Supplement 1 to

Effect of high flow nasal cannula therapy versus continuous positive airway pressure on liberation from respiratory support in acutely ill children admitted to pediatric critical care units: a randomized clinical trial

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for the FIRST-ABC Step-Up RCT Investigators and the Paediatric Critical Care Society Study Group

This supplement contains the following items:

1. Original protocol, final protocol, summary of changes
2. Original/final statistical analysis plan

Trial Protocol summary of changes

Master Protocol v1.1, 24 June 2019

Original approved protocol

Master Protocol v1.2, 23 January 2020

1) Section 2.2.2: addition of ‘Clinician decision to start other form of non-invasive respiratory support (i.e. not HFNC or CPAP)’ exclusion criteria
2) Sections 1.3.3. and 2.4.2: clarification that patient comfort (secondary outcome) will be assessed ‘during non-invasive respiratory support i.e. HFNC and/or CPAP’
3) Section 2.12.3: additional detail of pre-specified planned subgroup analyses added
4) Section 2.12.3: confirmation that the interim analysis will take place only in the step-up RCT due to faster than anticipated recruitment to the step-down RCT, and addition of safety monitoring of the step-down RCT by the DMEC
5) Section 2.5.2: algorithms updated and corrected
6) Minor administrative changes

Statistical analysis plan

Statistical analysis plan v1.0, 18 March 2020

Original/final statistical analysis plan, no changes required

UCL INSTITUTE OF CHILD HEALTH

icnarc intensive care national audit & research centre

Great Ormond Street Hospital for Children NHS Foundation Trust

Joint Research and Development Office
Division of Research and Innovation

FIRST-line support for **A**ssistance in **B**reathing in **C**hildren (**FIRST-ABC**): A master protocol of two randomised trials to evaluate the non-inferiority of high flow nasal cannula (HFNC) versus continuous positive airway pressure (CPAP) for non-invasive respiratory support in paediatric critical care

STUDY SHORT TITLE
FIRST-ABC

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Chief Investigator
Dr Padmanabhan Ramnarayan

Sponsor representative
Dr Jenny Rivers

Signature page

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to appropriate research governance frameworks and any subsequent amendments of regulations, Good Clinical Practice (GCP) guidelines, the Sponsor's Standard Operating Procedures (SOPs), and other regulatory requirements where relevant.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies from the trial as planned in this protocol will be explained.

For and on behalf of the Trial Sponsor:

Signature: Date:

..../...../.....

Name (please print):
Dr Jenny Rivers

Position:
Deputy Director of Research and Innovation

Chief Investigator:

Signature: Date:

..../...../.....

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Summary

Data category	Information
Primary registry and trial identifying number	ISRCTN60048867
Date of registration in primary registry	19/06/2019
Source(s) of monetary or material support	National Institute for Health Research Health Technology Assessment Programme
Primary Sponsor	Great Ormond Street Hospital for Children NHS Foundation Trust
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Public title	FIRST-line support for Assistance in Breathing in Children (FIRST-ABC)
Scientific title	FIRST-line support for Assistance in Breathing in Children (FIRST-ABC): a master protocol of two randomised trials to evaluate the non-inferiority of high flow nasal cannula (HFNC) versus continuous positive airway pressure (CPAP) for non-invasive respiratory support in paediatric critical care
Countries of recruitment	United Kingdom
Health condition(s) or problem(s) studied	Non-invasive respiratory support
Intervention(s)	Interventions: HFNC vs. CPAP
Key inclusion and exclusion criteria	Ages eligible for study: >36 weeks corrected gestational age and <16 years Sexes eligible for study: both Accepts healthy volunteers: no Inclusion criteria: 1. Admitted/Accepted for admission to PICU/HDU 2. Age >36 weeks corrected gestational age and <16 years 3. Assessed by the treating clinician to require non-invasive respiratory support, **EITHER** **a.** for an acute illness (step-up RCT) **OR**

Data category	Information
	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
Study type	Master protocol of two pragmatic, multi-centre, parallel groups, non-inferiority RCTs with shared infrastructure Interventional Allocation: randomised Blinding: cannot be blinded Primary purpose: prevention Phase IV
Date of first enrolment	Anticipated 1 July 2019
Target sample size	1,200 overall; 600 (step-up RCT) and 600 (step-down RCT)
Primary outcomes	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
Key secondary outcomes	• Mortality at PICU/HDU discharge, day 60 and day 180 • rate of (re)intubation at 48 hours • duration of PICU/HDU and hospital stay • patient comfort, during randomised treatment, measured using the COMFORT-B score • proportion of patients in whom sedation is used during non-invasive respiratory support

Data category	Information
	• parental stress, in hospital at the time of consent, measured using the Parental Stressor Scale: PICU (PSS:PICU) • Health-related Quality of Life at six months using age-appropriate Pediatric Quality of Life Inventory (Peds-QL) and The Child Health Utility 9D (CHU-9D)
Cost effectiveness analysis outcomes	• Total costs at six months • Quality-Adjusted Life Years (QALYs) at six months • Net monetary benefit gained at a willingness-to-pay of £20,000 per QALY at six months associated with HFNC vs. CPAP

Contents

Abbreviations

CHU 9D	The Child Health Utility 9D
CI	Chief Investigator
CPAP	Continuous Positive Airway Pressure
CRF	Case Report Form
CTU	Clinical Trials Unit
GCP	Good Clinical Practice
GOSH	Great Ormond Street Hospital
HDU	high dependency unit
HFNC	High Flow Nasal Cannula
HrQoL	Health-related Quality of Life
ICH	International Conference of Harmonisation
NHS	National Health Service
NRS	Non-invasive Respiratory Support
Peds-QL	Paediatric Quality of Life Inventory
PI	Principal Investigator
PICANet	The Paediatric Intensive Care Audit Network
PICS-SG	Paediatric Intensive Care Society Study Group
PICU	Paediatric Intensive Care Unit
PIS	Participant Information Sheet
PPI	Patient and Public Involvement
PSS:PICU	Parental stressor scale: PICU
QALYs	Quality-Adjusted Life Years
R&D	Research and Development
RCT	Randomised Clinical Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
UCL	University College London

1. Background and rationale

Over 20,000 critically ill children are admitted to paediatric critical care units in the UK and nearly three-quarters of these children receive some form of respiratory support (invasive and/or non-invasive), making it the most common treatment provided in paediatric critical care.[1] Although endotracheal intubation and invasive mechanical ventilation (IMV) can be a life-saving procedure, increasing recognition of its risks, such as ventilator-induced lung injury and nosocomial infections, have prompted greater use of non-invasive respiratory support (NRS) techniques in PICUs worldwide.[1 2]

NRS is currently used in two distinct clinical scenarios: 1) in acutely ill children, to prevent intubation and IMV (step-up treatment), and 2) in children who have just come off IMV, to prevent re-intubation and further IMV (step-down treatment). Continuous positive airway pressure (CPAP), involving the delivery of pressurised air/oxygen through a face mask or nasal prongs, is a mode of NRS that PICU clinicians have been familiar with and have used for over three decades.[3-5] Even though observational data suggest that CPAP is effective (~80% of children started on CPAP do not progress to need IMV), there have been few randomised clinical trials (RCTs) of CPAP in critically ill children.[5 6] CPAP can be uncomfortable and is associated with a small but significant risk of complications such as air-leak and nasal trauma, necessitating the use of sedation, close monitoring and a high level of nursing input.

More recently, an alternate mode of NRS, high-flow nasal cannula therapy (HFNC), has gained popularity since it is easy to use and well tolerated by patients.[7-10] Single-centre studies from the United States and Canada and audit data from the United Kingdom indicate that 16–35% of PICU admissions currently receive HFNC at some point during their stay.[1 11 12] Through diverse mechanisms such as reduction of airway resistance, reduction of dead space by nasopharyngeal washout with fresh gas and delivery of positive airway pressure (“CPAP effect”), HFNC has been shown to reduce the work of breathing and improve oxygenation and ventilation in children. In particular, the benefits of HFNC (improved patient comfort, safety profile and ease of nursing care) must 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 critical care/hospital stay).

However, there are few RCTs comparing HFNC with CPAP in the paediatric critical care setting.[13-15] The evidence available from RCTs[15 16] does not yet definitively support the effectiveness of either HFNC or CPAP in critically ill children. 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 paediatric critical care.

Therefore, the FIRST-ABC RCTs address an important clinical dilemma faced daily by paediatric critical care clinicians in the United Kingdom (UK): in a child requiring non-invasive respiratory support, which of the two commonly available modalities, HFNC or CPAP, should they use as first-line therapy to achieve the best patient outcomes?

Our research question was recently prioritised by the multi-disciplinary UK Paediatric Intensive Care Society Study Group (PICS-SG) as an important research topic for the NHS. In addition, as identified in our PPI work, parents/patients have identified this as an important topic for the NHS.

This Protocol has been written in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 statement.[17]

1.1 Pilot and feasibility work

A multi-centre pilot RCT was conducted to explore the feasibility of performing a pragmatic RCT comparing CPAP and HFNC in critically ill children.[18] The results of the pilot RCT confirmed that it was feasible to conduct a large pragmatic national RCT of non-invasive respiratory support in the paediatric critical care setting in both step-up and step-down NRS. Moreover, it informed the design and conduct of the current RCTs.

1.2 Hypothesis

In critically ill children assessed by the treating clinician to require non-invasive respiratory support (NRS), first-line use of high flow nasal cannula (HFNC) is non-inferior to continuous positive airway pressure (CPAP) in time to liberation from respiratory support.

1.3 Aims and objectives

1.3.1 Aim

The aim of the FIRST-ABC RCTs is to evaluate the clinical and cost effectiveness of the use of HFNC, as compared with CPAP, as the first-line mode of non-invasive respiratory support in critically ill children to (A) prevent progression to intubation/invasive ventilation (step-up RCT) or (B) prevent re-intubation after being extubated following a period of invasive ventilation (step-down RCT).

1.3.2 Primary objective

To evaluate the non-inferiority of HFNC, as compared with CPAP, for children requiring NRS 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.

1.3.3 Secondary objectives

To compare, between the groups:

- mortality at PICU/HDU discharge, day 60 and day 180;

- the rate of (re)intubation at 48 hours;
- the duration of PICU/HDU and hospital stay;
- patient comfort, during randomised treatment, measured using the validated COMFORT-B Score;[19]
- the proportion of patients receiving sedation while on non-invasive respiratory support;
- parental stress, in hospital at the time of consent, measured using the Parental Stressor Scale: PICU (PSS:PICU)[20]
- Health-related Quality of Life (HrQoL) at six months measured using the age-appropriate Paediatric Quality of Life Inventory (Peds-QL)[21] and The Child Health Utility 9D (CHU 9D) [22]

1.4 Design

FIRST-ABC is a master protocol comprising two pragmatic, multi-centre, 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 master protocol design allows 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.[23]

A non-inferiority design was chosen based on previous RCTs on this topic as well as feedback from PICS-SG 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.

1.4.1 Internal pilot

An internal pilot will run from months 7-12 (as per the grant timeline) and use a traffic light system to assess key progression criteria regarding site opening, recruitment and adherence to the study protocol.[24] The internal pilot will follow the same processes as the main trial; participants enrolled in the pilot will be included in the analysis of the main trial.

2. Methods

2.1 Setting

2.1.1 Trial sites

In this protocol, 'site' refers to the 25 NHS paediatric critical care units (paediatric intensive care units (PICU) and/or high dependency units (HDUs)) where FIRST-ABC will be conducted.

2.1.2 Site requirements

- Able to provide both treatments (HFNC and CPAP) to study participants
- Active participation in the Paediatric Intensive Care Audit Network for the UK and Ireland (PICANet) audit or able to collect detailed data on patient interventions and outcomes
- Compliance with all responsibilities as stated in the FIRST-ABC Clinical Trial Site Agreement (CTSA)
- Compliance with all requirements of the trial protocol including the trial treatments, consent procedures and data collection/follow-up schedules
- Compliance with the UK Policy Framework for Health and Social Care Research and International Conference on Harmonization Guidelines on Good Clinical Practice (ICH-GCP).

2.1.3 Site responsibilities

- Identify a Principal Investigator (PI) to lead the FIRST-ABC RCTs locally
- Identify a FIRST-ABC Research Nurse responsible for day-to-day local trial coordination
- Identify a doctor and nurse/allied health professional champion in each unit
- Agree to incorporate the FIRST-ABC RCTs into routine paediatric critical care clinical practice, highlighting the importance of systematic screening for potential eligible patients and prompt randomisation
- Agree to adhere to individual patient randomisation allocations and ensure adherence with the trial protocol
- Agree to randomise all eligible patients and maintain a Screening Log
- Agree to data collection and safety monitoring requirements.

2.1.4 Site initiation and activation

The following must be in place prior to a site being activated for recruitment:

- a completed site initiation visit
- all relevant institutional approvals (e.g. local confirmation of capacity and capability)
- a fully signed FIRST-ABC Clinical Trial Site Agreement
- a fully signed Delegation Log

Once the ICNARC Clinical Trials Unit (CTU) have confirmed that all necessary documentation is in place, a site activation email will be issued to the site PI, at which point, the site may start to screen for eligible patients. Once the site has been activated, the PI is responsible for ensuring:

- adherence with the most recent approved version of the trial protocol;
- training of relevant site staff in accordance with the trial protocol and, if overseeing the trial or seeking consent, Good Clinical Practice (GCP) requirements;
- appropriate means to identify and randomise eligible patients;
- timely data collection, entry and validation; and
- prompt notification of all adverse events (as specified in Section 2.8).

All local staff (i.e. PI, local investigators, research teams) involved in the conduct of the trial must be trained to carry out their assigned roles. Site research staff should be signed off on the Delegation Log, once trained, and the Delegation Log should be copied and sent to the ICNARC CTU whenever changes are made.

Staff members solely involved in the screening and randomisation of patients should be provided with study-specific training to carry out these tasks and recorded on the Training Log (full GCP training will not be required for these staff members) [25].

2.2 Population

Critically ill children requiring NRS to either (A) prevent progression to intubation/invasive ventilation (step-up RCT) or (B) prevent re-intubation after being extubated following a period of invasive ventilation (step-down RCT).

2.2.1 Inclusion criteria

1) Admitted/Accepted for admission to PICU/HDU
2) Age >36 weeks corrected gestational age and <16 years
3) Assessed by the treating clinician to require non-invasive respiratory support, EITHER
   A. for an acute illness (step-up RCT) OR
   B. within 72 hours of extubation following a period of invasive ventilation (step-down RCT).

2.2.2 Exclusion criteria

1. Assessed by the treating clinician to require immediate intubation and invasive ventilation due to severe hypoxia, acidosis and/or respiratory distress, upper airway obstruction, inability to manage airway secretions or recurrent apnoeas
2. Tracheostomy in place
3. Received HFNC/CPAP for >2 hours in the prior 24 hours
4. On home non-invasive ventilation prior to PICU/HDU admission
5. Presence of untreated air-leak (pneumothorax/pneumomediastinum)
6. Midfacial/craniofacial anomalies (unrepaired cleft palate, choanal atresia) or recent craniofacial surgery
7. Agreed 'not for intubation' or other limitation of critical care treatment plan in place.
8. Previously recruited to the FIRST-ABC trial*

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

2.2.3 Co-enrolment

Co-enrolment with observational studies is permitted without prior agreement. The FIRST-ABC Trial Management Group will consider co-enrolment with other interventional trials on a case by case basis. We will follow previous experience and existing guidelines from the Intensive Care Society regarding co-enrolment to other clinical trials to maximise patient involvement in research.[26 27]

2.2.4 Screening

Potentially eligible patients admitted/accepted for admission to the participating unit will be screened against the inclusion/exclusion criteria by the local clinical team, supported by the site research team. Screening and Enrolment Logs will record enrolled patients, reasons for exclusion and the reason eligible patients are not enrolled.

2.3 Recruitment and consent

2.3.1 Randomisation

Randomisation will be performed as soon as possible after confirming eligibility. In each RCT, eligible patients will be randomised on a 1:1 basis to either CPAP or HFNC using a central telephone/web-based randomisation service available 24 hours/seven days per week. The randomisation sequence will be computer generated and variable block sizes will be used to strengthen allocation concealment. Randomisation will be stratified by site and age (<12 months versus >/=12 months).

The trained staff member who randomised the patient will immediately inform the clinical team responsible for the patients care who will commence the randomised treatment. In addition, the local site research team will be notified of the randomisation by email. Following enrolment into FIRST-ABC, each participant will be assigned a unique FIRST-ABC Trial Number and a CRF completed by the local research team.

In addition, during the recruitment period a member of the FIRST-ABC study team will be available 24 hours/seven days per week to address emergency recruitment, randomisation or clinical issues that arise.

The health technologies used in this study cannot be blinded, since both devices (CPAP and HFNC) as well as the interface that delivers the treatments are already used in practice and easily recognisable by clinical staff.

2.3.2 Consent procedures

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

Children who are eligible for FIRST-ABC become so during a period of critical illness. This is a profoundly stressful time for children's' parents/legal guardians during which time there are ethical concerns both about the burden of trying to understand the trial and the ability of the parent/legal guardian to provide informed consent during a time of great distress. Furthermore, initiation of NRS is most often during an emergency time-sensitive situation where any delay to commencing treatment could be detrimental to the patient and to the scientific validity of the trial.

Considering these issues, the FIRST-ABC RCTs utilise a deferred consent model ('research without prior consent'). Once a patient is screened and confirmed as eligible for the study (i.e. satisfies inclusion and exclusion criteria), they will be randomised and the randomly assigned treatment (CPAP or HFNC) will be commenced as soon as possible.

This model, developed in line with the CONseNt methods in paediatric Emergency and urgent Care Trials (CONNECT) study guidance,[28] has been found to be acceptable to parents/guardians, as well as to clinicians, in several recent RCTs conducted in the paediatric critical care setting[18 29-33] and is also informed by experience and feedback gained directly from conducing the FIRST-ABC Pilot Study.[18] As part of the pilot RCT, we asked parents of children who were randomised into the study through 'research without prior consent' methods for their feedback through a survey. This covered feedback on: the timing and content of the approach; the use of 'research without prior consent'; the participant information documentation; the format of the discussions and decision making. Results included: positive feedback was received on all aspects of the consent procedure, especially the patient information documentation and all but one of the responding parents found research without prior consent acceptable in the trial. The

reasons identified for giving deferred consent included to help other children in the future (100%) and that they felt that medical studies like FIRST-ABC are important (95%). These findings have been incorporated into our consent procedures and will be used for training at sites.

2.3.3.1 Consent prior to hospital discharge - Deferred consent

Once notified of the randomisation of a patient to the study, a trained, delegated member of the site research team will approach the parents/legal guardians of the patient as soon as appropriate and practically possible after randomisation to discuss the study (this will usually occur within 24-48 hours of randomisation). If the participant has died or been discharged from hospital prior to their parents/legal guardians being approached, then the parents/legal guardians will be approached at a later point (see *Discharge prior to consent being sought* and *Death prior to consent being sought*).

Before approaching the parent/legal guardian, the research team member will check with the relevant clinical staff that the participant is stable and that timing is appropriate. If the participant's condition has not stabilised additional time should be allowed before approaching the parent/legal representative. Checks conducted to assess appropriate timing for approach will be recorded in the patients' clinical notes.

Once approached, a Participant Information Sheet (PIS) for parents/legal guardians will be provided. The PIS will identify the title of the study and the Chief Investigator (CI), and include 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. A Consent Form will be provided indicating that: the information given, orally and in writing, has been read and understood; participation is voluntary and can be withdrawn at any time without consequence; and that consent is given for access to medical records for data collection, to receive a follow-up questionnaire and for anonymised data to be shared with other researchers in the future. Parents/legal guardians will be given time to read the PIS and have an opportunity to ask any questions they may have about their child's participation in FIRST-ABC and to discuss with other family members or friends before confirming their decision.

After the person seeking consent has checked that the PIS and Consent Form have been understood, they will invite the parent/legal guardians to sign the Consent Form and will then add their own name and countersign it. A copy will be given to the parent/legal guardians to keep, a copy placed in the child's medical notes and the original kept in the Investigator Site File.

Due to age and severity of illness and its impact on the mental state of the target population, it will not be possible to involve study participants in the consenting process. Instead, assent will be obtained prior to hospital discharge if their condition allows (e.g. they regain mental capacity). Study participants will then be provided with an age-appropriate PIS and asked to sign an Assent Form, if appropriate, to confirm they have been informed and understand the study. Parents/legal guardians will be involved in this

discussion. If the participant is likely to regain capacity following hospital discharge, then an age-appropriate PIS will be provided to parents/legal guardians to discuss with the participant following recovery.

2.3.4 Discharge prior to consent being sought

In the rare situation where the patient is discharged from hospital prior to the parent/legal guardians confirming their consent decision, the most appropriate member of the site research team will attempt at least one phone call to the parents/legal guardians within five working days of hospital discharge to inform them of their involvement in the study and to provide information about the study. Following on from the call, as well as if there is no response to the call, the parents/legal guardians will be sent a covering letter, personalised by the most appropriate member of the site research team or clinical staff member, and a copy of the PIS and Consent Form (postal version) by post. The letter will direct the parents/legal guardians to the PIS for detailed information on the study and provide telephone contact details if the parents/legal guardians wish to discuss the trial with a member of the site research team. The letter will ask 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 is no response after four weeks of sending the covering letter, a follow-up letter, alongside second copies of the PIS and Consent Form, will be sent to the parent/legal guardians. This second letter will provide the same information as the first letter but will confirm that if no Consent Form is received within four weeks of the second letter being sent, then the participant will be included in the study unless they notify the site research team otherwise. In this event, the site research team should document the non-response on a File Note in the Investigator Site File.

If the participant is transferred to another hospital participating in FIRST-ABC before the consent procedures are complete, then the local research team will contact the research team at the receiving hospital to handover the consenting procedures.

2.3.5 Death prior to consent being sought

In the rare situation where a participant dies before consent has been obtained, a site research team member will obtain information from colleagues and 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 can be sought from parents/legal guardians following the death of their child and prior to their departure from the hospital; however, it is at the discretion of the site staff to determine if this is appropriate for each individual family. In this situation, the Participant Information Sheet for bereaved parents/legal guardians (B-PIS) and Consent Form (bereaved) would be used.

If deferred consent is not sought prior to the parents'/legal guardians' departure from the hospital, then the parents/legal guardians will be sent a covering letter, personalised by the most appropriate research/clinical team member, and a copy of the B-PIS and

Consent Form (bereaved) by post four weeks after randomisation. Where possible, the clinical or research team member should already be known to the family. The letter will explain how to opt out of the study, direct them to the B-PIS for detailed information on the study and provide telephone contact details if parents/legal guardians wish to discuss the study with a member of the site research team.

If there is no response after four weeks of sending the initial letter, a follow-up letter along with the B-PIS and Consent Form postal version for bereaved parents/legal guardians will be sent to the bereaved family. This second letter will provide the same information as the first letter. In addition, this letter will also confirm that if no Consent Form is received within four weeks of receipt of the letter, then the participant's data will be included in the study.

2.3.6 Refusal or withdrawals of consent

If informed consent is refused or withdrawn, this decision will be respected and abided by, and no further contact made. All data occurring up to the point of this decision will be retained in the trial, unless the parent/legal guardian requests otherwise.

2.4 Outcome measures

2.4.1 Internal pilot

The RCTs will use a traffic light system to assess progression from pilot stage to the full trial as below:

Criterion	Green light (Go)	Amber light (Amend)	Red light (Stop)
Number of sites open to recruitment	Minimum 15 sites	8-14 sites	Less than 8 sites
Overall recruitment rate in open sites	At least 75% of anticipated	Between 50 and 75% of anticipated	Less than 50% of anticipated
Proportion started on randomly allocated treatment (CPAP or HFNC)	Over 90%	Between 75 and 90%	Less than 75%
Changes to another form of NRS, escalation and weaning carried out as per protocol	At least two-thirds of cases	Between one-third and two-thirds of cases	Less than one-third of cases

2.4.2 Main trial

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.

Secondary outcomes:

- Mortality at PICU/HDU discharge, day 60 and day 180
- Rate of (re)intubation at 48 hours
- Duration of PICU/HDU and hospital stay
- Patient comfort, during randomised treatment, assessed using the validated COMFORT-B score
- Proportion of patients in whom sedation is used during non-invasive respiratory support
- parental stress, in hospital at the time of consent at 24-48 hours, measured using the Parental Stressor Scale: PICU
- HrQoL at six months using age-appropriate Peds-QL[32] and CHU-9D[22]

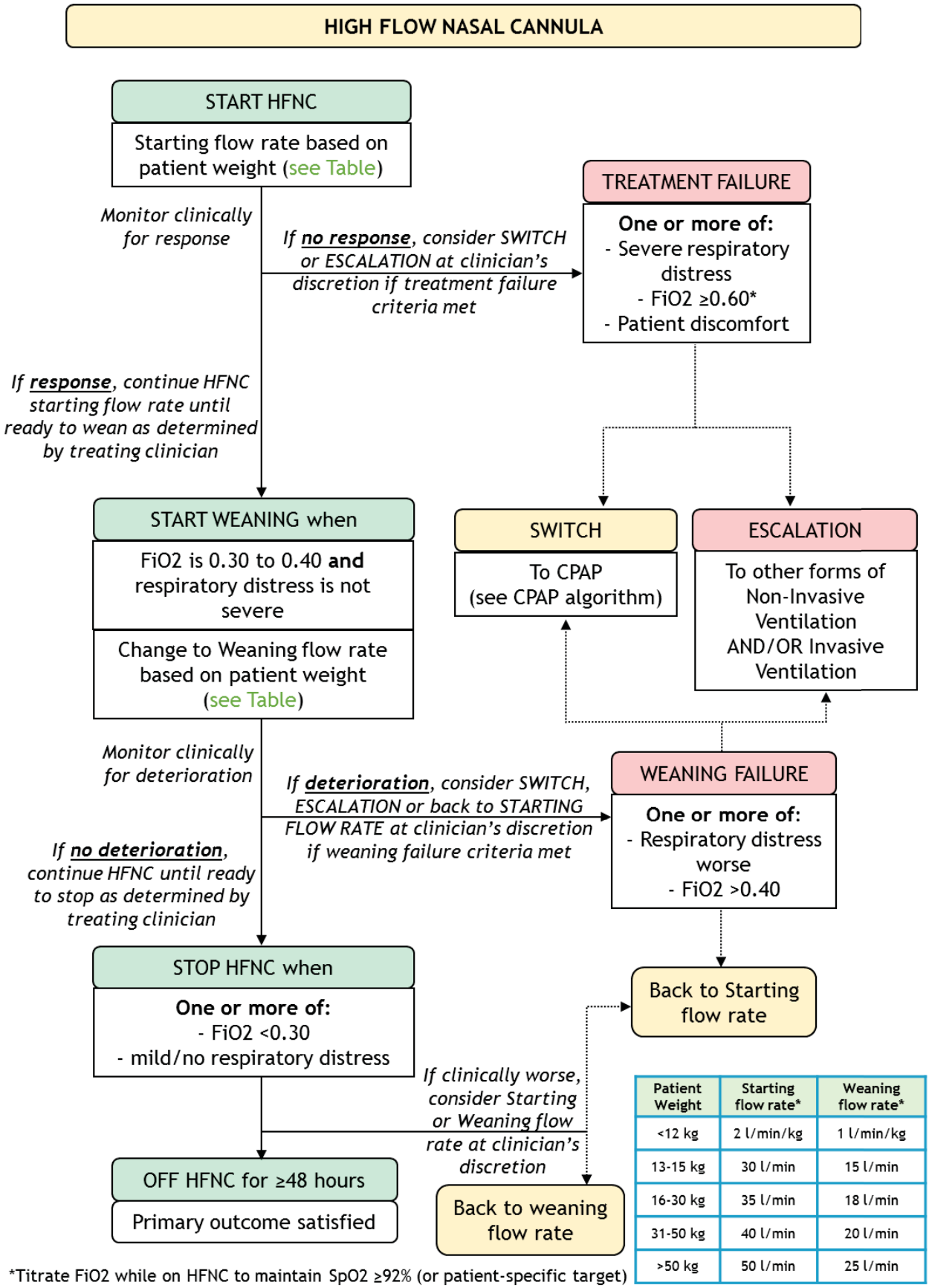
Cost effectiveness analysis (CEA) outcomes:

- Total costs at six months
- QALYs at six months
- Incremental net monetary benefit gained at a willingness-to-pay of £20,000 per QALY at six months associated with HFNC versus CPAP

2.5 Procedures

2.5.1 HFNC

A heated, humidified, HFNC device will be used to deliver a prescribed gas flow rate for the duration that the patient needs non-invasive respiratory support. The study protocol specifies clinical criteria and procedures for the initiation, maintenance and weaning of HFNC (see algorithm below).



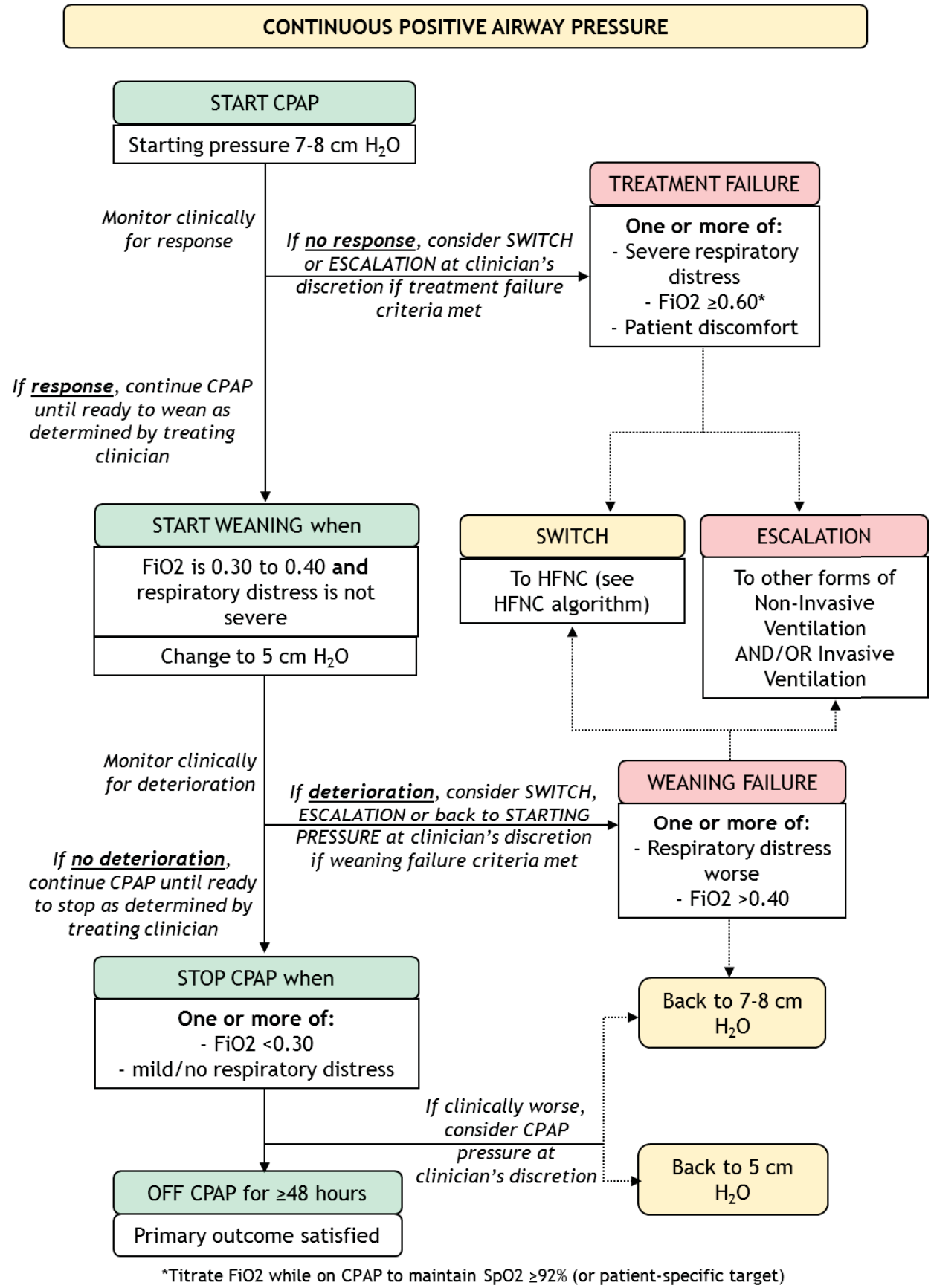
Patient Weight	Starting flow rate*	Weaning flow rate*
<12 kg	2 l/min/kg	1 l/min/kg
13-15 kg	30 l/min	15 l/min
16-30 kg	35 l/min	18 l/min
31-50 kg	40 l/min	20 l/min
>50 kg	50 l/min	25 l/min

Staff in all participating units already use HFNC – therefore, no additional training will be 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 will not be possible to blind the subject or the clinical staff.

As per current practice, clinicians in the study will be able to stop HFNC and switch to CPAP if clinically deemed necessary. Pre-specified objective criteria to identify non-responders to HFNC are provided (see algorithm above) as a guide for clinicians considering switching from HFNC to CPAP. Reasons for switching will be recorded. Patients who switch treatments will remain in the study and continue to be monitored until they are off respiratory support.

2.5.2 CPAP

Conventional nasal CPAP will be provided using a set expiratory pressure of 7-8 cm H_2O for the duration that the child needs non-invasive respiratory support. In order to standardise treatment, the study protocol specifies clinical criteria and procedures for the initiation, maintenance and weaning of CPAP (see algorithm below). Staff in all participating units already use CPAP – therefore, no additional training will be provided for the study.


CONTINUOUS POSITIVE AIRWAY PRESSURE
START CPAP
Starting pressure 7-8 cm H2O
Monitor clinically for response
If no response, consider SWITCH or ESCALATION at clinician's discretion if treatment failure criteria met
TREATMENT FAILURE
One or more of:
- Severe respiratory distress
- FiO2 ≥0.60*
- Patient discomfort
If response, continue CPAP until ready to wean as determined by treating clinician
START WEANING when
FiO2 is 0.30 to 0.40 and respiratory distress is not severe
Change to 5 cm H2O
SWITCH
To HFNC (see HFNC algorithm)
ESCALATION
To other forms of Non-Invasive Ventilation AND/OR Invasive Ventilation
Monitor clinically for deterioration
If deterioration, consider SWITCH, ESCALATION or back to STARTING PRESSURE at clinician's discretion if weaning failure criteria met
WEANING FAILURE
One or more of:
- Respiratory distress worse
- FiO2 >0.40
If no deterioration, continue CPAP until ready to stop as determined by treating clinician
STOP CPAP when
One or more of:
- FiO2 <0.30
- mild/no respiratory distress
Back to 7-8 cm H2O
If clinically worse, consider CPAP pressure at clinician's discretion
Back to 5 cm H2O
OFF CPAP for ≥48 hours
Primary outcome satisfied
*Titrate FiO2 while on CPAP to maintain SpO2 ≥92% (or patient-specific target)

As per current practice, clinicians in the study will be able to stop CPAP and switch to HFNC if clinically deemed necessary. Pre-specified objective criteria to identify non-responders to CPAP will be provided in the study protocol as a guide for clinicians considering switching from CPAP to HFNC. Reasons for switching will be recorded. Patients who switch treatments will remain in the study and continue to be monitored until they are off respiratory support.

2.5.3 co-interventions

All other usual care will be 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, does not include supplemental oxygen.

2.6 Questionnaire follow-up

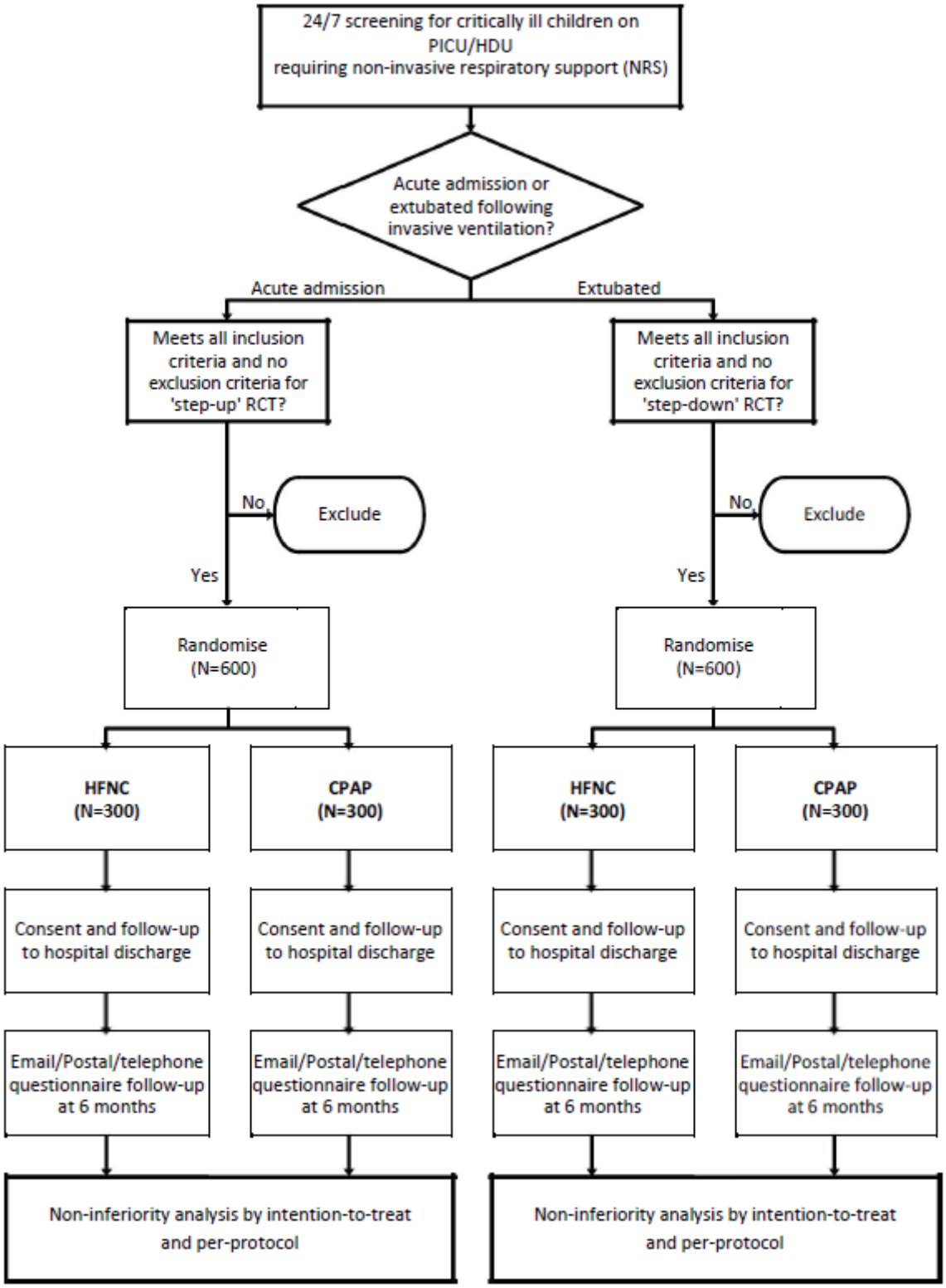
Each participant will be followed up with a questionnaire at six months post-randomisation to assess HrQoL. Prior to the sending of a questionnaire, survival status at six months will be ascertained either through review of medical records by local research teams and via data-linkage with nationally held records (decedents will be logged in the trial records and the follow-up process ended).

At the six-month time point, parents/legal guardians of recruited patients will be emailed or posted (as per their preference indicated at the time of consent) a questionnaire by the ICNARC CTU containing the PEDS-QL, CHU-9Dand a health services questionnaire. The questionnaires are designed to take no longer than 15 minutes to complete. If a parent requests a questionnaire to be sent via post, then a pen and self-addressed stamped envelope will be provided for ease of return.

If there is no response three weeks later, parents/legal guardians will be telephoned and asked to check whether they have received the questionnaire. If preferable for the parent/legal guardian, they will be offered the option of either being sent another copy of the questionnaire via email, in the post, or to complete the questionnaire over the telephone with a trained member of the FIRST-ABC trial team.

If a patient is an in-patient at a participating site at the follow-up time-point, the site research team will be asked to approach the parent/legal guardian and conduct the questionnaire with the parents/legal guardians in hospital, if willing.

2.7 Participant timeline



2.8 Safety Monitoring and Reporting

2.8.1 Definitions

Adverse Event (AE) reporting will follow the Health Research Authority guidelines on safety reporting in studies which do not use Investigational Medicinal Products (non-CTIMPs).

The following definitions have been adapted from Directive 2001/20/EC of the European Parliament (Clinical Trials Directive) and ICH-GCP guidelines (E6(R1), 1996).

2.8.2 Adverse Event

An Adverse Event (AE) is defined as: any untoward medical occurrence or effect in a patient participating in a study.

2.8.3 Serious Adverse Event

A serious adverse event (SAE) is defined as an Adverse Event that:

- results in death;
- is life-threatening;
- requires hospitalisation or prolongation of existing hospitalisation;
- results in persistent or significant disability or incapacity;
- consists of a congenital anomaly or birth defect.

“Life-threatening”, in the definition of a Serious Adverse Event, refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

“Hospitalisation” refers to inpatient admission, regardless of length of stay. This includes admission for continued observation. Any admission for pre-existing conditions that have not worsened, or elective procedures, do not constitute an SAE.

Important adverse events that are not immediately life-threatening, do not result in death or hospitalisation but may jeopardise the subject or require intervention to prevent one or any of the other outcomes listed in the definition above should also be considered as serious.

2.8.4 Unexpected and Related Serious Adverse Event

A suspected Adverse Event related (possibly, probably or definitely) to the trial treatment that is both unexpected (i.e. not consistent with the expected outcomes of the treatment being offered) and serious.

2.8.5 Assessment

The PI, or other medically qualified investigator as listed on the Delegation Log, should make an assessment of severity, relatedness and expectedness, categorised as follows:

2.8.5.1 Severity

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

2.8.5.2 Relatedness

- **None**: there is no evidence of any relationship to the study treatment.
- **Unlikely:** There is little evidence to suggest a causal relationship (e.g. because the event did not occur within a reasonable time after administration of the trial treatment). There is another reasonable explanation of the event (e.g. the participant's clinical condition, other concomitant medications).
- **Possibly:** There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial procedure). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant medications).
- **Probably:** There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
- **Definitely:** There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

2.8.5.3 Expectedness

- **Expected**: the event is listed as an expected AE in Appendix 2.

- **Unexpected**: the event is not listed as an expected AE in Appendix 2.

2.8.6 Recording and Reporting procedures

Occurrences of the specified, expected adverse events will be recorded for all randomised patients from the time of randomisation until time of liberation from all forms of respiratory support for 48 hours.

Considering that all children eligible for the FIRST-ABC RCTs are critically ill and, due to the complexity of their condition, are at an increased risk of experiencing AEs – occurrences of non-specified, unexpected adverse events will only be reported if they are considered to be related to the study treatment (possibly, probably or definitely).

The following events will not be reported as AEs or SAEs as they are collected as study outcomes:

- Intubation or re-intubation
- Sedation
- Death (note that death itself should not be reported as an SAE, but the suspected cause of death should be assessed for severity, relatedness and expectedness as above)

All SAEs (other than those defined in the protocol as not requiring reporting) must be reported to ICNARC CTU using the FIRST-ABC SAE Reporting Form within 24 hours of the site research team becoming aware of the event. Staff should not wait until all information about the event is available before sending SAE notification. Information not available at the time of the initial report must be documented and submitted as it becomes available.

SAEs must be recorded in the patients' medical notes, on the FIRST-ABC CRF, and reported to the ICNARC CTU using the FIRST-ABC SAE Reporting Form, by email to firstabc@icnarc.org or by uploading the form into the secure web-based data entry system, within 24 hours of observing or learning of the SAE(s). The process for recording and reporting adverse events and serious adverse events is summarised in Figure 1.

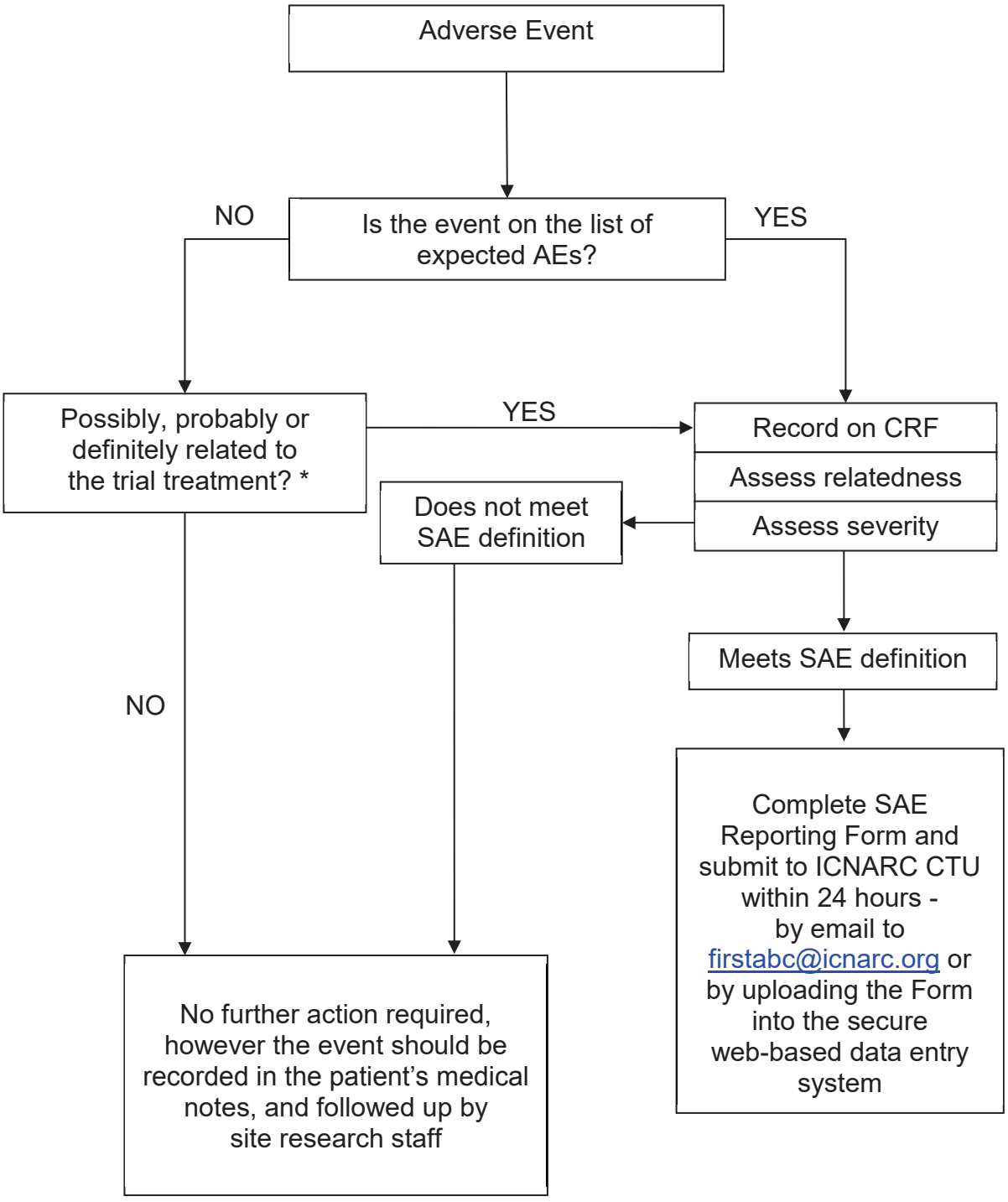
On receipt of an SAE report, a member of the ICNARC CTU will first evaluate the report for completeness and internal consistency. Then, a clinical member of the FIRST-ABC Trial Management Group (TMG) will evaluate the event for severity, relatedness and expectedness to determine whether or not the case qualifies for expedited reporting to the Research Ethics Committee (REC). If the event is evaluated by either the Chief Investigator or a clinical member of the FIRST-ABC TMG as a related and unexpected SAE, the ICNARC CTU will submit a report to the REC within 15 calendar days.

The ICNARC CTU will provide safety information to the Data Monitoring and Ethics Committee (DMEC) on a basis deemed appropriate by the DMEC.

2.8.7 Notifying the Research Ethics Committee

Adverse Events that do not require expedited reporting to the REC will be reported annually to the REC. This will commence annually from the date of REC favourable ethical opinion for the trial.

Figure 1: Adverse Event recording and reporting



*If there is any uncertainty about whether the AE is associated with trial treatment, then it should be reported.

2.9 Data collection

To maximise the efficiency of the design, FIRST-ABC will collaborate with PICANet to make best use of the established data collection infrastructure which exists in all PICUs in the UK. All participating PICUs routinely submit clinical data to the national audit of Paediatric Intensive Care. These data are used locally by participating PICUs to monitor activity and performance. They have full access to, and ownership of the data. Data are validated on entry and centrally on the PICANet server. PICANet will produce a download facility that allows participating units to extract data required for the trial, thus reducing the burden of data collection for unit staff.

Examples of data from PICANet used in the trial analysis will include:

- baseline demographics and risk factors, including the Paediatric Index of Mortality score;
- secondary outcomes of PICU/HDU and acute hospital mortality, duration of PICU/HDU and acute hospital stay; and
- critical care daily interventions (and associate costs), based on Healthcare Resource Groups, from the index admission and any subsequent readmissions.

All patients recruited to the trial will be consented for data linkage with routine sources (e.g. NHS Digital or equivalent). Data obtained from routine data sources will include:

date of death for deaths occurring after discharge from acute hospital, by data linkage with civil registration data

Additional data items collected specifically for the trial will be limited to the minimum required to deliver the trial objectives. These will include:

- parent/legal guardian name, address and telephone number for questionnaire follow-up at six months;
- data items to confirm eligibility;
- data to monitor adherence with the HFNC and CPAP algorithms, including escalation and weaning;
- time on any ventilation;
- secondary outcomes of modified COMFORT-B score, parental stress and sedation use; and
- adverse event reporting.

2.10 Data management

All participant data collected will be entered onto a secure electronic data entry system. The option of entry first onto paper CRFs will be available to participating sites. The site PI will oversee and be responsible for data collection, quality and recording. Collection of data can be delegated (as per the Delegation Log) by the site PI to qualified members of the research team, on the understanding that the site PI retains responsibility for the data collection oversight.

Data entered onto the secure electronic data entry system will undergo validation checks for completeness, accuracy and consistency of data. Queries on incomplete, inaccurate or inconsistent data will be sent to the local research team at participating sites for resolution. The local PI will be responsible for ensuring all queries are addressed and for overall quality of their site data.

Security of the electronic data entry system is maintained through user names and individual permissions approved centrally by the ICNARC CTU. Central back-up procedures are in place. Storage and handling of confidential trial data and documents will be in accordance with the Data Protection Act 2018.

2.11 Monitoring and auditing

2.11.1 Central monitoring

The trial team members at the ICNARC CTU will have regular communication with sites via email, telephone, teleconferences and newsletters. Adherence to the protocol will be paramount in the central monitoring plan, including a review of consent forms; eligibility data and adherence to the HFNC and CPAP algorithms.

2.11.2 Site monitoring

The on-site monitoring plan will be developed following a risk-based strategy. Selected sites will be visited at an early stage. The timing and frequency of visits to sites will be based on a risk assessment, including an assessment of the sites and local research team (e.g. experience of multicentre research, involvement in RCTs etc.). It is anticipated that 25% of sites will be visited at least once during the recruitment period to monitor and discuss adherence to the trial protocol and standard operating procedures. Directly following all site visits, the site PI will be verbally advised of the core monitoring findings and this will be followed with a written a report to the site summarising the visit, documents reviewed and any findings. Information learnt at site visits will be used to refine standard operating procedures, as required, ensuring clarity and consistency across sites.

2.12 Statistical Methods

2.12.1 Sample size

To achieve 90% power with a type I error rate of 2.5% (one-sided) to exclude the prespecified noninferiority margin of HR=0.75 requires 508 events to be observed. Based on data from the FIRST-ABC pilot RCT, we anticipate 5% censoring due to death or transfer, leading to a required sample size of 268 patients per group in each of the two RCTs. To allow for withdrawal/refusal of deferred consent, and for exclusion due to non-adherence in the PP population, we will recruit a total sample size of 600 patients in each of the two RCTs. A single interim analysis at 50% recruitment in each RCT will test for superiority of either HFNC or CPAP.

2.12.2 Internal pilot

Data will be analysed at the end of the internal pilot trial stage (months 7-12 of the grant timeline) on patients recruited during the first six months of the trial in both the step-up and step-down RCTs. The analysis will take place in month 14 of the grant to allow data to be collected and entered to assess all progression criteria. The objectives of the feasibility analysis will be to assess whether there has been successful site set-up, screening and recruitment, and adherence to both the HFNC and CPAP algorithms. The RCTs will progress from the pilot stage to full trial based on the progression criteria (see section 2.4.1). Where any of the progression criteria are given an 'Amber light', a management plan will be put in place by the TMG and discussed with the Trial Steering Committee (TSC). The final decision on progression from the pilot stage to the full trial will be made by the NIHR HTA programme after recommendation, or not, by the TSC.

2.12.3 Clinical effectiveness analysis

All analyses will be lodged in a statistical analysis plan, a priori, before the investigators are unblinded to any study outcomes. Following best practice for non-inferiority trials, the primary analyses will be undertaken in both intention-to-treat (ITT) and per protocol (PP) populations with robust conclusions possible in the situation where both populations provide concordant results. Results will be reported in accordance with the CONSORT statement extension for non-inferiority and equivalence trials.

Analyses will be undertaken independently for each of the two RCTs. In each RCT, baseline patient characteristics will be compared between the two groups to observe balance and the success of randomisation. These comparisons will not be subjected to statistical testing. The delivery of the intervention will be described for each group in detail, including (but not limited to) number and percentage of patients who commence the randomised treatment, number and percentage who remain on the randomised treatment until liberation from ventilation, and number and percentage of patients who are changed to a different method of respiratory support or treatment escalation.

HFNC will be considered non-inferior to CPAP if the lower bounds of the 95% confidence intervals for the hazard ratio (HR) from Cox regression models on time to liberation from respiratory support fitted in both the ITT and PP populations exclude the pre-specified non-inferiority margin of 0.75 (corresponding to approximately a 16-hour increase in median time to liberation). This margin was considered adequate such that the other potential benefits of HFNC in terms of comfort and tolerability would mean that it would be likely to be preferred in usual practice. The Cox regression models will be adjusted for important baseline characteristics. The covariates for inclusion in the regression models will be selected a priori based on an established relationship with outcome for critically ill children, and not because of observed imbalance, significance in univariable analyses or by a stepwise selection method.

Subgroup analyses will be performed to test for interactions between the effect of allocated treatment group and the following baseline covariates:

- age (<12 months versus ≥12 months)
- severity of respiratory distress (severe versus mild/moderate)
- for the step-up RCT only, clinical indication (obstructive airway disease, e.g. asthma/bronchiolitis, versus parenchymal lung disease, e.g. pneumonia/ARDS, versus cardiac disease)
- for the step-down RCT only, length of prior IMV (<5 days versus ≥5 days).

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

Secondary analyses of binary outcomes (mortality, reintubation) will be performed by Fisher's exact test and adjusted logistic regression. Duration of survival to day 180 will be plotted as Kaplan-Meier survival curves, compared unadjusted with the log rank test and adjusted using Cox regression models. Analyses of duration of PICU/HDU and hospital stay will be performed by Wilcoxon rank-sum tests, stratified by survival status. Analyses of COMFORT-B score, sedation use, PSS:PICU and HrQoL will be performed by t-tests and adjusted linear regression.

A single interim analysis will be carried out in each RCT after the recruitment and follow-up to day 60 of 300 patients using a Peto-Haybittle stopping rule to recommend early termination due to superiority of either intervention (P<0.001) in time to liberation from respiratory support or evidence of harm from either intervention (P<0.05) in mortality at day 60. Further interim analyses will be performed only if requested by the Data Monitoring and Ethics Committee.

2.12.4 Integrated health economic evaluation

The cost-effectiveness analysis (CEA) will take an NHS and Personal Social Services perspective.[34] Patient-level resource use data will be obtained from trial case report forms (CRFs), PICANet, and health services questionnaire (HSQ). Resource use data from the PICU/HDU stay will be taken from the CRF and linked routine data from PICANet. Information on subsequent PICU/HDU and hospital admissions will be obtained via data linkage with PICANet and through completion of the health services questionnaire. Data on the level of care for PICU bed-days will be gathered through routine collection of the Paediatric Critical Care Minimum Dataset (PCCMDS) in the participating centres via the PICANet database. Information will also be collected on the additional resources (e.g. staff time, medications etc.) required to administer the interventions from site visits. Use of primary care and community health services will be assessed by HSQ at six months. Patient-level resource use data will be combined with appropriate unit costs from the NHS payment by results database and PSSRU to report total costs per patient for up to six months since randomisation. Data from the PedsQL-4.0 and CHU-9Dquestionnaires at six months will be combined with survival data to report QALYs at six months. The CEA will follow the intention-to-treat principle and report the mean (95% confidence interval) incremental costs, QALYs and net monetary benefit at six months. The CEA will use multilevel linear regression models that allow for

clustering of patients at site. The analysis will adjust for key baseline covariates at both patient and site level.

3. Ethics, approvals and dissemination

3.1 Research ethics

The FIRST-ABC RCTs will be conducted in accordance with the approved trial protocol, ICH-GCP guidelines, the UK Data Protection Act 2018, the Mental Capacity Act, as well as the ICNARC CTU research policies and procedures.

3.1.1 Trial registration

This trial has been registered with the ISRCTN Registry (ISRCTN60048867).

3.1.2 Central NHS ethical compliance

The trial has received a favourable ethical opinion from the NHS East of England - Cambridge South Research Ethics Committee (reference number: 19/EE/0185) and approval from the Health Research Authority (Integrated Research Application System (IRAS) number: 260536).

3.1.2 Local ethical compliance

It is the responsibility of the site PI to obtain the necessary local approvals for FIRST-ABC, including formal confirmation of capacity and capability. Evidence of confirmation of capacity and capability at each participating site must be provided to the ICNARC CTU prior to site activation (see section 2.1).

3.2 Protocol amendments

The study will be conducted in accordance with the current approved version of the Protocol. Any proposed amendments to the research will be considered by the Sponsor in the first instance and then categorised as either substantial or minor (non-substantial) and the research Protocol modified accordingly. Agreed trial/protocol amendments will be submitted for review to NHS ethics and/or HRA dependent on the categorisation and, following the respective favourable opinion/approval, the amendment will be carried out and implemented in accordance with the HRA guidance.

3.3 Confidentiality

Identifiable patient data, including full name, contact details, date of birth and NHS number will be required by the ICNARC CTU to successfully follow-up participants. The ICNARC CTU will act to preserve participant confidentiality and will not disclose or

reproduce any information by which participants could be identified. Data will be stored securely.

We will also seek consent to share the patients' anonymised data or to be contacted by the study team for future research.

All data will be securely stored in a locked cabinet or in an encrypted electronic file. ICNARC is registered under the Data Protection Act (Registration number: Z6289325) and will preserve the confidentiality of participants taking part in the study.

3.4 Declaration of interests

The FIRST-ABC Investigators report no conflicts of interest.

3.7 Dissemination policy

3.7.1 Trial results

The results of the FIRST-ABC RCTs will be disseminated actively and extensively. The research team has strong links with the paediatric critical care community via the Paediatric Intensive Care Society (PICS), PICS Study Group (PICS-SG), and the NIHR CRN: Children Clinical Studies Group (CSG) in Anaesthesia, Intensive Care and Cardiology, and similarly with the nursing community through the British Association of Critical Care Nurses (BACCN), the Royal College of Nursing Critical Care and In-flight Nursing Forum (RCN CCINF) and the European Society of Paediatric and Neonatal Intensive Care (ESPNIC). We also have links with the Healthcare Quality Improvement Partnership national audit programme through the Paediatric Intensive Care Audit Network (PICANet). A study website and links to social media will be created to actively publicise progress with the research and disseminate our findings.

The findings from our work will be presented at national and international conferences. A Study Report to the NIHR HTA Programme will present a detailed description of the project and the results along with recommendations for future policy, practice and research. The study findings will also be published in high-impact, open-access, peer reviewed scientific journals and relevant professional journals.

The results of the study will be disseminated to patients and their families, facilitated by the co-applicants, members of the research team who have links with PICS and the NIHR CSG, and via Family Groups we have liaised with already.

3.7.3 Data sharing

We shall make data available to the scientific community with as few restrictions as feasible, while retaining exclusive use until the publication of major outputs. Once the data from the study are fully analysed and published, the dataset will be made available in line with the National Institute for Health Research (NIHR) current recommendations.

4. Trial closure

4.1 End of trial

The end of the trial will be defined as when the last participant has completed follow-up (last participant, last follow-up). At this point, the ICNARC CTU will submit the 'Declaration of end of trial' to the REC.

4.2 Archiving trial documents

At the end of the trial, the ICNARC CTU will securely archive all centrally held trial-related documents for a minimum of 15 years, in accordance with ICH-GCP guidelines. Arrangements for confidential destruction of all documents will then be made. The site PI will be responsible for archiving all trial-related documents (including CRFs and other essential documents) held at the participating site for a minimum of 15 years after the end of the trial. Essential documents are those which enable both the conduct of the study and the quality of the data produced to be evaluated and to show whether the site complied with the principles of ICH-GCP and other applicable regulatory requirements.

Guidance on archiving will be provided to sites in the trial-specific SOP. All archived documents, held centrally and locally, should be available for inspection by appropriate authorities upon request.

4.3 Early discontinuation of the trial

A single interim analysis will be carried out in each RCT after the recruitment and follow-up to day 60 of 300 patients using a Peto-Haybittle stopping rule to recommend early termination due to superiority of either intervention ($P<0.001$) in time to liberation from respiratory support or evidence of harm from either intervention ($P<0.05$) in mortality at day 60. Further interim analyses will be performed if requested by the Data Monitoring and Ethics Committee.

5. Trial management and oversight

As Chief Investigator, PR – supported closely by the ICNARC CTU - will take overall responsibility for delivery of FIRST-ABC RCTs and overseeing progress against timelines/milestones.

5.1 Good research practice

FIRST-ABC will be managed by the ICNARC CTU according to the Medical Research Council's Good Research Practice: Principles and Guidelines[35] based on the principles of the International Conference on Harmonisation guidelines on Good Clinical Practice[36] and the UK Department of Health's Policy Framework for Health and Social Care Research.[37]The ICNARC CTU has developed policies and procedures based on these

guidelines, which are adhered to for all research activities at ICNARC. In addition, ICNARC has contractual confidentiality agreements with all members of staff and policies regarding alleged scientific misconduct and breach of confidentiality are reinforced by disciplinary procedures.

5.2 Trial Management Group (TMG)

The TMG comprises the FIRST-ABC Trial Investigators (listed on page 5) – led by the Chief Investigator (PR). The day-to-day trial team will comprise the Chief Investigator, Clinical Trials Unit co-investigators (Professor Kathy Rowan, Professor David Harrison and Mr Paul Mouncey) alongside the Trial Manager (Mr Alvin Richards-Belle), Trial Statisticians (Ms Izabella Orzechowska and Ms Karen Thomas), Research Assistant (Ms Laura Drikite) and Data Manager (Ms Michelle Saull).

Quarterly meetings of the TMG will be held to ensure effective communication. In addition, the day-to-day trial team will meet regularly to discuss the progress of the trial and findings from other related research.

5.3 Trial Steering Committee (TSC)

A Trial Steering Committee (TSC) will be established in line with the latest NIHR HTA guidelines. The TSC will be responsible for overall supervision on behalf of the Sponsor and Funder and will ensure that the trial is conducted in accordance with the rigorous standards set out in the UK Framework for Health and Social Care research and the Guidelines for Good Clinical Practice. The TSC will be comprised by a majority of independent members (including the Chair) and include Patient and Public Involvement (PPI) representatives, in addition to the Chief Investigator.

5.4 Data Monitoring and Ethics Committee (DMEC)

An independent Data Monitoring and Ethics Committee (DMEC) will be set-up to monitor recruitment and retention, adherence with the intervention and patient safety. Meetings will take place immediately prior to TSC meetings.

5.5 Patient and Public Involvement (PPI)

We had considerable PPI input into the FIRST-ABC pilot RCT as well as for this proposal. Two parents of children who received breathing support are co-applicants on this grant application and have actively contributed to the study design and procedures, including the use of deferred consent. In addition, independent PPI representative(s) will be sought for membership of the TSC.

6. Sponsorship and funding

6.1 Sponsorship and indemnity

The Great Ormond Street Hospital for Children NHS Foundation Trust are the Sponsor for FIRST-ABC (reference: 17IA05). As the sponsor is an NHS organisation, NHS indemnity will apply for legal liability arising from the design, management and conduct of the research.

6.2 Funding

National Institute for Health Research (NIHR) – Health Technology Assessment Programme (HTA) (Project: 17/94/28).

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8. Appendices

8.1 Appendix 1 – Protocol version history

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
-	-	-	-	-

8.2 Appendix 2 - Specified, expected Adverse Events (AEs)

Specified, expected AEs that could be 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

[This list is not exhaustive. If an AE, as defined in Section 2.8, occurs this should be recorded and reported as described in Section 2.8.6]

UCL INSTITUTE OF CHILD HEALTH

icnarc intensive care national audit & research centre

Great Ormond Street Hospital for Children NHS Foundation Trust

Joint Research and Development Office
Division of Research and Innovation

FIRST-line support for **A**ssistance in **B**reathing in **C**hildren (**FIRST-ABC**): A master protocol of two randomised trials to evaluate the non-inferiority of high flow nasal cannula (HFNC) versus continuous positive airway pressure (CPAP) for non-invasive respiratory support in paediatric critical care

STUDY SHORT TITLE
FIRST-ABC

FUNDED BY
NIHR | National Institute for Health Research

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National Institute for Health Research (NIHR) Health Technology Assessment (HTA) Programme (Project number: 17/94/28)

Chief Investigator
Dr Padmanabhan Ramnarayan

Sponsor representative
Dr Jenny Rivers

Signature page

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to appropriate research governance frameworks and any subsequent amendments of regulations, Good Clinical Practice (GCP) guidelines, the Sponsor's Standard Operating Procedures (SOPs), and other regulatory requirements where relevant.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies from the trial as planned in this protocol will be explained.

For and on behalf of the Trial Sponsor:

Signature: Date:

..../...../.....

Name (please print):
Dr Jenny Rivers

Position:
Deputy Director of Research and Innovation

Chief Investigator:

Signature: Date:

..../...../.....

Name:
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Position:
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Mrs Julie Lester	-	Parent representative

Summary

Data category	Information
Primary registry and trial identifying number	ISRCTN60048867
Date of registration in primary registry	19/06/2019
Source(s) of monetary or material support	National Institute for Health Research Health Technology Assessment Programme
Primary Sponsor	Great Ormond Street Hospital for Children NHS Foundation Trust
Contact for public queries	Mr Alvin Richards-Belle Tel: 020 7269 9277 Email: firstabc@icnarc.org
Contact for scientific queries	Dr Padmanabhan Ramnarayan Tel: 020 7430 5850 Email: p.ramnarayan@gosh.nhs.uk
Public title	FIRST-line support for Assistance in Breathing in Children (FIRST-ABC)
Scientific title	FIRST-line support for Assistance in Breathing in Children (FIRST-ABC): a master protocol of two randomised trials to evaluate the non-inferiority of high flow nasal cannula (HFNC) versus continuous positive airway pressure (CPAP) for non-invasive respiratory support in paediatric critical care
Countries of recruitment	United Kingdom
Health condition(s) or problem(s) studied	Non-invasive respiratory support
Intervention(s)	Interventions: HFNC vs. CPAP
Inclusion and exclusion criteria	Ages eligible for study: >36 weeks corrected gestational age and <16 years Sexes eligible for study: both Accepts healthy volunteers: no 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** **a.** for an acute illness (step-up RCT) **OR** **b.** within 72 hours of extubation following a period of invasive ventilation (step-down RCT).

Data category	Information
	Exclusion criteria: 1) Assessed by the treating clinician to require immediate intubation and invasive ventilation due to severe hypoxia, acidosis and/or respiratory distress, upper airway obstruction, inability to manage airway secretions or recurrent apnoeas 2) Tracheostomy in place 3) Received HFNC/CPAP for >2 hours in the prior 24 hours 4) On home non-invasive ventilation prior to PICU/HDU admission 5) Presence of untreated air-leak (pneumothorax/pneumomediastinum) 6) Midfacial/craniofacial anomalies (unrepaired cleft palate, choanal atresia) or recent craniofacial surgery 7) Agreed 'not for intubation' or other limitation of critical care treatment plan in place. 8) Previously recruited to the FIRST-ABC trial 9) Clinician decision to start other form of non-invasive respiratory support (i.e. not HFNC or CPAP)
Study type	Master protocol of two pragmatic, multi-centre, parallel groups, non-inferiority RCTs with shared infrastructure Interventional Allocation: randomised Blinding: cannot be blinded Primary purpose: prevention Phase IV
Date of first enrolment	Anticipated 1 July 2019
Target sample size	1,200 overall; 600 (step-up RCT) and 600 (step-down RCT)
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
Secondary outcomes	• Mortality at PICU/HDU discharge, day 60 and day 180 • rate of (re)intubation at 48 hours • duration of PICU/HDU and hospital stay • patient comfort, during randomised treatment and during non-invasive respiratory support (i.e. HFNC and/or CPAP), measured using the COMFORT-B score • proportion of patients in whom sedation is used during non-invasive respiratory support • parental stress, in hospital at/around the time of

Data category	Information
	consent, measured using the Parental Stressor Scale: PICU (PSS:PICU) • Health-related Quality of Life at six months using age-appropriate Pediatric Quality of Life Inventory (Peds-QL) and The Child Health Utility 9D (CHU-9D)
Cost effectiveness analysis outcomes	• Total costs at six months • Quality-Adjusted Life Years (QALYs) at six months • Net monetary benefit gained at a willingness-to-pay of £20,000 per QALY at six months associated with HFNC vs. CPAP

Contents

Abbreviations

CHU 9D	The Child Health Utility 9D
CI	Chief Investigator
CPAP	Continuous Positive Airway Pressure
CRF	Case Report Form
CTU	Clinical Trials Unit
GCP	Good Clinical Practice
GOSH	Great Ormond Street Hospital
HDU	high dependency unit
HFNC	High Flow Nasal Cannula
HrQoL	Health-related Quality of Life
ICH	International Conference of Harmonisation
NHS	National Health Service
NRS	Non-invasive Respiratory Support
Peds-QL	Paediatric Quality of Life Inventory
PI	Principal Investigator
PICANet	The Paediatric Intensive Care Audit Network
PICS-SG	Paediatric Intensive Care Society Study Group
PICU	Paediatric Intensive Care Unit
PIS	Participant Information Sheet
PPI	Patient and Public Involvement
PSS:PICU	Parental stressor scale: PICU
QALYs	Quality-Adjusted Life Years
R&D	Research and Development
RCT	Randomised Clinical Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
UCL	University College London

1. Background and rationale

Over 20,000 critically ill children are admitted to paediatric critical care units in the United Kingdom (UK) and nearly three-quarters of these children receive some form of respiratory support (invasive and/or non-invasive), making it the most common treatment provided in paediatric critical care.[1] Although endotracheal intubation and invasive mechanical ventilation (IMV) can be a life-saving procedure, increasing recognition of its risks, such as ventilator-induced lung injury and nosocomial infections, have prompted greater use of non-invasive respiratory support (NRS) techniques in paediatric intensive care units (PICUs) worldwide.[1 2]

NRS is currently used in two distinct clinical scenarios: 1) in acutely ill children, aiming to prevent intubation and IMV (*step-up* treatment), and 2) in children who have just come off IMV, aiming to prevent re-intubation and further IMV (*step-down* treatment). Continuous positive airway pressure (CPAP), involving the delivery of pressurised air/oxygen through a face mask or nasal prongs, is a mode of NRS that PICU clinicians have been familiar with and have used for over three decades.[3-5] Even though observational data suggest that CPAP is effective (~80% of children started on CPAP do not progress to need IMV), there have been few randomised clinical trials (RCTs) of CPAP in critically ill children.[5 6] CPAP can be uncomfortable for some children and is associated with a small but significant risk of complications such as air-leak and nasal trauma, often necessitating the use of sedation, close monitoring and a high level of nursing input.

More recently, an alternate mode of NRS, high-flow nasal cannula (HFNC), has gained popularity since it is appears easy to use and well tolerated by patients.[7-10] Single-centre studies from the United States and Canada and audit data from the United Kingdom and Ireland indicate that 16–35% of PICU admissions currently receive HFNC at some point during their stay.[1 11 12] Through diverse mechanisms such as reduction of airway resistance, reduction of dead space by nasopharyngeal washout with fresh gas and delivery of positive airway pressure ("CPAP effect"), HFNC has been shown to reduce the work of breathing and improve oxygenation and ventilation in children. In particular, the potential benefits of HFNC (improved patient comfort, safety profile and ease of nursing care) must 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 critical care unit/hospital stay).

There are few RCTs comparing HFNC with CPAP in the paediatric critical care setting.[13-15] Evidence available from RCTs[15 16] does not yet definitively support the comparative effectiveness of either HFNC or CPAP as first line use for non-invasive respiratory support in critically ill children. Importantly, RCTs to date have also not studied the effectiveness of these interventions 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 the UK paediatric critical care setting.

FIRST-ABC therefore addresses an important clinical dilemma faced daily by paediatric critical care clinicians in the UK: in a child requiring non-invasive respiratory support, which of the two commonly available modalities, HFNC or CPAP, should they use as first-line therapy to achieve the best patient outcomes?

Our research question was recently prioritised by the multi-disciplinary UK Paediatric Intensive Care Society Study Group (PICS-SG) as an important research topic for the NHS. In addition, as identified in our PPI work, parents/patients have identified this as an important topic for the NHS.

This Protocol has been written in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 statement.[17]

1.1 Pilot and feasibility work

A multi-centre pilot RCT was conducted to explore the feasibility of performing a pragmatic RCT comparing CPAP and HFNC in critically ill children.[18] The results of the pilot RCT confirmed that it was feasible to conduct a large, pragmatic, national RCT of non-invasive respiratory support in the paediatric critical care setting in both *step-up* and *step-down* NRS. Moreover, it informed the design and conduct of the current RCTs.

1.2 Hypothesis

In critically ill children assessed by the treating clinician to require non-invasive respiratory support (NRS), the first-line use of high flow nasal cannula (HFNC) is non-inferior to continuous positive airway pressure (CPAP) in terms of time to liberation from respiratory support.

1.3 Aims and objectives

1.3.1 Aim

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

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

1.3.2 Primary objective

To evaluate the non-inferiority of HFNC, as compared with CPAP, when used as the first-line mode of non-invasive respiratory support, both as a step-up treatment (*step-up RCT*) and as a step-down treatment (*step-down RCT*), on the time to liberation from

respiratory support, defined as the start of a 48-hour period during which the child was free of all forms of respiratory support.

1.3.3 Secondary objectives

To compare, between the groups:

- mortality at PICU/HDU discharge, day 60 and day 180;
- the rate of (re)intubation at 48 hours;
- the duration of PICU/HDU and hospital stay;
- patient comfort, during randomised treatment and during non-invasive respiratory support (i.e. HFNC and/or CPAP), measured using the validated COMFORT-B Score;[19]
- the proportion of patients receiving sedation during non-invasive respiratory support (i.e. HFNC and/or CPAP);
- parental stress, in hospital at/around the time of consent, measured using the Parental Stressor Scale: PICU (PSS:PICU)[20]
- Health-related Quality of Life (HrQoL) at six months measured using the age-appropriate Paediatric Quality of Life Inventory (Peds-QL)[21] and The Child Health Utility 9D (CHU 9D)[22]

1.4 Design

FIRST-ABC is a master protocol comprising two pragmatic, multi-centre, 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 master protocol design allows 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.[23]

A non-inferiority design was chosen based on previous RCTs on this topic as well as feedback from PICS-SG 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.

1.4.1 Internal pilot

An internal pilot will run from months 7-12 (as per the grant timeline) and use a traffic light system to assess key progression criteria regarding site opening, recruitment and adherence to the study protocol for each of the RCTs.[24] The internal pilot will follow the same processes as the main trial; participants enrolled in the pilot will be included in the analysis of the main trial.

2. Methods

2.1 Setting

2.1.1 Trial sites

In this protocol, 'site' refers to the 25 NHS paediatric critical care units (paediatric intensive care units (PICU) and/or high dependency units (HDUs)) where FIRST-ABC will be conducted.

2.1.2 Site requirements

- Able to provide both treatments (HFNC and CPAP) to study participants
- Active participation in the Paediatric Intensive Care Audit Network for the UK and Ireland (PICANet) audit or able to collect detailed data on patient interventions and outcomes
- Compliance with all responsibilities as stated in the FIRST-ABC Clinical Trial Site Agreement (CTSA)
- Compliance with all requirements of the trial protocol including the trial treatments, consent procedures and data collection/follow-up schedules
- Compliance with the UK Policy Framework for Health and Social Care Research and International Conference on Harmonization Guidelines on Good Clinical Practice (ICH-GCP).

2.1.3 Site responsibilities

- Identify a Principal Investigator (PI) to lead FIRST-ABC locally
- Identify a FIRST-ABC Research Nurse responsible for day-to-day local trial coordination
- Identify a doctor and nurse/allied health professional champion in each unit
- Agree to incorporate the FIRST-ABC into routine paediatric critical care clinical practice, highlighting the importance of systematic screening for potential eligible patients and prompt randomisation
- Agree to adhere to individual patient randomisation allocations and ensure adherence with the trial protocol
- Agree to randomise all eligible patients and maintain a Screening and Enrolment Log
- Agree to data collection and safety monitoring requirements.

2.1.4 Site initiation and activation

The following must be in place prior to a site being activated for recruitment:

- a completed site initiation visit
- all relevant institutional approvals (e.g. local confirmation of capacity and capability)
- a fully signed FIRST-ABC Clinical Trial Site Agreement
- a fully signed Delegation Log

Once the ICNARC Clinical Trials Unit (CTU) have confirmed that all necessary documentation is in place, a site activation email will be issued to the site PI, at which point, the site may start to screen for eligible patients. Once the site has been activated, the PI is responsible for ensuring:

- adherence with the most recent approved version of the trial protocol;
- training of relevant site staff in accordance with the trial protocol and, if overseeing the trial or seeking consent/assent, Good Clinical Practice (GCP) requirements;
- appropriate means to identify and randomise eligible patients;
- timely data collection, entry and validation; and
- prompt notification of all adverse events (as specified in Section 2.8).

All local staff (i.e. PI, local investigators, research teams) involved in the conduct of the trial must be trained to carry out their assigned roles. Site research staff should be signed off on the Delegation Log, once trained, and the Delegation Log should be copied and sent to the ICNARC CTU whenever changes are made.

Staff members solely involved in the screening and randomisation of patients should be provided with study-specific training to carry out these tasks and recorded on the Training Log (full GCP training will not be required for these staff members).[25]

2.2 Population

Critically ill children requiring NRS for (A) an acute illness (step-up RCT) or (B) within 72 hours of extubation following a period of invasive ventilation (step-down RCT).

2.2.1 Inclusion criteria

1) Admitted/Accepted for admission to PICU/HDU
2) Age >36 weeks corrected gestational age and <16 years
3) Assessed by the treating clinician to require non-invasive respiratory support, EITHER
   A. for an acute illness (step-up RCT) OR
   B. within 72 hours of extubation following a period of invasive ventilation (step-down RCT).

2.2.2 Exclusion criteria

1. Assessed by the treating clinician to require immediate intubation and invasive ventilation due to severe hypoxia, acidosis and/or respiratory distress, upper airway obstruction, inability to manage airway secretions or recurrent apnoeas
2. Tracheostomy in place
3. Received HFNC/CPAP for >2 hours in the prior 24 hours
4. On home non-invasive ventilation prior to PICU/HDU admission
5. Presence of untreated air-leak (pneumothorax/pneumomediastinum)
6. Midfacial/craniofacial anomalies (unrepaired cleft palate, choanal atresia) or recent craniofacial surgery
7. Agreed 'not for intubation' or other limitation of critical care treatment plan in place.
8. Previously recruited to the FIRST-ABC trial*
9. Clinician decision to start other form of non-invasive respiratory support (i.e. not HFNC or CPAP)

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

2.2.3 Co-enrolment

Co-enrolment with observational studies is permitted without prior agreement. The FIRST-ABC Trial Management Group will consider co-enrolment with other interventional trials on a case by case basis. We will follow previous experience and existing guidelines from the Intensive Care Society regarding co-enrolment to other clinical trials to maximise patient involvement in research.[26 27]

2.2.4 Screening

Potentially eligible patients admitted/accepted for admission to the participating unit will be screened against the inclusion/exclusion criteria by the local clinical team, supported by the site research team. For the step-up RCT, all admissions to the critical care unit will be screened. For the step-down RCT, all patients extubated during critical care admission will be screened. From these, Screening and Enrolment Logs will record enrolled patients, reasons for exclusion and the reason eligible patients are not enrolled.

2.3 Recruitment and consent

2.3.1 Randomisation

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

In each RCT, eligible patients will be randomised on a 1:1 basis to either CPAP or HFNC using a central telephone/web-based randomisation service available 24 hours/seven days per week. The randomisation sequence will be computer generated and variable block sizes will be used to strengthen allocation concealment. Randomisation will be stratified by site and age (<12 months versus >/=12 months).

The trained staff member who randomises the patient will immediately inform the clinical team responsible for the patients care who will commence the randomised treatment as soon as practically possible. In addition, the local site research team will be notified of the randomisation by email. Following enrolment into FIRST-ABC, each participant will be assigned a unique FIRST-ABC Trial Number and a CRF completed by the local research team.

During the recruitment period a member of the FIRST-ABC study team will be available 24 hours/seven days per week to address emergency recruitment, randomisation or clinical issues that arise.

The health technologies used in this study cannot be blinded, since both CPAP and HFNC, as well as the interfaces that deliver the treatments are already used in clinical practice and are easily recognisable by clinical staff.

2.3.2 Consent procedures

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

Children who are eligible for FIRST-ABC become so during a period of critical illness. This is a profoundly stressful time for children's' parents/legal guardians during which time there are ethical concerns both about the burden of trying to understand the trial and the ability of the parent/legal guardian to provide informed consent during a time of great distress. Furthermore, initiation of NRS is most often during an emergency time-sensitive situation where any delay to commencing treatment could be detrimental to the patient and to the scientific validity of the trial.

Considering these issues, FIRST-ABC utilises a deferred consent model ('research without prior consent'). Once a patient is screened and confirmed as eligible for the study (i.e. satisfies inclusion and exclusion criteria), they will be randomised and the randomly assigned treatment (CPAP or HFNC) will be commenced as soon as possible.

This model, developed in line with the CONseNt methods in paediatric Emergency and urgent Care Trials (CONNECT) study guidance,[28] has been found to be acceptable to parents/guardians, as well as to clinicians, in several recent RCTs conducted in the paediatric critical care setting[18 29-33] and is also informed by experience and feedback gained directly from conducing the FIRST-ABC Pilot Study.[18] As part of the pilot RCT, we asked parents of children who were randomised into the study through 'research

without prior consent' methods for their feedback through a survey. This covered feedback on: the timing and content of the approach; the use of 'research without prior consent'; the participant information documentation; the format of the discussions and decision making. Results included: positive feedback was received on all aspects of the consent procedure, especially the patient information documentation and all but one of the responding parents found research without prior consent acceptable in the trial. The reasons identified for giving deferred consent included to help other children in the future (100%) and that they felt that medical studies like FIRST-ABC are important (95%). These findings have been incorporated into our consent procedures and will be used for training at sites.

2.3.3.1 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 will approach the parents/legal guardians of the patient as soon as appropriate and practically possible after randomisation to discuss the study (this will usually occur within 24-48 hours of randomisation). If the participant has died or been discharged from hospital prior to their parents/legal guardians being approached, then the parents/legal guardians will be approached at a later point (see *Discharge prior to consent being sought* and *Death prior to consent being sought*).

Before approaching the parent/legal guardian, the research team member will check with the relevant clinical staff that the participant is stable and that timing is appropriate. If the participant's condition has not stabilised additional time should be allowed before approaching the parent/legal representative. Checks conducted to assess appropriate timing for approach will be recorded in the patients' clinical notes.

Once approached, a Participant Information Sheet (PIS) for parents/legal guardians will be provided. The PIS will identify the title of the study and the Chief Investigator (CI), and include 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. A Consent Form will be provided indicating that: the information given, orally and in writing, has been read and understood; participation is voluntary and can be withdrawn at any time without consequence; and that consent is given for access to medical records to continue data collection, to receive a follow-up questionnaire and for anonymised data to be shared with other researchers in the future. Parents/legal guardians will be given time to read the PIS and have an opportunity to ask any questions they may have about their child's participation in FIRST-ABC and to discuss with other family members or friends before confirming their decision.

After the person seeking consent has checked that the PIS and Consent Form have been understood, they will invite the parent/legal guardians to sign the Consent Form and will then add their own name and countersign it. A copy will be given to the parent/legal guardians to keep, a copy placed in the child's medical notes and the original kept in the Investigator Site File.

Due to age and severity of illness and its impact on the mental state of the target population, it will not be possible to involve study participants in the consenting process. Instead, assent will be obtained prior to hospital discharge if their condition allows (e.g. they regain mental capacity). Study participants will then be provided with an age-appropriate PIS and asked to sign an Assent Form, if appropriate, to confirm they have been informed and understand the study. Parents/legal guardians will be involved in this discussion. If the participant is likely to regain capacity following hospital discharge, then an age-appropriate PIS will be provided to parents/legal guardians to discuss with the participant following recovery.

2.3.4 Discharge prior to consent being sought

In the rare situation where the patient is discharged from hospital prior to the parent/legal guardians confirming their consent decision, the most appropriate member of the site research team will attempt at least one phone call to the parents/legal guardians within five working days of hospital discharge to inform them of their involvement in the study and to provide information about the study. Following on from the call, as well as if there is no response to the call, the parents/legal guardians will be sent a covering letter, personalised by the most appropriate member of the site research team or clinical staff member, and a copy of the PIS and Consent Form (postal versions) by post. The letter will direct the parents/legal guardians to the PIS for detailed information on the study and provide telephone contact details if the parents/legal guardians wish to discuss the trial with a member of the site research team. The letter will ask 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 is no response after four weeks of sending the covering letter, a follow-up letter, alongside second copies of the PIS and Consent Form (postal versions), will be sent to the parent/legal guardians. This second letter will provide the same information as the first letter but will confirm that if no Consent Form is received within four weeks of the second letter being sent, then the participant will be included in the study unless they notify the site research team otherwise. In this event, the site research team should document the non-response on a File Note in the Investigator Site File.

If the participant is transferred to another hospital participating in FIRST-ABC before the consent procedures are complete, then the local research team will contact the research team at the receiving hospital to handover the consenting procedures.

2.3.5 Death prior to consent being sought

In the rare situation where a participant dies before consent has been obtained, a site research team member will obtain information from colleagues and 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 can be sought from parents/legal guardians following the death of their child and prior to their departure from the hospital; however, it is at the discretion of the site staff to determine if this is

appropriate for each individual family. In this situation, the Participant Information Sheet for bereaved parents/legal guardians (B-PIS) and Consent Form (bereaved) would be used.

If deferred consent is not sought prior to the parents'/legal guardians' departure from the hospital, then the parents/legal guardians will be sent a covering letter, personalised by the most appropriate research/clinical team member, and a copy of the B-PIS and Consent Form (bereaved) by post four weeks after randomisation. Where possible, the clinical or research team member should already be known to the family. The letter will explain how to opt out of the study, direct them to the B-PIS for detailed information on the study and provide telephone contact details if parents/legal guardians wish to discuss the study with a member of the site research team.

If there is no response after four weeks of sending the initial letter, a follow-up letter along with the B-PIS and Consent Form postal version for bereaved parents/legal guardians will be sent to the bereaved family. This second letter will provide the same information as the first letter. In addition, this letter will also confirm that if no Consent Form is received within four weeks of receipt of the letter, then the participant's data will be included in the study.

2.3.6 Refusal or withdrawals of consent

If informed consent is refused or withdrawn, this decision will be respected and abided by, and no further contact made. All data occurring up to the point of this decision will be retained in the trial, unless the parent/legal guardian requests otherwise.

2.4 Outcome measures

2.4.1 Internal pilot

Each RCT will use a traffic light system to assess progression from pilot stage to the full trial as below:

Criterion	Green light (Go)	Amber light (Amend)	Red light (Stop)
Number of sites open to recruitment	Minimum 15 sites	8-14 sites	Less than 8 sites
Overall recruitment rate in open sites	At least 75% of anticipated	Between 50 and 74% of anticipated	Less than 50% of anticipated
Proportion started on randomly allocated treatment (CPAP or HFNC)	Over 90%	Between 75 and 90%	Less than 75%
Changes to another form of NRS, escalation and weaning carried out as per protocol	At least two-thirds of cases	Between one-third and two-thirds of cases	Less than one-third of cases

2.4.2 Main trial

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.

Secondary outcomes:

- Mortality at PICU/HDU discharge, day 60 and day 180
- Rate of (re)intubation at 48 hours
- Duration of PICU/HDU and hospital stay
- Patient comfort, during randomised treatment and during non-invasive respiratory support (i.e. HFNC and/or CPAP), assessed using the validated COMFORT-B score
- Proportion of patients in whom sedation is used during non-invasive respiratory support
- parental stress, in hospital at/around the time of consent at 24-48 hours, measured using the Parental Stressor Scale: PICU
- HrQoL at six months using age-appropriate Peds-QL[32] and CHU-9D[22]

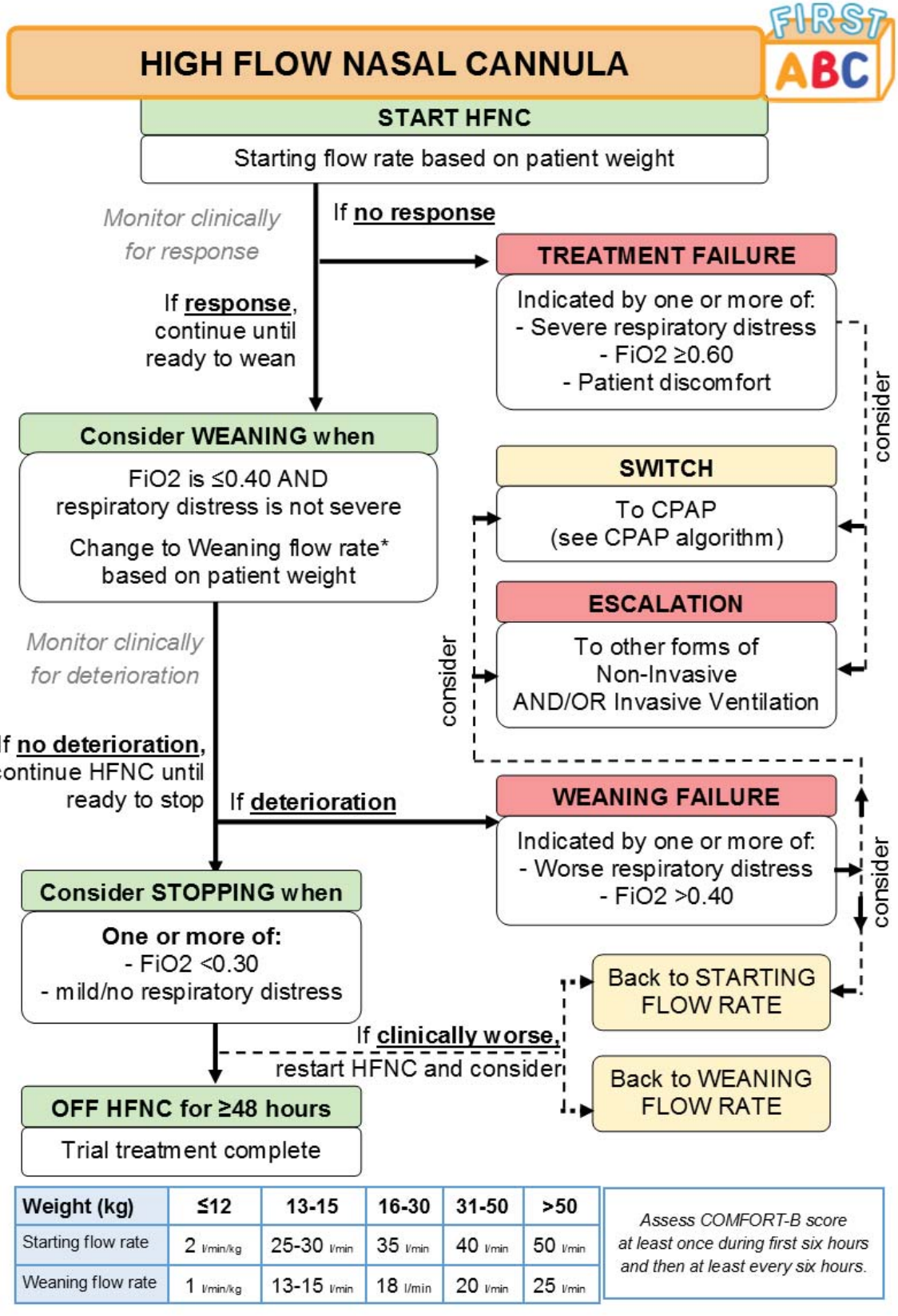
Cost effectiveness analysis (CEA) outcomes:

- Total costs at six months
- QALYs at six months
- Incremental net monetary benefit gained at a willingness-to-pay of £20,000 per QALY at six months associated with HFNC versus CPAP

2.5 Procedures

2.5.1 HFNC

Any approved medical device capable of delivering heated, humidified, high flow through nasal cannulae can be used to provide HFNC at the prescribed gas flow rate during the trial. The study protocol specifies clinical criteria and guidance for the initiation, maintenance and weaning of HFNC (see algorithm below). It is recommended that study participants are 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).



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

Assess COMFORT-B score at least once during first six hours and then at least every six hours.

Staff in all participating units already use HFNC – therefore, no additional technical training related to the use of HFNC will be 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 will not be possible to blind the subject or the clinical staff.

As per current practice, clinicians in the study will be 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 are provided (see algorithm above) as a guide for clinicians considering switching or escalating respiratory support. Reasons for switches and escalations will be recorded. Patients who switch or escalate treatments will remain in the study and continue to be monitored until they are off respiratory support.

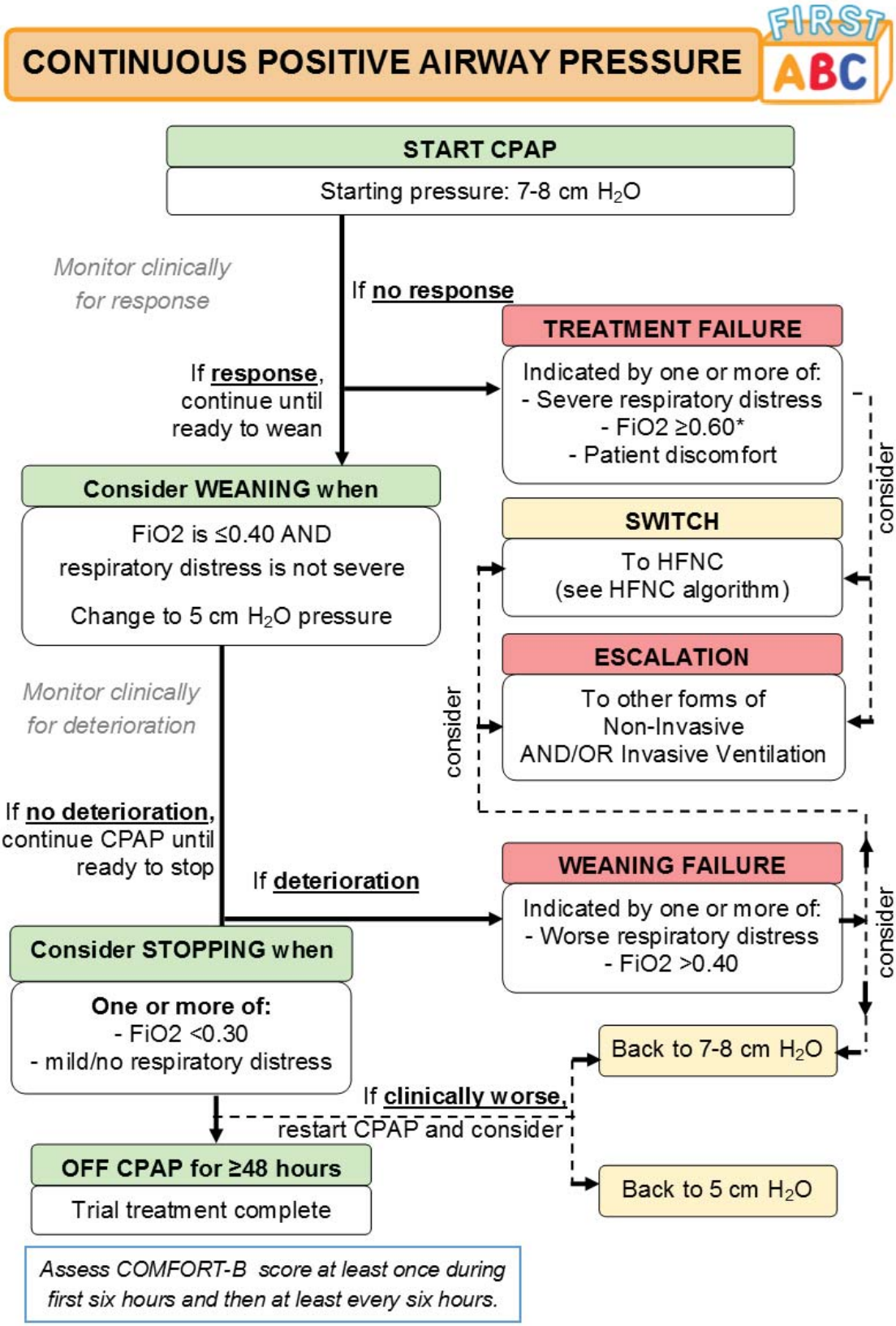
The algorithm will be followed until the patient has been liberated from all forms of respiratory support for at least 48 continuous hours.

2.5.2 CPAP

Conventional CPAP will be started using an approved medical device at a set expiratory pressure of 7-8 cm H_2O. The trial does not specify any particular device or patient interface for the provision of CPAP. In order to standardise treatment, the study protocol specifies clinical criteria and guidance for the initiation, maintenance and weaning of CPAP (see algorithm below).

It is recommended that study participants are 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 use CPAP – therefore, no additional technical training related to the use of CPAP will be provided for the study.


CONTINUOUS POSITIVE AIRWAY PRESSURE
FIRST ABC
START CPAP
Starting pressure: 7-8 cm H2O
Monitor clinically for response
If no response
If response, continue until ready to wean
TREATMENT FAILURE
Indicated by one or more of:
- Severe respiratory distress
- FiO2 ≥0.60*
- Patient discomfort
consider
Consider WEANING when
FiO2 is ≤0.40 AND
respiratory distress is not severe
Change to 5 cm H2O pressure
SWITCH
To HFNC
(see HFNC algorithm)
ESCALATION
To other forms of
Non-Invasive
AND/OR Invasive Ventilation
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
Consider STOPPING when
One or more of:
- FiO2 <0.30
- mild/no respiratory distress
Back to 7-8 cm H2O
If clinically worse, restart CPAP and consider
OFF CPAP for ≥48 hours
Trial treatment complete
Back to 5 cm H2O
Assess COMFORT-B score at least once during first six hours and then at least every six hours.

As per current practice, clinicians in the study will be 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 will be provided in the study protocol as a guide for clinicians considering switching or escalating respiratory support. Reasons for switches or escalations will be recorded. Patients who switch or escalate treatments will remain in the study and continue to be monitored until they are off respiratory support.

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

2.5.3 Co-interventions

All other usual care will be 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, does not include supplemental/low-flow oxygen.

2.6 Questionnaire follow-up

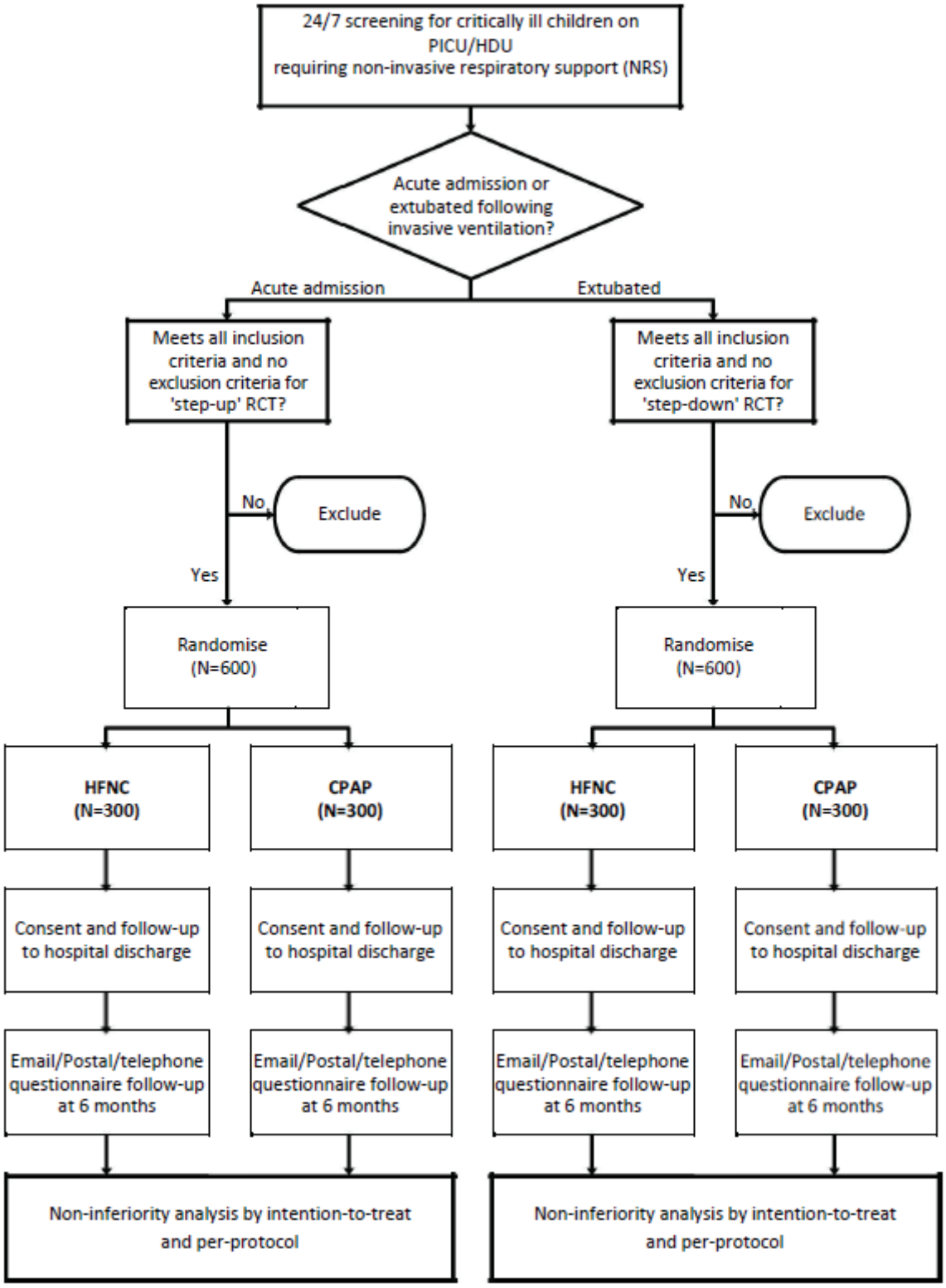
Each consenting participant will be followed up with a questionnaire at six months post-randomisation to assess HrQoL and health service and resource use. Prior to the sending of a questionnaire, survival status at six months will be ascertained either through review of medical records by local research teams and/or via data-linkage with nationally held records (decedents will be logged in the trial records and the follow-up process ended).

At the six-month time point, parents/legal guardians of recruited patients will be emailed or posted (as per their preference indicated at the time of consent) a questionnaire by the ICNARC CTU containing the PEDS-QL, CHU-9D and a health services questionnaire. The questionnaires are designed to take no longer than 15 minutes to complete. If a parent requests a questionnaire to be sent via post, then a pen and self-addressed stamped envelope will be provided for ease of return.

If there is no response three weeks later, parents/legal guardians will be telephoned and asked to check whether they have received the questionnaire. If preferable for the parent/legal guardian, they will be offered the option of either being sent another copy of the questionnaire via email, in the post, or to complete the questionnaire over the telephone with a trained member of the FIRST-ABC trial team.

If a patient is an in-patient at a participating site at the follow-up time-point, the site research team will be asked to approach the parent/legal guardian and conduct the questionnaire with the parents/legal guardians in hospital, if willing.

2.7 Participant timeline



2.8 Safety Monitoring and Reporting

2.8.1 Definitions

Adverse Event (AE) reporting will follow the Health Research Authority guidelines on safety reporting in studies which do not use Investigational Medicinal Products (non-CTIMPs).

The following definitions have been adapted from Directive 2001/20/EC of the European Parliament (Clinical Trials Directive) and ICH-GCP guidelines (E6(R1), 1996).

2.8.2 Adverse Event

An Adverse Event (AE) is defined as: any untoward medical occurrence or effect in a patient participating in a study.

2.8.3 Serious Adverse Event

A serious adverse event (SAE) is defined as an Adverse Event that:

- results in death;
- is life-threatening;
- requires hospitalisation or prolongation of existing hospitalisation;
- results in persistent or significant disability or incapacity;
- consists of a congenital anomaly or birth defect.

“Life-threatening”, in the definition of a Serious Adverse Event, refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

“Hospitalisation” refers to inpatient admission, regardless of length of stay. This includes admission for continued observation. Any admission for pre-existing conditions that have not worsened, or elective procedures, do not constitute an SAE.

Important adverse events that are not immediately life-threatening, do not result in death or hospitalisation but may jeopardise the subject or require intervention to prevent one or any of the other outcomes listed in the definition above should also be considered as serious.

2.8.4 Unexpected and Related Serious Adverse Event

A suspected Adverse Event related (possibly, probably or definitely) to the trial treatment that is both unexpected (i.e. not consistent with the expected outcomes of the treatment being offered) and serious.

2.8.5 Assessment

The PI, or other medically qualified investigator as listed on the Delegation Log, should make an assessment of severity, relatedness and expectedness, categorised as follows:

2.8.5.1 Severity

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

2.8.5.2 Relatedness

- **None**: there is no evidence of any relationship to the study treatment.
- **Unlikely:** There is little evidence to suggest a causal relationship (e.g. because the event did not occur within a reasonable time after administration of the trial treatment). There is another reasonable explanation of the event (e.g. the participant's clinical condition, other concomitant medications).
- **Possibly:** There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial procedure). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant medications).
- **Probably:** There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
- **Definitely:** There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

2.8.5.3 Expectedness

- **Expected**: the event is listed as an expected AE in Appendix 2.

- **Unexpected**: the event is not listed as an expected AE in Appendix 2.

2.8.6 Recording and Reporting procedures

Occurrences of the specified, expected adverse events will be recorded for all randomised patients from the time of randomisation until time of liberation from all forms of respiratory support for 48 hours.

Considering that all children eligible for the FIRST-ABC RCTs are critically ill and, due to the complexity of their condition, are at an increased risk of experiencing AEs – occurrences of non-specified, unexpected adverse events will only be reported if they are considered to be related to the study treatment (possibly, probably or definitely).

The following events will not be reported as AEs or SAEs as they are collected as study outcomes:

- Intubation or re-intubation
- Sedation
- Death (note that death itself should not be reported as an SAE, but the suspected cause of death should be assessed for severity, relatedness and expectedness as above)

All SAEs (other than those defined in the protocol as not requiring reporting) must be reported to ICNARC CTU using the FIRST-ABC SAE Reporting Form within 24 hours of the site research team becoming aware of the event. Staff should not wait until all information about the event is available before sending SAE notification. Information not available at the time of the initial report must be documented and submitted as it becomes available.

SAEs must be recorded in the patients' medical notes, on the FIRST-ABC CRF, and reported to the ICNARC CTU using the FIRST-ABC SAE Reporting Form, by email to firstabc@icnarc.org or by uploading the form into the secure web-based data entry system, within 24 hours of observing or learning of the SAE(s). The process for recording and reporting adverse events and serious adverse events is summarised in Figure 1.

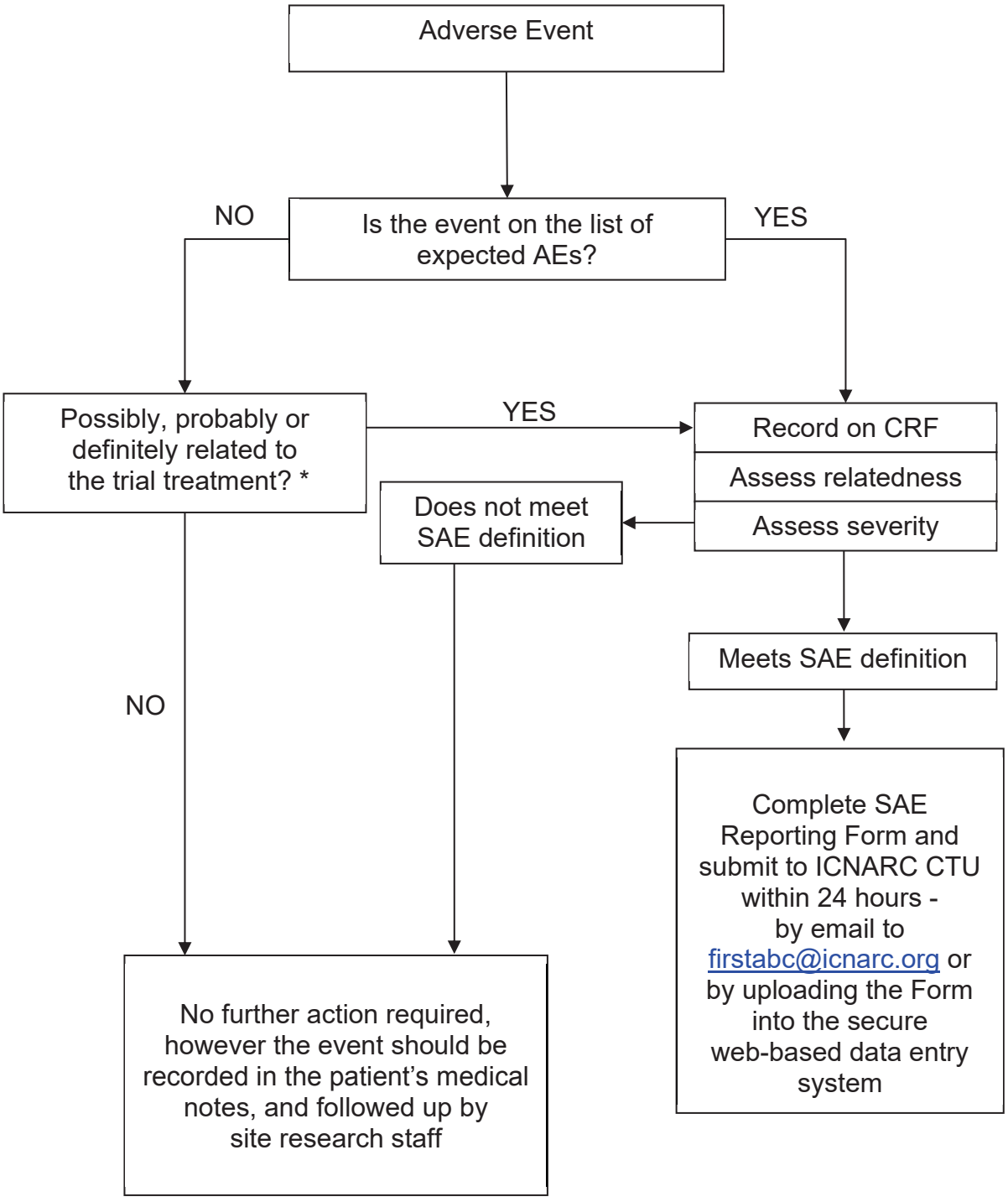
On receipt of an SAE report, a member of the ICNARC CTU will first evaluate the report for completeness and internal consistency. Then, a clinical member of the FIRST-ABC Trial Management Group (TMG) will evaluate the event for severity, relatedness and expectedness to determine whether or not the case qualifies for expedited reporting to the Research Ethics Committee (REC). If the event is evaluated by either the Chief Investigator or a clinical member of the FIRST-ABC TMG as a related and unexpected SAE, the ICNARC CTU will submit a report to the REC within 15 calendar days.

The ICNARC CTU will provide safety information to the Data Monitoring and Ethics Committee (DMEC) on a basis deemed appropriate by the DMEC.

2.8.7 Notifying the Research Ethics Committee

Adverse Events that do not require expedited reporting to the REC will be reported annually to the REC. This will commence annually from the date of REC favourable ethical opinion for the trial.

Figure 1: Adverse Event recording and reporting



*If there is any uncertainty about whether the AE is associated with trial treatment, then it should be reported.

2.9 Data collection

To maximise the efficiency of the design, FIRST-ABC will collaborate with PICANet to make best use of the established data collection infrastructure which exists in all PICUs in the UK. All participating PICUs routinely submit clinical data to the national audit of Paediatric Intensive Care. These data are used locally by participating PICUs to monitor activity and performance. They have full access to, and ownership of the data. Data are validated on entry and centrally on the PICANet server. PICANet will produce a download facility that allows participating units to extract data required for the trial, thus reducing the burden of data collection for unit staff.

Examples of data from PICANet used in the trial analysis will include:

- baseline demographics and risk factors;
- secondary outcomes of PICU/HDU and acute hospital mortality, duration of PICU/HDU and acute hospital stay; and
- critical care daily interventions (and associate costs), based on Healthcare Resource Groups, from the index admission and any subsequent readmissions.

All patients recruited to the trial will be consented for data linkage with routine sources (e.g. NHS Digital or equivalent). Data obtained from routine data sources will include:

- date of death for deaths occurring after discharge from acute hospital, by data linkage with civil registration data

Additional data items collected specifically for the trial will be limited to the minimum required to deliver the trial objectives. These will include:

- parent/legal guardian name, address and telephone number for questionnaire follow-up at six months;
- data items to confirm eligibility;
- data to monitor adherence with the HFNC and CPAP algorithms, including escalation and weaning;
- time on any ventilation;
- secondary outcomes of modified COMFORT-B score, parental stress and sedation use; and
- adverse event reporting.

2.10 Data management

All participant data collected will be entered onto a secure electronic data entry system. The option of entry first onto paper CRFs will be available to participating sites. The site PI will oversee and be responsible for data collection, quality and recording. Collection of data can be delegated (as per the Delegation Log) by the site PI to qualified members of the research team, on the understanding that the site PI retains responsibility for the data collection oversight.

Data entered onto the secure electronic data entry system will undergo validation checks for completeness, accuracy and consistency of data. Queries on incomplete, inaccurate or inconsistent data will be sent to the local research team at participating sites for resolution. The local PI will be responsible for ensuring all queries are addressed and for overall quality of their site data.

Security of the electronic data entry system is maintained through usernames and individual permissions approved centrally by the ICNARC CTU. Central back-up procedures are in place. Storage and handling of confidential trial data and documents will be in accordance with the Data Protection Act 2018.

2.11 Monitoring and auditing

2.11.1 Central monitoring

The trial team members at the ICNARC CTU will have regular communication with sites via email, telephone, teleconferences and newsletters. Adherence to the protocol will be paramount in the central monitoring plan, including a review of consent forms; eligibility data and adherence to the HFNC and CPAP algorithms.

2.11.2 Site monitoring

The on-site monitoring plan will be developed following a risk-based strategy. Selected sites will be visited at an early stage. The timing and frequency of visits to sites will be based on a risk assessment, including an assessment of the sites and local research team (e.g. experience of multicentre research, involvement in RCTs etc.). It is anticipated that 25% of sites will be visited at least once during the recruitment period to monitor and discuss adherence to the trial protocol and standard operating procedures. Directly following all site visits, the site PI will be verbally advised of the core monitoring findings and this will be followed with a written a report to the site summarising the visit, documents reviewed and any findings. Information learnt at site visits will be used to refine standard operating procedures, as required, ensuring clarity and consistency across sites.

2.12 Statistical Methods

2.12.1 Sample size

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

2.12.2 Internal pilot

Data will be analysed at the end of the internal pilot trial stage (months 7-12 of the grant timeline) on patients recruited during the first six months in both the step-up RCT and the step-down RCT. The analysis will take place in month 14 of the grant to allow data to be collected and entered to assess all progression criteria. The objectives of the feasibility analysis will be to assess whether there has been successful site set-up, screening and recruitment, and adherence to both the HFNC and CPAP algorithms. The RCTs will progress from the pilot stage to full trial based on the progression criteria (see section 2.4.1). Where any of the progression criteria are given an 'Amber light', a management plan will be put in place by the TMG and discussed with the Trial Steering Committee (TSC). The final decision on progression from the pilot stage to the full trial will be made by the NIHR HTA programme after recommendation, or not, by the TSC.

2.12.3 Clinical effectiveness analysis

All analyses will be lodged in a statistical analysis plan, a priori, before the investigators are unblinded to any study outcomes. Following best practice for non-inferiority trials, the primary analyses will be undertaken in both intention-to-treat (ITT) and per protocol (PP) populations with robust conclusions possible in the situation where both populations provide concordant results. Results will be reported in accordance with the CONSORT statement extension for non-inferiority and equivalence trials.

Analyses will be undertaken independently for each of the two RCTs. In each RCT, baseline patient characteristics will be compared between the two groups to observe balance and the success of randomisation. These comparisons will not be subjected to statistical testing. The delivery of the intervention will be described for each group in detail, including (but not limited to) number and percentage of patients who commence the randomised treatment, number and percentage who remain on the randomised treatment until liberation from ventilation, and number and percentage of patients who are changed to a different method of respiratory support or treatment escalation.

HFNC will be considered non-inferior to CPAP if the lower bounds of the 95% confidence intervals for the hazard ratio (HR) from Cox regression models on time to liberation from respiratory support fitted in both the ITT and PP populations exclude the pre-specified non-inferiority margin of 0.75 (corresponding to approximately a 16-hour increase in median time to liberation). This margin was considered adequate such that the other potential benefits of HFNC in terms of comfort and tolerability would mean that it would be likely to be preferred in usual practice. The Cox regression models will be adjusted for important baseline characteristics. The covariates for inclusion in the regression models will be selected a priori based on an established relationship with outcome for critically ill children, and not because of observed imbalance, significance in univariable analyses or by a stepwise selection method.

Subgroup analyses will be performed to test for interactions between the effect of allocated treatment group and the following baseline covariates:

- age (<12 months versus ≥12 months)
- severity of respiratory distress at randomisation (severe versus mild/moderate)
- Co-morbidities (None versus Neurological/neuromuscular versus Other)
- Sp02/Fi02 SF ratio at randomisation
- for the step-up RCT only:
    - clinical indication (bronchiolitis versus other respiratory versus cardiac)
    - whether child was on non-invasive respiratory support at randomisation (Yes/No)
- for the step-down RCT only:
    - length of prior IMV (<5 days versus ≥5 days)
    - reason for IMV (cardiac versus other)
    - planned versus rescue initiation of non-invasive respiratory support

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

Secondary analyses of binary outcomes (mortality, reintubation) will be performed by Fisher's exact test and adjusted logistic regression. Duration of survival to day 180 will be plotted as Kaplan-Meier survival curves, compared unadjusted with the log rank test and adjusted using Cox regression models. Analyses of duration of PICU/HDU and hospital stay will be performed by Wilcoxon rank-sum tests, stratified by survival status. Analyses of COMFORT-B score, sedation use, PSS:PICU and HrQoL will be performed by t-tests and adjusted linear regression.

In the step-up RCT, a single interim analysis will be carried out after the recruitment and follow-up to day 60 of 300 patients. The interim analysis will use a Peto-Haybittle stopping rule to recommend early termination due to superiority of either intervention ($P<0.001$) in time to liberation from respiratory support or evidence of harm from either intervention ($P<0.05$) in mortality at day 60. Both tests will be performed using a log-rank test on all available data within the ITT population. Further interim analyses will be performed only if requested by the Data Monitoring and Ethics Committee (DMEC).

In the step-down RCT, due to faster than anticipated recruitment, no formal interim analysis will be performed. Safety data (counts and percentages of adverse events by arm, and a line listing of SAEs) will be available for scrutiny by the DMEC, by the end of the internal pilot stage.

2.12.4 Integrated health economic evaluation

The cost-effectiveness analysis (CEA) will take an NHS and Personal Social Services perspective.[34] Patient-level resource use data will be obtained from trial case report forms (CRFs), PICANet, and health services questionnaire (HSQ). Resource use data from the PICU/HDU stay will be taken from the CRF and linked routine data from PICANet. Information on subsequent PICU/HDU and hospital admissions will be obtained via data linkage with PICANet and through completion of the health services

questionnaire. Data on the level of care for PICU bed-days will be gathered through routine collection of the Paediatric Critical Care Minimum Dataset (PCCMDS) in the participating centres via the PICANet database. Use of primary care and community health services will be assessed by HSQ at six months. Patient-level resource use data will be combined with appropriate unit costs from the NHS payment by results database and PSSRU to report total costs per patient for up to six months since randomisation. Data from the PedsQL-4.0 and CHU-9D questionnaires at six months will be combined with survival data to report QALYs at six months. The CEA will follow the intention-to-treat principle and report the mean (95% confidence interval) incremental costs, QALYs and net monetary benefit at six months. The CEA will use multilevel linear regression models that allow for clustering of patients at site. The analysis will adjust for key baseline covariates at both patient and site level.

3. Ethics, approvals and dissemination

3.1 Research ethics

FIRST-ABC will be conducted in accordance with the approved trial protocol, ICH-GCP guidelines, the UK Data Protection Act 2018, the Mental Capacity Act, as well as the ICNARC CTU research policies and procedures.

3.1.1 Trial registration

This trial has been registered with the ISRCTN Registry (ISRCTN60048867).

3.1.2 Central NHS ethical compliance

The trial has received a favourable ethical opinion from the NHS East of England - Cambridge South Research Ethics Committee (reference number: 19/EE/0185) and approval from the Health Research Authority (Integrated Research Application System (IRAS) number: 260536).

3.1.2 Local ethical compliance

It is the responsibility of the site PI to obtain the necessary local approvals for FIRST-ABC, including formal confirmation of capacity and capability. Evidence of confirmation of capacity and capability at each participating site must be provided to the ICNARC CTU prior to site activation (see section 2.1).

3.2 Protocol amendments

The study will be conducted in accordance with the current approved version of the Protocol. Any proposed amendments to the research will be considered by the Sponsor in the first instance and then categorised as either substantial or minor (non-substantial)

and the research Protocol modified accordingly. Agreed trial/protocol amendments will be submitted for review to NHS ethics and/or HRA dependent on the categorisation and, following the respective favourable opinion/approval, the amendment will be carried out and implemented in accordance with the HRA guidance.

3.3 Confidentiality

Identifiable patient data, including full name, contact details, date of birth and NHS number will be required by the ICNARC CTU to successfully follow-up participants. The ICNARC CTU will act to preserve participant confidentiality and will not disclose or reproduce any information by which participants could be identified. Data will be stored securely.

We will also seek consent to share the patients' anonymised data or to be contacted by the study team for future research.

All data will be securely stored in a locked cabinet or in an encrypted electronic file. ICNARC is registered under the Data Protection Act (Registration number: Z6289325) and will preserve the confidentiality of participants taking part in the study.

3.4 Declaration of interests

The FIRST-ABC Investigators report no conflicts of interest.

3.7 Dissemination policy

3.7.1 Trial results

The results of FIRST-ABC will be disseminated actively and extensively. The research team has strong links with the paediatric critical care community via the Paediatric Intensive Care Society (PICS), PICS Study Group (PICS-SG), and the NIHR CRN: Children Clinical Studies Group (CSG) in Anaesthesia, Intensive Care and Cardiology, and similarly with the nursing community through the British Association of Critical Care Nurses (BACCN), the Royal College of Nursing Critical Care and In-flight Nursing Forum (RCN CCINF) and the European Society of Paediatric and Neonatal Intensive Care (ESPNIC). We also have links with the Healthcare Quality Improvement Partnership national audit programme through the Paediatric Intensive Care Audit Network (PICANet). A study website and links to social media will be created to actively publicise progress with the research and disseminate our findings.

The findings from our work will be presented at national and international conferences. A Study Report to the NIHR HTA Programme will present a detailed description of the project and the results along with recommendations for future policy, practice and research. The study findings will also be published in high-impact, open-access, peer reviewed scientific journals and relevant professional journals.

The results of the study will be disseminated to patients and their families, facilitated by the co-applicants, members of the research team who have links with PICS and the NIHR CSG, and via Family Groups we have liaised with already.

3.7.3 Data sharing

We shall make data available to the scientific community with as few restrictions as feasible, while retaining exclusive use until the publication of major outputs. Once the data from the study are fully analysed and published, the dataset will be made available in line with the National Institute for Health Research (NIHR) current recommendations.

4. Trial closure

4.1 End of trial

The end of the trial will be defined as when the last participant has completed follow-up (last participant, last follow-up). At this point, the ICNARC CTU will submit the 'Declaration of end of trial' to the REC.

4.2 Archiving trial documents

At the end of the trial, the ICNARC CTU will securely archive all centrally held trial-related documents for a minimum of 15 years, in accordance with ICH-GCP guidelines. Arrangements for confidential destruction of all documents will then be made. The site PI will be responsible for archiving all trial-related documents (including CRFs and other essential documents) held at the participating site for a minimum of 15 years after the end of the trial. Essential documents are those which enable both the conduct of the study and the quality of the data produced to be evaluated and to show whether the site complied with the principles of ICH-GCP and other applicable regulatory requirements.

Guidance on archiving will be provided to sites in the trial-specific SOP. All archived documents, held centrally and locally, should be available for inspection by appropriate authorities upon request.

4.3 Early discontinuation of the trial

A single interim analysis will be carried out in the step-up trial as described in section 2.12.3 of this protocol. It will use a Peto-Haybittle stopping rule to recommend early termination due to superiority of either intervention ($P<0.001$) in time to liberation from respiratory support or evidence of harm from either intervention ($P<0.05$) in mortality at day 60. Further interim analyses will be performed if requested by the Data Monitoring and Ethics Committee.

5. Trial management and oversight

As Chief Investigator, Dr Padmanabhan Ramnarayan – supported closely by the ICNARC CTU - will take overall responsibility for delivery of FIRST-ABC and overseeing progress against timelines/milestones.

5.1 Good research practice

FIRST-ABC will be managed by the ICNARC CTU according to the Medical Research Council's Good Research Practice: Principles and Guidelines[35] based on the principles of the International Conference on Harmonisation guidelines on Good Clinical Practice[36] and the UK Department of Health's Policy Framework for Health and Social Care Research.[37]The ICNARC CTU has developed policies and procedures based on these guidelines, which are adhered to for all research activities at ICNARC. In addition, ICNARC has contractual confidentiality agreements with all members of staff and policies regarding alleged scientific misconduct and breach of confidentiality are reinforced by disciplinary procedures.

5.2 Trial Management Group (TMG)

The TMG comprises the FIRST-ABC Investigators (listed on page 5) – led by the Chief Investigator (PR). The day-to-day trial team will comprise the Chief Investigator, Clinical Trials Unit co-investigators (Professor Kathy Rowan, Professor David Harrison and Mr Paul Mouncey) alongside the Trial Manager (Mr Alvin Richards-Belle), Trial Statisticians (Ms Izabella Orzechowska and Ms Karen Thomas), Research Assistant (Ms Laura Drikite) and Data Manager (Ms Michelle Saull).

Quarterly meetings of the TMG will be held to ensure effective communication. In addition, the day-to-day trial team will meet regularly to discuss the progress of the trial and findings from other related research.

5.3 Trial Steering Committee (TSC)

A Trial Steering Committee (TSC) will be established in line with the latest NIHR HTA guidelines. The TSC will be responsible for overall supervision on behalf of the Sponsor and Funder and will ensure that the trial is conducted in accordance with the rigorous standards set out in the UK Framework for Health and Social Care research and the Guidelines for Good Clinical Practice. The TSC will be comprised by a majority of independent members (including the Chair) and include Patient and Public Involvement (PPI) representatives, in addition to the Chief Investigator.

5.4 Data Monitoring and Ethics Committee (DMEC)

An independent Data Monitoring and Ethics Committee (DMEC) will be set-up to monitor recruitment and retention, adherence with the intervention and patient safety. Meetings will take place immediately prior to TSC meetings.

5.5 Patient and Public Involvement (PPI)

We had considerable PPI input into the FIRST-ABC pilot RCT as well as for this proposal. Two parents of children who received breathing support are co-applicants on this grant application and have actively contributed to the study design and procedures, including the use of deferred consent. In addition, independent PPI representative(s) will be sought for membership of the TSC.

6. Sponsorship and funding

6.1 Sponsorship and indemnity

The Great Ormond Street Hospital for Children NHS Foundation Trust are the Sponsor for FIRST-ABC (reference: 17IA05). As the sponsor is an NHS organisation, NHS indemnity will apply for legal liability arising from the design, management and conduct of the research.

6.2 Funding

National Institute for Health Research (NIHR) – Health Technology Assessment Programme (HTA) (Project: 17/94/28).

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8. Appendices

8.1 Appendix 1 – Protocol version history

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
SA01	1.2	9 December 2019	Alvin Richards-Belle	• Section 2.2.2: addition of 'Clinician decision to start other form of non-invasive respiratory support (i.e. not HFNC or CPAP)' exclusion criteria • Sections 1.3.3. and 2.4.2: clarification that patient comfort (secondary outcome) will be assessed 'during non-invasive respiratory support i.e. HFNC and/or CPAP' • Section 2.12.3: additional detail of pre-specified planned subgroup analyses added • Section 2.12.3: confirmation that the interim analysis will take place only in the step-up RCT due to faster than anticipated recruitment to the step-down RCT, and addition of safety monitoring of the step-down RCT by the DMEC. • Section 2.5.2: algorithms updated and corrected • Minor administrative changes.

8.2 Appendix 2 - Specified, expected Adverse Events (AEs)

Specified, expected AEs that could be 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

[This list is not exhaustive. If an AE, as defined in Section 2.8, occurs this should be recorded and reported as described in Section 2.8.6]

UCL INSTITUTE OF CHILD HEALTH

icnarc intensive care national audit & research centre

Great Ormond Street Hospital for Children NHS Foundation Trust

Joint Research and Development Office
Division of Research and Innovation

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

Statistical Analysis Plan, Version 1.0

REC number:	19/EE/0185
Trial Sponsor:	Great Ormond Street Hospital for Children NHS Foundation Trust
Trial Sponsor reference:	17IA05
Trial Funder:	NIHR HTA Programme
Trial Funder reference:	17/94/28
ISRCTN number:	ISRCTN60048867
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Protocol version (date):	v1.2, 9 December 2019

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Roles and responsibilities

Role, Name and Position	Signature	Date
Authors:		
Izabella Orzechowska, Statistician, ICNARC		
Karen Thomas, Senior Statistician, ICNARC		
Chief Investigator:		
Dr Padmanabhan Ramnarayan, GOSH		

Version history

Version	Date	Summary of main changes/justification	Timing
1.0			

Contents

1 Introduction

1.1 Background and rationale

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

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

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

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

1.2 Aim and Objectives

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

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

1.2.1 Primary Objectives

To evaluate the non-inferiority of HFNC, as compared with CPAP, when used as the first-line mode of non-invasive respiratory support, both as a step-up treatment (*step-up RCT*) and as a step-down treatment (*step-down RCT*), on the time to liberation from respiratory support, defined as the start of a 48-hour period during which the child was free of all forms of respiratory support.

1.2.2 Secondary Objectives

To compare, between the groups:

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

2 Study Methods

2.1 Trial design

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

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

2.2 Randomisation

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

2.3 Sample size

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

2.4 Framework

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

2.5 Analysis of internal pilot

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

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

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

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

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

2.6 Statistical interim analysis and stopping criteria

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

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

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

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

2.7 Timing of final analysis

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

2.8 Timing of outcome assessments

Following randomisation, details of respiratory support (type of support, flow rate/pressure), physiological parameters (respiratory rate, heart rate, SpO2, FiO2), and measures of patients comfort (respiratory distress scored as none/mild/moderate/severe, sedation delivered yes/no, and COMFORT-B scores) are recorded hourly for the first 6 hours, and six hourly thereafter until the end of respiratory support (or to at least 48 hours following randomisation, if patients are transferred to another unit or ward).

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

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

3 Statistical Principles

3.1 Confidence intervals and p-values

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

3.2 Adherence and protocol deviations

3.2.1 Exposure

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

- In patients randomised to CPAP, pressure (in cm H2O as a continuous variable, and grouped as <7cm, 7-8cm, >8cm), by hour during the first 6 hours from randomisation.
- In patients randomised to HNFC, flow rate (as % of recommended starting rate, and group ed as <=50%, 51-75%, 76-85%, 86-95%, >=95% of recommended starting rate), by hour during the first 6 hours from randomisation.
- Time from first recorded observation meeting weaning/failure/stopping criteria to time of weaning/switch or escalation/treatment stop

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

3.2.2 Protocol adherence

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

- Did not start randomised treatment (i.e. first recorded respiratory support post-randomisation is not the randomised treatment)
- Switched or escalated from randomised treatment without meeting treatment failure criteria
- Weaning attempt made, when weaning criteria is not met in last recorded observation prior to weaning
- Respiratory support is discontinued while FiO2>=0.3 and moderate or severe respiratory distress is present

3.3 Analysis Population

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

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

4 Trial population

4.1 Screening data

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

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

4.2 Eligibility

4.2.1 Inclusion Criteria

1) Admitted/Accepted for admission to PICU/HDU
2) Age >36 weeks corrected gestational age and <16 years
3) Assessed by the treating clinician to require non-invasive respiratory support, EITHER
   A. for an acute illness (step-up RCT) OR
   B. within 72 hours of extubation following a period of invasive ventilation (step-down RCT).

4.2.2 Exclusion Criteria

1. Assessed by the treating clinician to require immediate intubation and invasive ventilation due to severe hypoxia, acidosis and/or respiratory distress, upper airway obstruction, inability to manage airway secretions or recurrent apnoeas
2. Tracheostomy in place
3. Received HFNC/CPAP for >2 hours in the prior 24 hours
4. On home non-invasive ventilation prior to PICU/HDU admission
5. Presence of untreated air-leak (pneumothorax/pneumomediastinum)
6. Midfacial/craniofacial anomalies (unrepaired cleft palate, choanal atresia) or recent craniofacial surgery
7. Agreed ‘not for intubation’ or other limitation of critical care treatment plan in place.

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

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

4.3 Recruitment

The following CONSORT[15] flow diagrams for the ITT and PP populations will be completed for each trial:

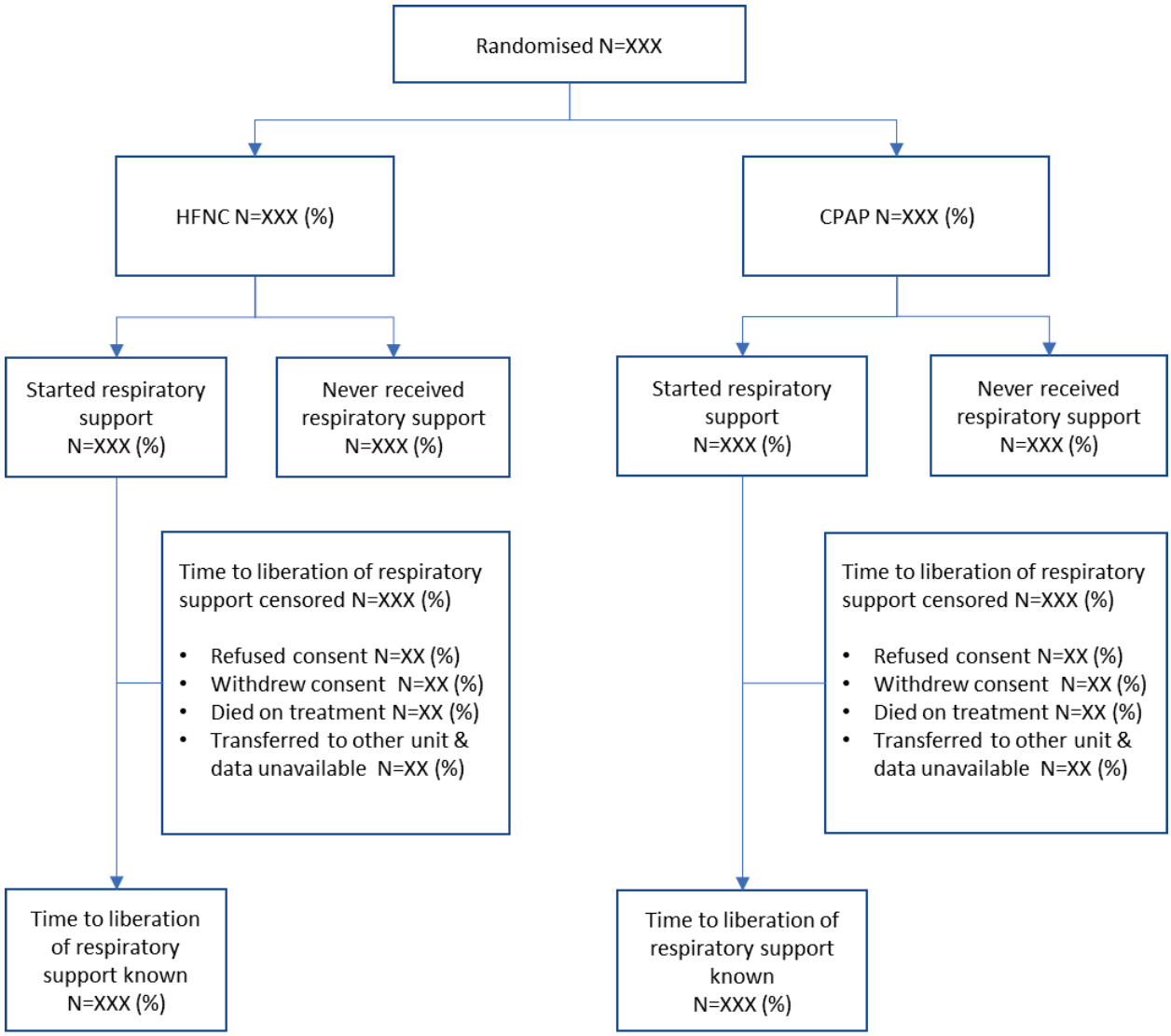

Figure 1: CONSORT diagram for ITT population

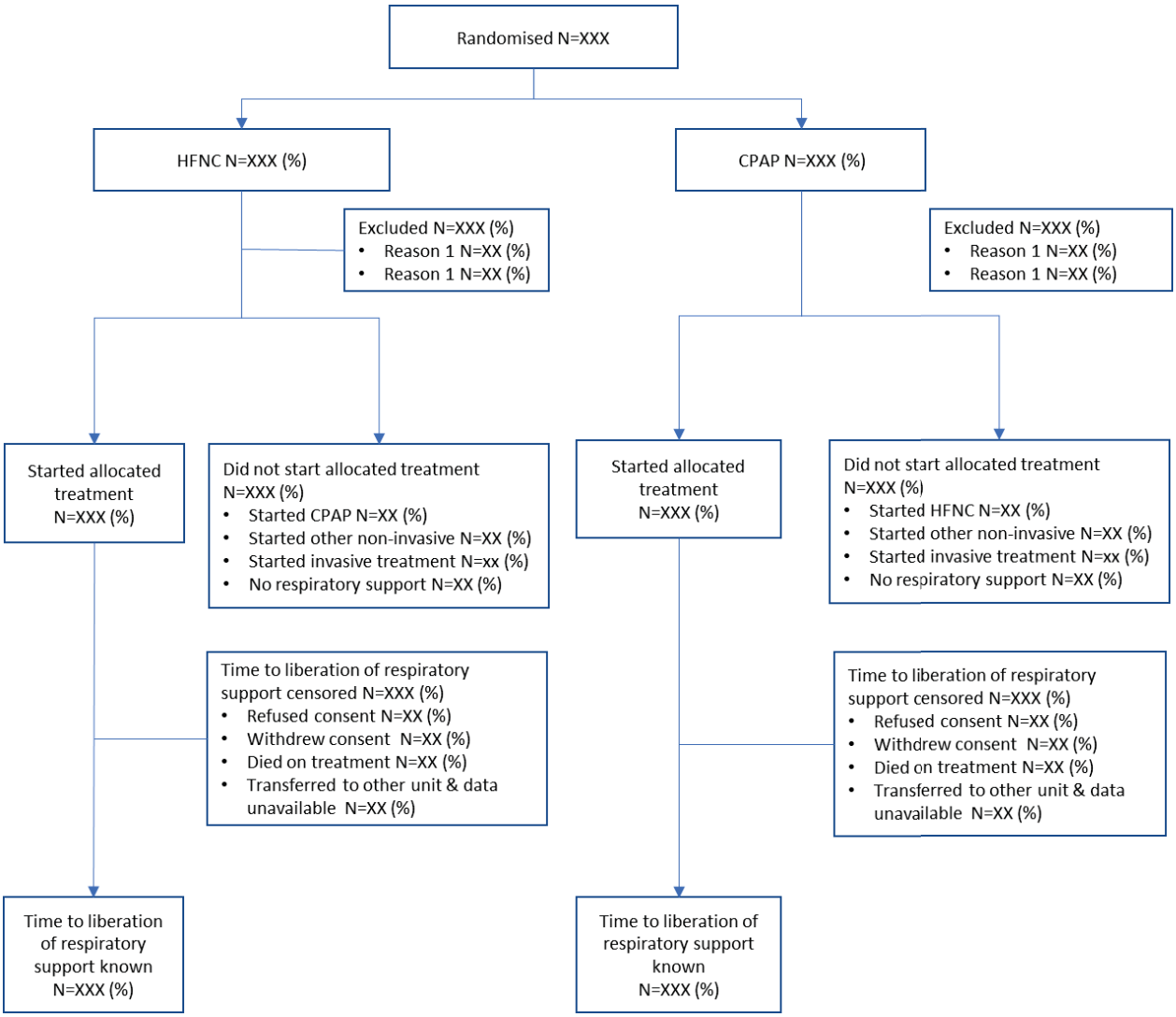

Figure 2: CONSORT diagram for PP population

4.4 Consent

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

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

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

4.5 Withdrawal/follow-up

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

4.6 Baseline patient characteristics

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

In both trials:

- Age (years)– median and IQR, and number and % by age group (<=28 days, 29-180 days, 181-364 days, 1 year, 2 years, 3 years, 4 years, 5-10 years, 11-15 years)
- Sex (male, female) – number and %
- Respiratory distress at randomisation – number and % by category
- Heart rate at randomisation (both as absolute values, and converted to centile for age) – median and IQR, mean and SD
- SpO2 at randomisation – median and IQR, mean and SD
- FiO2 at randomisation – median and IQR, mean and SD
- Ratio of SpO2:FiO2 at randomisation – median and IQR, mean and SD
- Comfort-B score at randomisation (last available) – mean and IQR, number and % with COMFORT-B score >=23 (representing possible distress[16])
- Comorbidities – number and % by type of comorbidities (as specified on the CRF)

Step-up only:

- Main reason for admission to critical care – number and %
- Any respiratory support received in 24hrs prior to randomisation (overall, and by type and duration of support) – number and %
- Whether on respiratory support at time of randomisation – number and %
- Received general anaesthesia for surgery/procedure in the 6 hours preceding randomisation – number and %

Step-down only:

Main reason for invasive ventilation

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

5 Analysis

5.1 Outcome definitions

5.1.1 Primary outcome

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

5.1.2 Secondary outcomes

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

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

5.1.2.2 Rate of (re)intubation at 48 hours

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

5.1.2.3 Duration of PICU/HDU and acute hospital stay

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

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

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

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

5.1.2.5 Need for Sedation

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

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

5.1.2.6 Parental stress at 24-48h

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

5.1.2.7 Health-related quality of life at 6 months

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

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

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

5.1.2.8 Total costs at 6 months

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

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

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

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

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

5.2 Clinical effectiveness analysis methods

5.2.1 Primary outcome

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

In both trials

- age (<12 months versus ≥12 months)
- severity of respiratory distress at randomisation (severe versus mild/moderate)
- SpO2:FiO2 ratio at randomisation (linear)
- Co-morbidities (None versus Neurological/neuromuscular versus Other)

Step-up only

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

Step-down only

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

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

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

(both trials)

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

(step-up only)

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

(step-down only)

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

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

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

5.2.2 Secondary outcomes

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

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

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

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

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

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

5.3 Cost effectiveness analysis methods

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

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

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

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

5.3.1 Sensitivity analysis for cost-effectiveness

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

a. HRQoL data

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

b. Cost data

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

5.4 Handling of missing data

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

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

5.5 Additional analyses

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

5.6 Safety

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

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

5.7 Statistical software

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

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