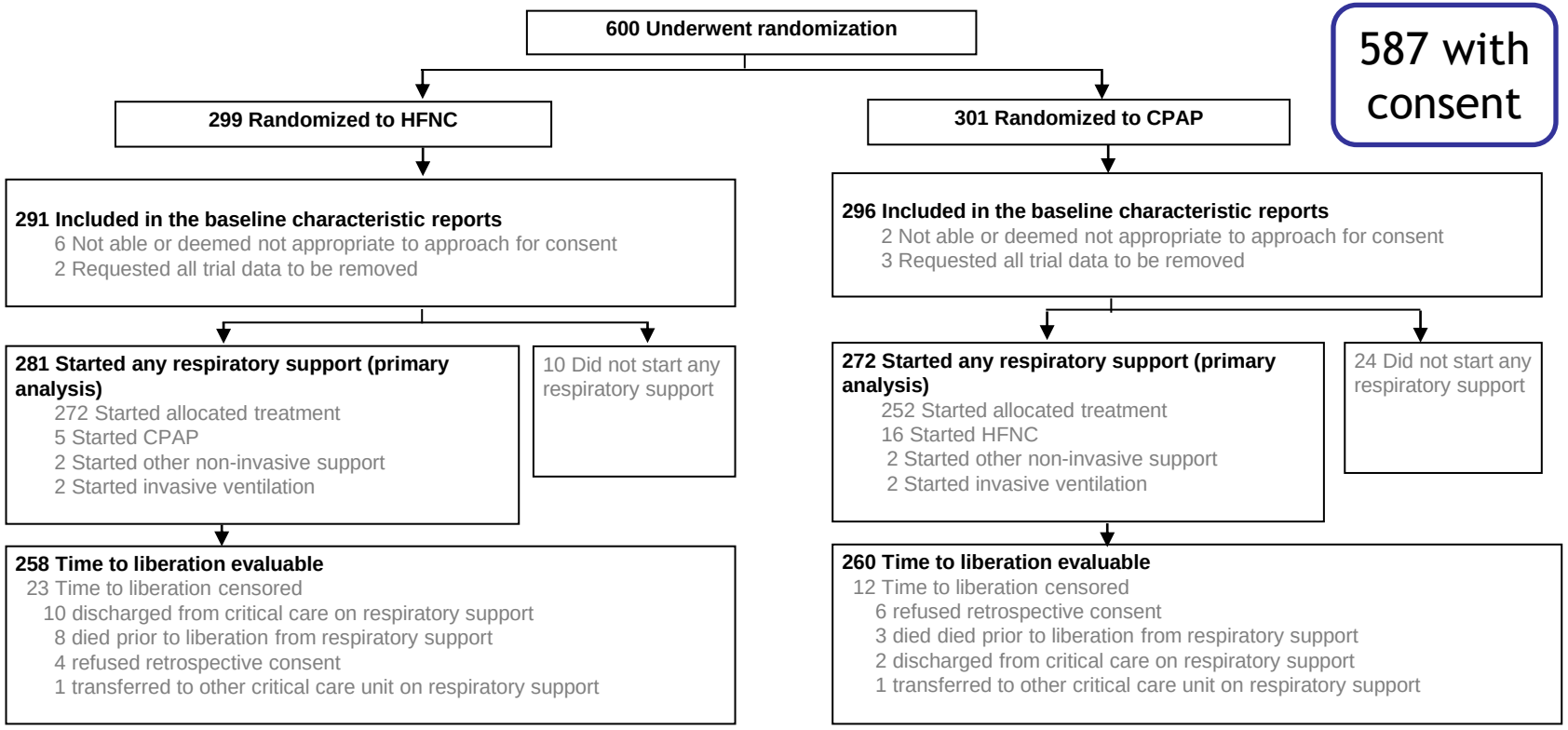
45% of extubated children received post-extubation support**

57% of eligible patients were randomized

**Badruddin et al, VPS cohort: 783/1765 (43.7%) infants with bronchiolitis were started on NRS post-extubation.

**Richter et al, single centre CHD cohort: 260/514 (50.6%) started on NRS post-extubation after CHD surgery.

Step down RCT: CONSORT diagram



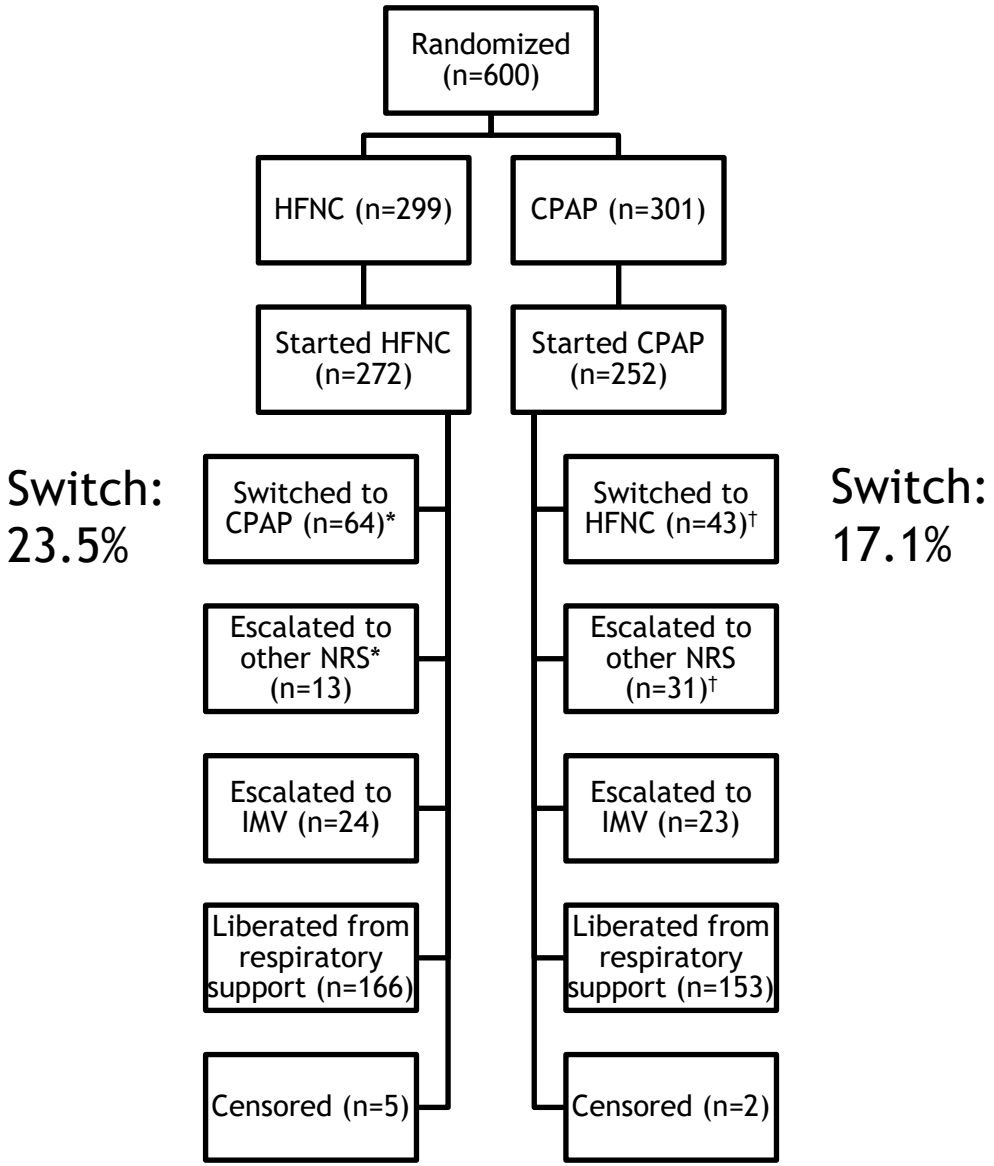
Baseline characteristics

Characteristic	HFNC (N=281)	CPAP (N=272)
Age, median (IQR), months	3 (1-10)	3 (1-11)
Sex - Female, no. (%)	111 (39.5)	130 (47.8)
At least one comorbidity, no. (%)	171 (60.9)	155 (57.0)
Main reason for invasive ventilation, no. (%)		
Bronchiolitis	97 (34.5)	122 (44.9)
Cardiac	81 (28.8)	55 (20.2)
Other respiratory condition	42 (14.9)	34 (12.5)
Sepsis/infection	12 (4.3)	10 (3.7)
Upper airway problem	9 (3.2)	13 (4.8)
Neurological	7 (2.5)	13 (4.8)
Asthma/Wheeze	1 (0.4)	5 (1.8)
Other	32 (11.4)	20 (7.4)
Duration of prior invasive ventilation, median (IQR), hours	89 (56-145)	87 (51-140)
Nature of post-extubation non-invasive respiratory support, no. (%)		
Planned (*randomized before extubation*)	178 (63.3)	168 (61.8)
Indeterminate (*randomized within 1 hr of extubation*)	49 (17.4)	49 (18.0)
Rescue (*randomized at least 1 hour after extubation*)	54 (19.2)	55 (20.2)

Baseline characteristics

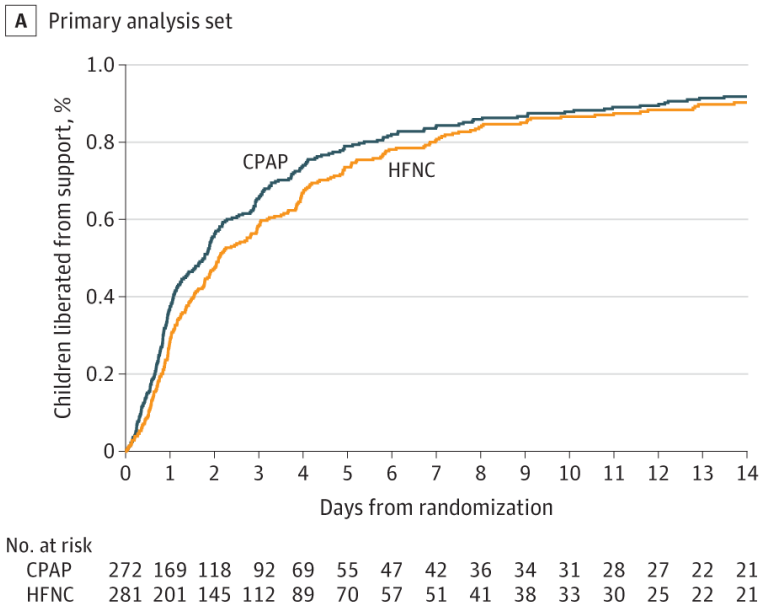
Clinical characteristics at randomization	HFNC (N=281)	CPAP (N=272)
Respiratory distress, no. (%)	N=210	N=198
None	126 (60.0)	112 (56.6)
Mild	58 (27.6)	52 (26.3)
Moderate	22 (10.5)	29 (14.6)
Severe	4 (1.9)	5 (2.5)
Respiratory rate, median (IQR), breaths/min	35 (27-45)	36 (28-45)
Peripheral oxygen saturation, median (IQR), %	96 (94-98)	97 (94-99)
Fraction of inspired oxygen, median (IQR)	0.30 (0.24-0.35)	0.30 (0.25-0.35)
SpO2/FiO2 ratio, median (IQR)	327 (271-400)	327 (274-396)
Heart rate, median (IQR), beats/minute	128 (115-145)	132 (115-147)
COMFORT-B score, mean (SD)	13.8 (2.7)	14.3 (3.2)

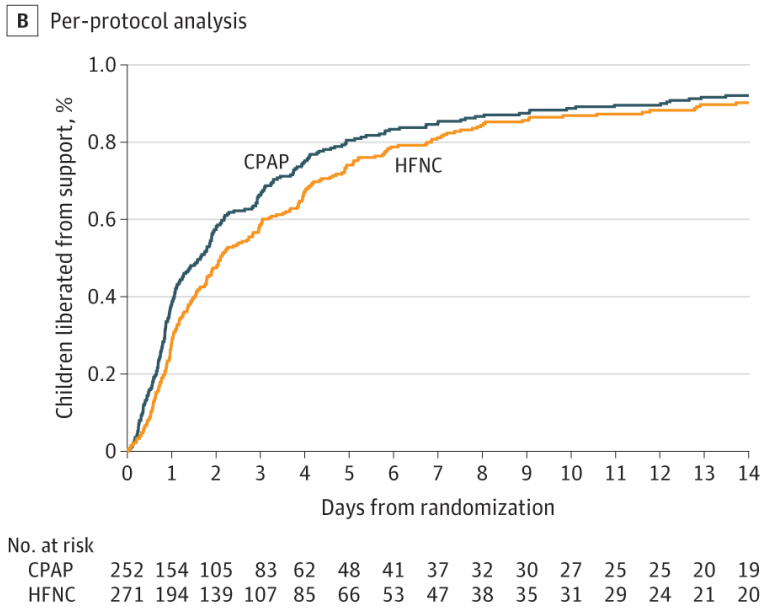
Switch and escalation



Treatment 'failure'
HFNC: 101/272 (**37.1%**)
CPAP: 85/252 (**33.7%**)

Step-down RCT





Median time to liberation:
HFNC: 50.5 hrs (95% CI 43-68)
CPAP: 42.9 hrs (95% CI 31-48)

aHR 0.83 (95% CI 0.70, 0.99)

HFNC was NOT noninferior to CPAP following extubation

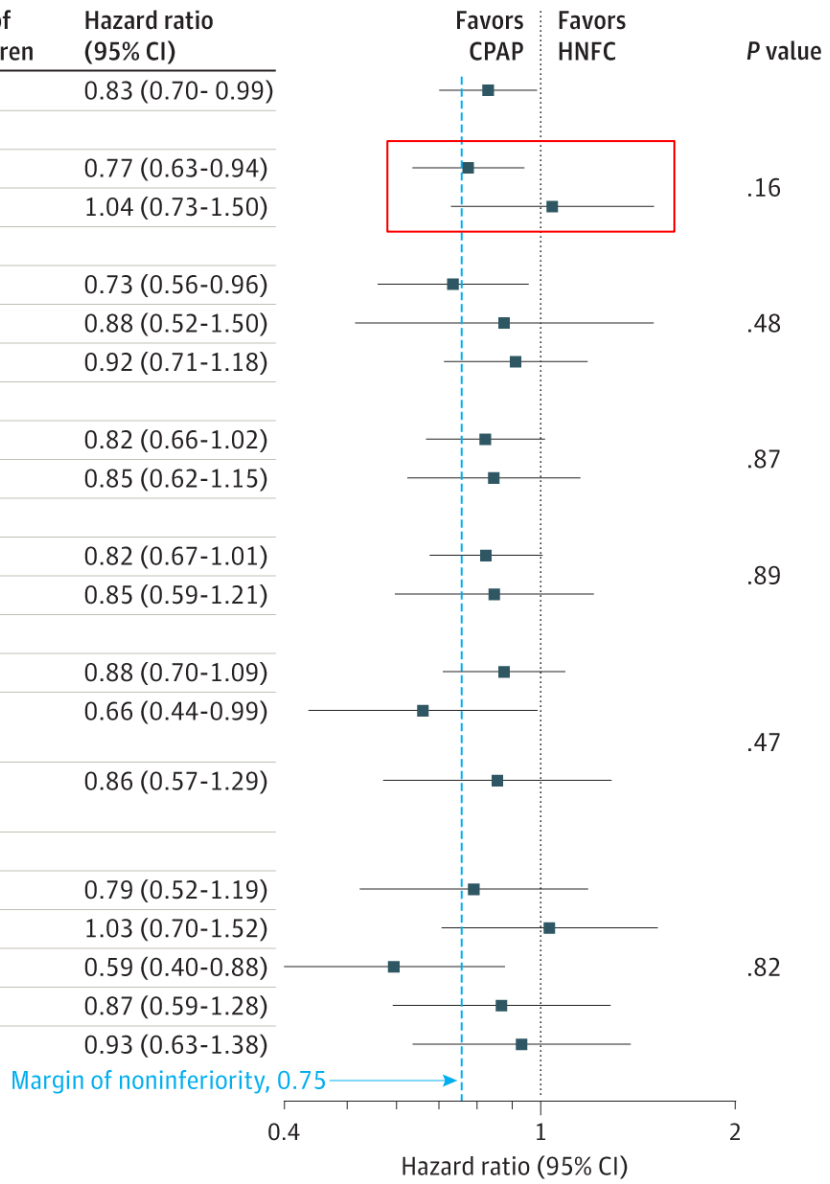
Secondary outcomes

Outcome	Primary analysis HFNC (N=281)	Primary analysis CPAP (N=272)	Adjusted effect estimate
Reintubation at 48 hours, no./N (%)	37/279 (13.3)	31/269 (11.5)	OR 1.11 (0.7, 1.9)
Mean (SD) COMFORT-B score while on randomized treatment	13.6 (2.7)	13.2 (2.2)	MD 0.44 (-0.1, 1.0)
Sedation used during non-invasive support, no./N (%)	168/276 (60.9)	149/264 (56.4)	OR 1.14 (0.8, 1.6)
Mean (SD) Parental stress (PSS:PICU) score	1.8 (0.7)	1.8 (0.8)	MD 0.07 (-0.1, 0.3)
Mean (SD) duration of PICU stay	6.6 (13.4)	6.9 (16.0)	MD -0.56 (-3.0, 1.9)
Mean (SD) duration of acute hospital stay	20.6 (35.3)	20.6 (34.5)	MD -1.01 (-6.9, 4.8)
Mortality			
At PICU discharge	5/277 (1.8)	3/267 (1.1)	OR 2.69 (0.5, 15.4)
At day 60	11/270 (4.1)	3/256 (1.2)	OR 5.99 (1.2, 28.7)
At day 180	15/268 (5.6)	6/253 (2.4)	OR 3.07 (1.1, 8.8)

OR, odds ratio; MD, mean difference

Subgroup analyses

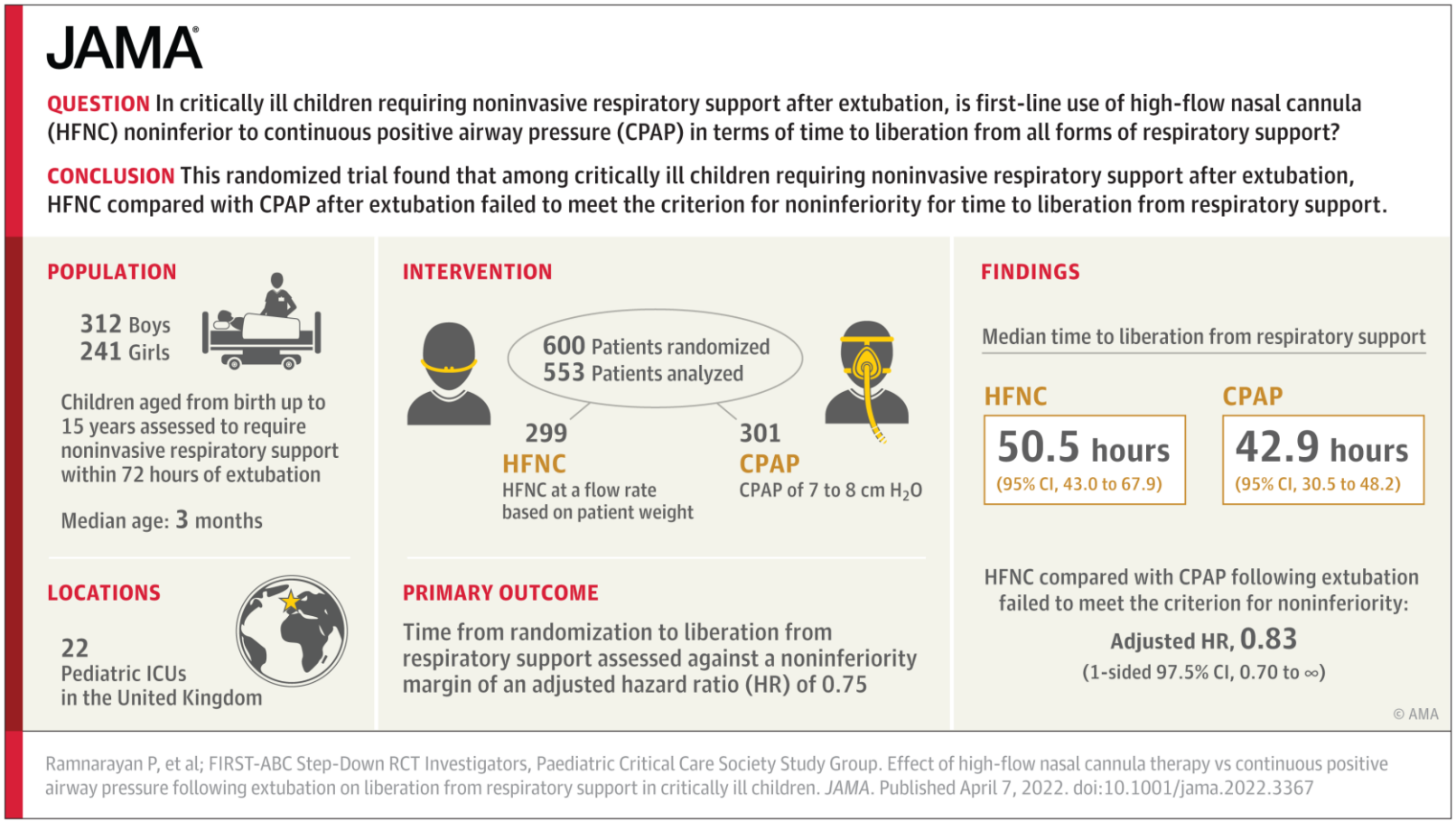
Subgroup	No. of children	Hazard ratio (95% CI)	*P* value
Overall	553	0.83 (0.70- 0.99)	
Age (grouped), mo			
<12	422	0.77 (0.63-0.94)	.16
≥12	131	1.04 (0.73-1.50)	
Comorbidities (grouped)			
None	227	0.73 (0.56-0.96)	
Neurologic/neuromuscular	63	0.88 (0.52-1.50)	.48
Other	263	0.92 (0.71-1.18)	
Duration of prior IMV, d			
0-4	372	0.82 (0.66-1.02)	.87
≥5	181	0.85 (0.62-1.15)	
Main reason for invasive ventilation			
Not cardiac	417	0.82 (0.67-1.01)	.89
Cardiac	136	0.85 (0.59-1.21)	
Nature of respiratory support			
Planned (extubation after randomization)	346	0.88 (0.70-1.09)	
Indeterminate (<1 h extubation to randomization)	98	0.66 (0.44-0.99)	.47
Rescue (≥1 h from extubation to randomization)	109	0.86 (0.57-1.29)	
Quintiles of Spo_2:FIO_2			
5 (≥417)	100	0.79 (0.52-1.19)	
4 (357-416)	112	1.03 (0.70-1.52)	
3 (317-356)	109	0.59 (0.40-0.88)	.82
2 (263–316)	113	0.87 (0.59-1.28)	
1 (<263)	112	0.93 (0.63-1.38)	



Step up RCT versus Step down RCT

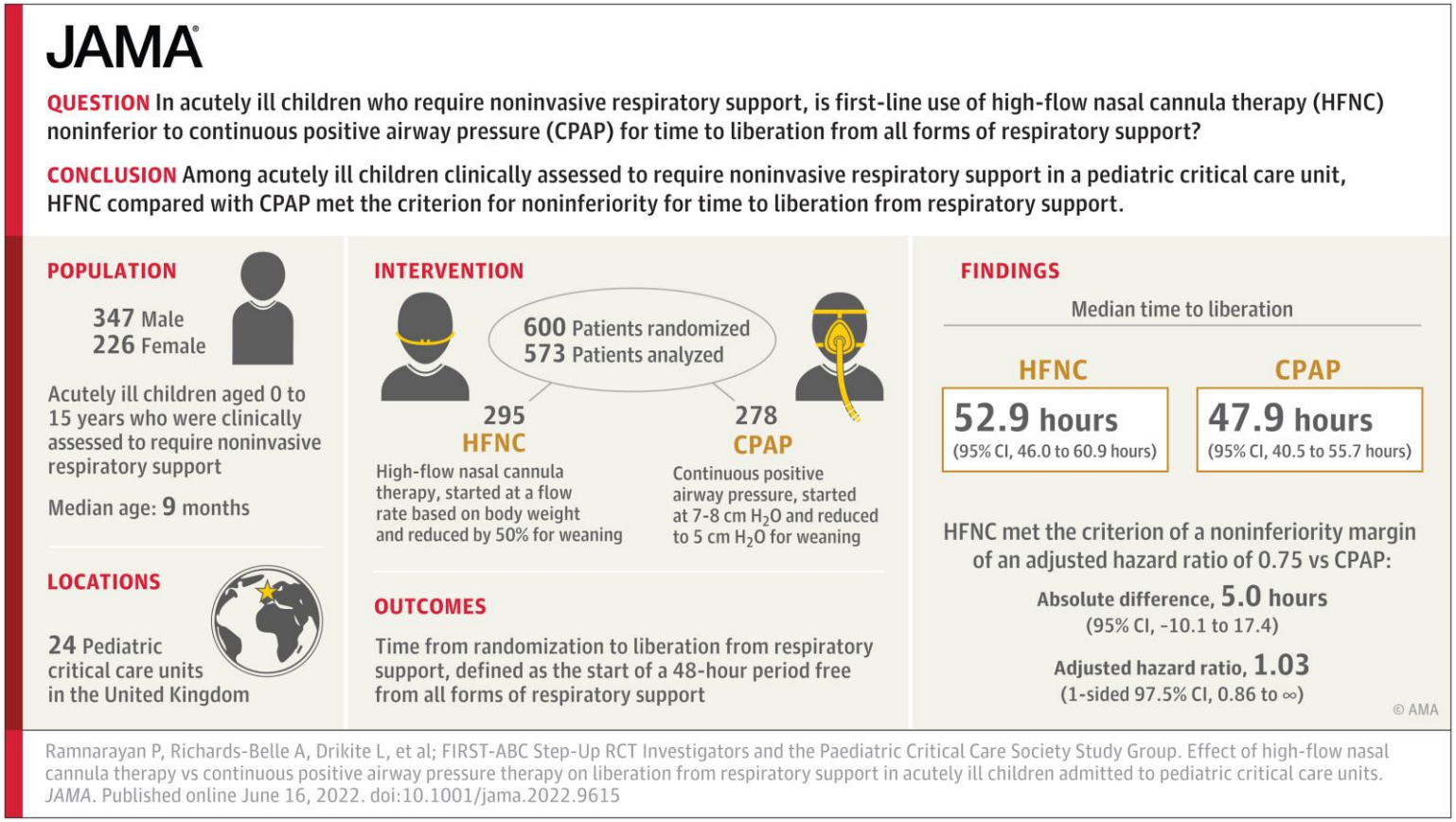
	Step-up RCT		Step-down RCT	
Clinical characteristics	**HFNC**	**CPAP**	**HFNC**	**CPAP**
Age in months, median (IQR)	10 (2, 31)	9 (1, 27)	3 (1, 10)	3 (1, 11)
SpO2/FiO2 ratio, median	313	330	327	327
Main diagnosis - bronchiolitis	48.5%	49.6%	34.5%	44.9%
Post-surgical admission	4.7%	3.6%	21.4%	19.1%
Outcomes				
Sedation while on HFNC/CPAP	27.7%	37.0%	60.9%	56.4%
(Re)Intubation	15.4%	15.9%	13.3%	11.5%

From: **Effect of High-Flow Nasal Cannula Therapy vs Continuous Positive Airway Pressure Following Extubation on Liberation From Respiratory Support in Critically Ill Children: A Randomized Clinical Trial**



HFNC was NOT noninferior to CPAP following extubation

From: **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**



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. *JAMA*. Published online June 16, 2022. doi:10.1001/jama.2022.9615

HFNC was noninferior to CPAP in acutely ill children in critical care

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