Welcome to the Integrated Research Application System

IRAS Project Filter

The integrated dataset required for your project will be created from the answers you give to the following questions. The system will generate only those questions and sections which (a) apply to your study type and (b) are required by the bodies reviewing your study. Please ensure you answer all the questions before proceeding with your applications.

Please complete the questions in order. If you change the response to a question, please select 'Save' and review all the questions as your change may have affected subsequent questions.

Please enter a short title for this project (maximum 70 characters)
FIRST-line support for Assistance in Breathing in Children (FIRST-ABC)

1. Is your project research?

(●) Yes ( ) No

2. Select one category from the list below:

( ) Clinical trial of an investigational medicinal product

( ) Clinical investigation or other study of a medical device

( ) Combined trial of an investigational medicinal product and an investigational medical device

(●) Other clinical trial to study a novel intervention or randomised clinical trial to compare interventions in clinical practice

( ) Basic science study involving procedures with human participants

( ) Study administering questionnaires/interviews for quantitative analysis, or using mixed quantitative/qualitative methodology

( ) Study involving qualitative methods only

( ) Study limited to working with human tissue samples (or other human biological samples) and data (specific project only)

( ) Study limited to working with data (specific project only)

( ) Research tissue bank

( ) Research database

If your work does not fit any of these categories, select the option below:

( ) Other study

2a. Will the study involve the use of any medical device without a CE Mark, or a CE marked device which has been modified or will be used outside its intended purposes?

( ) Yes (●) No

2b. Please answer the following question(s):

a) Does the study involve the use of any ionising radiation? ( ) Yes (●) No

b) Will you be taking new human tissue samples (or other human biological samples)? ( ) Yes (●) No

c) Will you be using existing human tissue samples (or other human biological samples)? ( ) Yes (●) No

3. In which countries of the UK will the research sites be located?*(Tick all that apply)*

- [x] England
- [x] Scotland
- [x] Wales
- [x] Northern Ireland

3a. In which country of the UK will the lead NHS R&D office be located:

- (•) England
- ( ) Scotland
- ( ) Wales
- ( ) Northern Ireland
- ( ) This study does not involve the NHS

4. Which applications do you require?

- [x] IRAS Form
- [ ] Confidentiality Advisory Group (CAG)
- [ ] Her Majesty's Prison and Probation Service (HMPPS)

5. Will any research sites in this study be NHS organisations?

(•) Yes ( ) No

5a. Are all the research costs and infrastructure costs (funding for the support and facilities needed to carry out research e.g. NHS Support costs) for this study provided by a NIHR Biomedical Research Centre, NIHR Collaboration for Leadership in Health Research and Care (CLAHRC), NIHR Patient Safety Translational Research Centre or Medtech and In Vitro Diagnostic Cooperative in all study sites?

Please see information button for further details.

( ) Yes (•) No

Please see information button for further details.

5b. Do you wish to make an application for the study to be considered for NIHR Clinical Research Network (CRN) Support and inclusion in the NIHR Clinical Research Network Portfolio?

Please see information button for further details.

(•) Yes ( ) No

The NIHR Clinical Research Network provides researchers with the practical support they need to make clinical studies happen in the NHS e.g. by providing access to the people and facilities needed to carry out research "on the ground".

If you select yes to this question, you must complete a NIHR Clinical Research Network (CRN) Portfolio Application Form (PAF) immediately after completing this project filter question and before submitting other applications. Failing to complete the PAF ahead of other applications e.g. HRA Approval, may mean that you will be unable to access NIHR CRN Support for your study.

6. Do you plan to include any participants who are children?

◉ Yes ○ No

7. Do you plan at any stage of the project to undertake intrusive research involving adults lacking capacity to consent for themselves?

○ Yes ◉ No

Answer Yes if you plan to recruit living participants aged 16 or over who lack capacity, or to retain them in the study following loss of capacity. Intrusive research means any research with the living requiring consent in law. This includes use of identifiable tissue samples or personal information, except where application is being made to the Confidentiality Advisory Group to set aside the common law duty of confidentiality in England and Wales. Please consult the guidance notes for further information on the legal frameworks for research involving adults lacking capacity in the UK.

8. Do you plan to include any participants who are prisoners or young offenders in the custody of HM Prison Service or who are offenders supervised by the probation service in England or Wales?

○ Yes ◉ No

9. Is the study or any part of it being undertaken as an educational project?

○ Yes ◉ No

10. Will this research be financially supported by the United States Department of Health and Human Services or any of its divisions, agencies or programs?

○ Yes ◉ No

11. Will identifiable patient data be accessed outside the care team without prior consent at any stage of the project (including identification of potential participants)?

○ Yes ◉ No

Integrated Research Application System
Application Form for Other clinical trial or investigation

IRAS Form (project information)

Please refer to the E-Submission and Checklist tabs for instructions on submitting this application.

The Chief Investigator should complete this form. Guidance on the questions is available wherever you see this symbol displayed. We recommend reading the guidance first. The complete guidance and a glossary are available by selecting Help.

Please define any terms or acronyms that might not be familar to lay reviewers of the application.

Short title and version number: (maximum 70 characters - this will be inserted as header on all forms)
FIRST-line support for Assistance in Breathing in Children (FIRST-ABC)

Please complete these details after you have booked the REC application for review.

REC Name:
East of England - Cambridge South Research Ethics Committee

REC Reference Number:
19/EE/0185

Submission date:
26/04/2019

PART A: Core study information

1. ADMINISTRATIVE DETAILS

A1. Full title of the research:

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

A3-1. Chief Investigator:

	Title	Forename/Initials	Surname
	Dr	Padmanabhan	Ramnarayan
Post	Consultant in Paediatric Intensive Care & Retrieval		
Qualifications	MBBS - Medicine, MD - Medical Informatics Applications, Fellow - Paediatrics, Global Clinical Scholar - Research, Member - Paediatrics, Fellow - Intensive Care Medicine		
ORCID ID	0000 0003 0784 8154		
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Work Address	Children's Acute Transport Service 26-27 Boswell Street London		
Post Code	WC1N 3JZ		
Work E-mail	p.ramnarayan@gosh.nhs.uk		
* Personal E-mail			

Work Telephone	020 7430 5850
* Personal Telephone/Mobile	
Fax	

** This information is optional. It will not be placed in the public domain or disclosed to any other third party without prior consent.*
A copy of a current CV (maximum 2 pages of A4) for the Chief Investigator must be submitted with the application.

A4. Who is the contact on behalf of the sponsor for all correspondence relating to applications for this project?
This contact will receive copies of all correspondence from REC and HRA/R&D reviewers that is sent to the CI.

	Title	Forename/Initials	Surname
	Dr	Jenny	Rivers
Address	UCL Great Ormond Street Institute of Child Health (ICH) & Great Ormond Street Hospital (GOSH)		
	30 Guilford Street		
	London		
Post Code	WC1N 1EH		
E-mail	research.governance@gosh.nhs.uk		
Telephone	020 7905 2700		
Fax	020 7905 2201		

A5-1. Research reference numbers. *Please give any relevant references for your study:*

Applicant's/organisation's own reference number, e.g. R & D (if available):	17IA05
Sponsor's/protocol number:	1.0
Protocol Version:	1.0
Protocol Date:	22/03/2019
Funder's reference number (enter the reference number or state not applicable):	17/94/28
Project website:	https://www.icnarc.org/Our-Research/Studies/First-Abc

Registry reference number(s):
The UK Policy Framework for Health and Social Care Research sets out the principle of making information about research publicly available. Furthermore: Article 19 of the World Medical Association Declaration of Helsinki adopted in 2008 states that "every clinical trial must be registered on a publicly accessible database before recruitment of the first subject"; and the International Committee of Medical Journal Editors (ICMJE) will consider a clinical trial for publication only if it has been registered in an appropriate registry. Please see guidance for more information.

International Standard Randomised Controlled Trial Number (ISRCTN):

ClinicalTrials.gov Identifier (NCT number):

Additional reference number(s):

Ref.Number Description	Reference Number

A5-2. Is this application linked to a previous study or another current application?

(●) Yes ( ) No

Please give brief details and reference numbers.
FIRST-ABC Pilot Study -
IRAS number: 185074
REC reference: 15/NE/0296

2. OVERVIEW OF THE RESEARCH

To provide all the information required by review bodies and research information systems, we ask a number of specific questions. This section invites you to give an overview using language comprehensible to lay reviewers and members of the public. Please read the guidance notes for advice on this section.

A6-1. Summary of the study. *Please provide a brief summary of the research (maximum 300 words) using language easily understood by lay reviewers and members of the public. Where the research is reviewed by a REC within the UK Health Departments' Research Ethics Service, this summary will be published on the Health Research Authority (HRA) website following the ethical review. Please refer to the question specific guidance for this question.*

Many of the 20,000 children admitted to NHS paediatric critical care units yearly need support for their breathing. The most invasive form of breathing support is when a child has a tube inserted into their windpipe and is put on a breathing machine. To reduce the number of children needing invasive support, non-invasive methods like Continuous Positive Airway Pressure (CPAP) are used. CPAP provides oxygen/air through a face mask or into the nose. Although CPAP is beneficial, some children find it uncomfortable and some have complications.

A more recent alternative is called High Flow Nasal Cannula (HFNC). HFNC provides oxygen/air through tiny tubes inserted into the nostrils. Less is known about benefits or safety of HFNC, however, hospitals are starting to use HFNC instead of CPAP as it is easier to use and some children appear more comfortable on it. Thus, there is widespread variation across the country in which method is used. Before HFNC is adopted more widely, it is crucial that its role is studied closely.

We will study whether HFNC is as effective as CPAP by doing two randomised clinical trials (RCTs) under one framework (FIRST-ABC). Each RCT will include 600 children, from 25 paediatric critical care units, who require non-invasive breathing support to either help:
1. prevent them from going onto a ventilator (step-up RCT) or
2. prevent them from going back on a ventilator after having just come off one (step-down RCT).

Children will be randomly assigned to either CPAP or HFNC as first-line method of non-invasive breathing support. Previously, we tested the trial procedures in a small study and confirmed that it was feasible to do this trial.

FIRST-ABC will provide much needed evidence and will have a large and immediate impact on how sick children are cared for in the NHS.

A6-2. Summary of main issues. *Please summarise the main ethical, legal, or management issues arising from your study and say how you have addressed them.*

Not all studies raise significant issues. Some studies may have straightforward ethical or other issues that can be identified and managed routinely. Others may present significant issues requiring further consideration by a REC, HRA, or other review body (as appropriate to the issue). Studies that present a minimal risk to participants may raise complex organisational or legal issues. You should try to consider all the types of issues that the different reviewers may need to consider.

Purpose and design

Each year, around 20,000 critically ill children are admitted to NHS paediatric critical care units (Paediatric Intensive Care Units (PICUs) and High Dependency Units (HDUs). A high proportion (around three-quarters) of these children need respiratory (breathing) support while in the unit. The most invasive form of breathing support is when a child has a tube inserted into their windpipe and is put on a breathing machine (a ventilator). This often involves sedating the child and is very distressing to parents and families, as well as the child.

To reduce the number of children who are put on a ventilator (invasive support), non-invasive methods are frequently used in paediatric critical care. Continuous Positive Airway Pressure (CPAP) has been traditionally used for this purpose, although a newer method called High Flow Nasal Cannula therapy (HFNC) has become popular recently owing to its ease of use and patient comfort.

CPAP provides oxygen or air through a face mask or into the nose. Although CPAP is beneficial, some children find it uncomfortable and some have complications such as air leaking outside the lungs, vomiting from stomach bloating from the oxygen/air, and pressure sores on the nose or cheeks from the face mask. HFNC provides oxygen or air through tiny tubes inserted into the nostrils. There is little research on whether HFNC is beneficial or safe, however, many hospitals are starting to use HFNC instead of CPAP as it is easier to use and some children appear more

comfortable on it.

Although HFNC is now being increasingly used to treat critically ill children in paediatric critical care, there is no randomised clinical trial (RCT) evidence to support its clinical and cost-effectiveness, especially in comparison to CPAP. There are significant potential clinical benefits associated with the use of HFNC: it appears to be much more comfortable and appears to be associated with a low risk of complications. However, concerns regarding its safety (risk of air-leak syndromes, nosocomial infections, and abdominal distension) and inadvertent adverse effects on patient outcomes (delaying invasive ventilation and prolonging length of PICU or hospital stay) have also been reported.

In the absence of evidence supporting one treatment over the other, clinicians are currently using CPAP and HFNC interchangeably based on personal preference and anecdotal practice. Therefore, before an expensive health technology such as HFNC is adopted more widely across the NHS, it is crucial that evidence from well-conducted RCTs are available to clarify its effectiveness compared to established practice (CPAP). It is important that such evidence is provided in a timely fashion and while there is still sufficient equipoise amongst paediatric critical care clinicians, before a potentially ineffective and expensive intervention is fully adopted into standard practice without rigorous evaluation.

FIRST-ABC is a master protocol comprising two pragmatic, multi-centre, parallel groups, non-inferiority RCTs with shared infrastructure, including an internal pilot stage and integrated health-economic evaluation. FIRST-ABC addresses an important clinical dilemma faced daily by paediatric critical care clinicians: 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?

The master protocol design allows the research question to be addressed in each of the two important populations - step-up support (i.e. aiming to prevent a child from needed invasive support) and step-down support (i.e. aiming to prevent a child from going back on invasive support after coming off it) in an efficient way by minimising time and infrastructure costs as compared with conducting two sequential RCTs.

A non-inferiority design was chosen based on previous RCTs on this topic as well as feedback from the Paediatric Intensive Care Society - Study Group (PICS-SG) 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.

Data on safety/adverse events will be collected on all study participants. Safety will be monitored by the Data Monitoring and Ethics Committee (at a schedule the Committee deem appropriate) who will recommend the continuation (or not) of the trial to the Trial Steering Committee.

The FIRST-ABC master protocol was designed by experts in critical care – both from clinical and methodological backgrounds. The Chief Investigator is Dr Padmanabhan Ramnarayan (Consultant in Paediatric Intensive Care & Retrieval at Great Ormond Street Hospital for Children NHS Foundation Trust) and the study will be managed by the ICNARC CTU - both with extensive experience in coordinating complex clinical trials in critical and emergency care settings. The Trial Management Group also includes parent representatives who will provide vital parent/patient engagement and have reviewed all parent/patient materials used in the trial. The full Trial Management Group will meet regularly to review progress of the trial against timelines and milestones. In addition, the research proposal was reviewed and recommended for funding by the National Institute for Health Research anonymous peer reviewers.

Previously, we conducted the FIRST-ABC Pilot Study which demonstrated the feasibility of conducting the large-scale trial described in the current application. The pilot study included 121 children requiring non-invasive breathing support admitted to PICUs in three NHS hospitals, of which half were randomly allocated to CPAP and the other half to HFNC.

Inclusion / exclusion

Inclusion criteria are as follows:
1) Accepted for admission to PICU/HDU
2) Age >36 weeks corrected gestational age and <16 years AND
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).

Exclusion criteria are as follows:
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 critical care unit admission
5) Presence of untreated air-leak (pneumothorax and/or 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

Recruitment and consent

Patients will be screened for eligibility by local research and clinical teams (members of the direct health care team) at participating critical care units (PICUs or HDUs) in NHS hospitals.

The main ethical issue in this study is consent. The decision to initiate non-invasive respiratory support is most often made during a time-sensitive emergency situation, where any delay in commencing treatment could be detrimental to the patient and the scientific validity of the trial. This makes attempts to obtain fully informed prior consent from parents/legal guardians during such an emergency situation inappropriate and could cause additional stress to families who are already very distressed by their child's critical illness. In addition, both modes of non-invasive respiratory support evaluated as first-line treatment in this study (CPAP and HFNC) are relatively safe, commonly used and in current clinical practice - only determined by individual clinician preferences.

Considering these reasons, we will utilise a deferred consent model ('research without prior consent') in the FIRST-ABC RCTs, a model that has been found to be acceptable to parents/guardians as well as clinicians in several previous RCTs conducted in the paediatric critical care setting (including by our research group). This consent model has been informed and refined by extensive patient and public involvement (PPI) work conducted by our group and others, and is based on the CONseNt methods in paediatric Emergency and urgent Care Trials (CONNECT) study guidance - developed by Dr Kerry Woolfall (a lead researcher in this area) and her team.

Recruitment and consent

Study information will be provided in advance whenever possible (such as when potentially eligible patients are identified prior to extubation in the step-down RCT); written informed consent will be obtained from parents/legal guardians as soon as practically possible and appropriate after randomisation (usually within 24 to 48 hours).

Once notified of the randomisation of a patient to the study, a trained, delegated member of the site research team (typically a research nurse or a critical care doctor/consultant) will approach the parents/legal guardians of the child (patient) as soon as appropriate and practically possible after randomisation to discuss the study (this will usually occur within 24-48 hours of randomisation).

Before approaching the parent/legal guardian, the research team member will check with the relevant clinical staff (e.g. bedside nurse) 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 guardian. 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. The shorter Patient Information Leaflet may be given initially before following up with the PIS with full details of the study (note that consent will not be taken on the basis of the Patient Information Leaflet alone). 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. In addition, consent will be sought for continuation in the trial, to collect routine clinical data from medical records, to permit data linkage with national routine sources (e.g. NHS Digital or equivalent), to receive a questionnaire in six months' time and for anonymised data to be shared with other researchers to support future research.

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

Due to age (e.g. the majority of children in the pilot study were ≤2 years of age), severity of illness and its impact on 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. Parents/legal guardians will be involved in this discussion. In all other respects, the assenting procedures will follow the consenting procedures as described above. If the participant is likely to regain capacity following hospital discharge, then an age-appropriate PIS will be provided to parents/legal guardian to discuss with the participant following recovery.

Due to the use of deferred consent, there may be rare situations where the patient is either discharged from hospital prior to consent being confirmed/obtained from the parents/legal guardians or dies prior to consent being sought. We will utilise postal consent procedures developed and successfully implemented during the FIRST-ABC pilot RCT (and other studies in the PICU setting) for these rare situations.

In the rare situation where a participant dies before consent has been obtained, a local 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 guardian of the involvement in the study. Deferred consent can be sought from parents/legal guardian 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 approached using the postal consent procedure, 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 (bereaved) 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. These consent procedures have been extensively tested in similar studies in the paediatric critical care setting.

Local research team members working in paediatric critical care are very experienced in communicating with bereaved (and non-bereaved) families and will be supported by the local Principal Investigator as required.

Risks, burdens and benefits

With regards to the clinical treatments, there are no additional risks over and above the current clinical practice. As the study will use identifiable and health data, there is a small risk that data could be lost or breached. Robust measure will be in place to prevent this from occurring – e.g. through the implementation of regular data back up arrangements and data disaster recovery procedures. To minimise the possibility of data security breaches, all data leaving the recruiting NHS hospital will be encrypted. Identifiable data will only be collected where essential. Participants will be allocated a unique Trial Number to minimise processing of identifiable data. Data sharing agreements will be put in place where needed (e.g. between ICNARC and NHS Digital to permit data linkage).

Confidentiality

Patient identifiable data (name and contact details) will be required at ICNARC CTU to enable the FIRST-ABC study team to contact and follow-up patients at six months post-randomisation and to conduct data linkage with national organisations (e.g. NHS Digital or equivalent). Only individuals vital to these FIRST-ABC study activities will have access to any identifiable data. Following completion of the trial, all data will be anonymised.

ICNARC will act to preserve patient confidentiality and will not disclose or reproduce any information by which patients could be identified to a third party without permission. Data will be stored in a secure manner and all of ICNARC CTU trials and studies are carried out in accordance with the Data Protection Act 2018. Any data leaving the NHS will be encrypted to an appropriate standard. The Sponsor will not receive any patient identifiable data.

Conflicts of interest

None

Use of tissue samples in future research

None

3. PURPOSE AND DESIGN OF THE RESEARCH

A7. Select the appropriate methodology description for this research. *Please tick all that apply*:

- ☐ Case series/ case note review
- ☐ Case control
- ☐ Cohort observation
- ☐ Controlled trial without randomisation
- ☐ Cross-sectional study
- ☐ Database analysis
- ☐ Epidemiology
- ☐ Feasibility/ pilot study
- ☐ Laboratory study
- ☐ Metanalysis
- ☐ Qualitative research
- ☐ Questionnaire, interview or observation study
- ☑ Randomised controlled trial
- ☐ Other (please specify)

A10. What is the principal research question/objective? *Please put this in language comprehensible to a lay person.*

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

The primary outcome will evaluate the non-inferiority of HFNC 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.

A11. What are the secondary research questions/objectives if applicable? *Please put this in language comprehensible to a lay person.*

In each RCT (step-up RCT and step-down RCT), between the groups (HFNC and CPAP):

- What is the mortality at PICU/HDU discharge, day 60 and day 180?
- What is the rate of (re)intubation at 48 hours?
- What is the duration of PICU/HDU and hospital stay?
- To assess patient comfort using the validated COMFORT-B score
- What is the proportion of patients in whom sedation is used during non-invasive respiratory support?
- To assess parental stress in hospital at time of consent using a validated Parental Stressor Scale:PICU (PSS:PICU)
- To assess Health-related Quality of Life at six months using the age-appropriate Peds-QL, HUI2 questionnaire, and health services questionnaire
- What are the total costs at 6 months?
- To assess QALYs at 6 months
- What is the net monetary benefit gained at a willingness-to-pay of £20,000 per QALY at 6 months associated with HFNC versus CPAP?

A12. What is the scientific justification for the research? *Please put this in language comprehensible to a lay person.*

Respiratory support is the most common intervention delivered in paediatric critical care units. Respiratory support can be delivered either by sedating the child and inserting a breathing tube into their windpipe (invasive ventilation) or by non-invasive means such as Continuous Positive Airway Pressure (CPAP) or High Flow Nasal Cannula (HFNC). Although invasive ventilation is life-saving, non-invasive breathing support has several advantages, such as the ability to avoid sedation, allowing the child to spontaneously breathe and cough, and minimising the risk of ventilator associated adverse events. As such, it is frequently used to: a) prevent progression to intubation and invasive ventilation (as ‘step-up’ treatment), or b) to prevent re-intubation after being extubated following a period of invasive ventilation (as ‘step-down’ treatment).

Due to the absence of scientific evidence to support the effectiveness of non-invasive breathing support, several different modes of non-invasive respiratory support are currently used according to clinician preference. The most commonly used modes are:

Continuous positive airway pressure (CPAP)
CPAP has been in use for over two decades. It can be provided via a variety of patient interfaces (e.g. face mask, nasal prongs, helmet); however, the effective use of CPAP is limited by two main problems: a) the need for a tight-fitting patient interface to avoid leakage of gas from the ventilator circuit, and b) the small but significant risk of serious complications such as air leak in the lungs. The former causes patient discomfort/agitation and nasal/facial pressure sores with prolonged use, frequently leading to CPAP treatment failure. The latter usually necessitates close patient monitoring and a high level of skilled nursing input.

High Flow Nasal Cannula therapy (HFNC)
Over the past decade, heated-humidified high flow nasal cannula therapy (HFNC) has rapidly gained popularity in the paediatric critical care setting. HFNC involves the administration of a mixture of oxygen and air at high gas flow rates. HFNC has been shown to be effective in managing acute respiratory failure from various causes. Despite the absence of clinical trial evidence to support its effectiveness, HFNC has become popular due to its ease of use. HFNC does not require a tight seal around the face/nose, and its patient interface (nasal prongs) appears to be well tolerated by children and requires less nursing input.

CURRENT EVIDENCE
There are no randomised trials in paediatric critical care comparing the effectiveness of CPAP with HFNC. Trials from critically ill adults and newborns have shown conflicting results. In general, neonatal trials in preterm babies found that HFNC was no different to CPAP for breathing support after extubation. Two trials from sick adults were recently published: one did not show any important differences between CPAP and HFNC in terms of avoiding invasive ventilation while the other demonstrated non-inferiority of HFNC compared to CPAP.

There is plenty of evidence from observational studies in children that supports HFNC use in critically ill children. HFNC has been shown to be associated with improvement in breathing difficulties within the first 60-90 minutes of initiation, with sustained improvement demonstrated over the subsequent 8-12 hours. A gas flow rate of 2 L/kg/min has been shown to be effective. In Brisbane, the rate of invasive ventilation fell dramatically in their PICU coinciding with the adoption of HFNC over a period of 5 years (2005-2009).

However, not all studies have reported beneficial effects with the use of HFNC. In a French study, no differences could be found between infants with bronchiolitis who received CPAP in one winter season and infants who received HFNC in the next winter season. Worryingly, it has been reported that HFNC may delay invasive ventilation and increase mortality. There have also been concerns regarding the complications of HFNC, namely air-leak in the lungs, chest infection, and abdominal distension.

STUDY RATIONALE
Although HFNC appears to be used widely in critically ill children, there is no scientific evidence to support its clinical and cost-effectiveness.

Benefits of HFNC
There are significant potential clinical benefits associated with the use of HFNC: it appears to be much more comfortable for the child and associated with a low risk of complications. As such, it may have significant advantages as the first line mode of noninvasive support in terms of a) reducing the need for invasive ventilation; b) improving patient comfort and the ability for parents to better interact with their child; and c) reducing PICU length of stay by allowing the child to be safely cared for in a ward bed while still receiving respiratory support.

Risks of HFNC
Concerns exist regarding the safety of HFNC (risk of air-leak, infections, and abdominal distension) and inadvertent adverse effects on patient outcomes (such as delaying invasive ventilation and prolonging length of ICU or hospital stay).

Before an expensive health technology such as HFNC is adopted more widely, it is crucial that evidence from a well-conducted RCT is available. It is also important that any evidence is generated in a timely fashion, since loss of clinical equipoise regarding the risks and benefits of HFNC is likely to occur in the not too distant future.

This master protocol of two RCTs will compare the two most commonly used modes of non-invasive respiratory support (CPAP and HFNC) in the PICU setting and will determine whether or not an ineffective treatment has been introduced across PICUs with no evidence. This will therefore have a large and immediate impact on how we treat very sick children in the NHS.

A13. Please summarise your design and methodology. *It should be clear exactly what will happen to the research participant, how many times and in what order. Please complete this section in language comprehensible to the lay person. Do not simply reproduce or refer to the protocol. Further guidance is available in the guidance notes.*

The FIRST-ABC step-up and step-down RCTs NULL HYPOTHESIS
In critically ill children assessed by the treating clinician to require non-invasive respiratory support, the first-line use of high flow nasal cannula (HFNC) is superior to continuous positive airway pressure (CPAP) in terms of the time to liberation from respiratory support.

STUDY DESIGN/SETTING
Master protocol comprising two multi-centre, parallel groups, non-inferiority RCTs with shared infrastructure, and integrated health-economic evaluation. The master study will involve 1,200 patients (600 in each RCT) from 25 paediatric critical care units (PICUs and HDUs). The RCT design was chosen as this is considered to be the gold standard design for clinical trials.

Procedures
The decision to start the patient on non-invasive respiratory support (which patient and when) is left to the discretion of the treating clinician and constitutes the pragmatic inclusion criterion in both RCTs. Once an eligible patient is identified and screened as eligible for FIRST-ABC, they will be randomised as soon as possible (on the basis of deferred consent – see A6-2 for more details).

In both the step-up and step-down RCTs, patients will be randomised to either CPAP or HFNC as first-line treatment option for non-invasive respiratory support. Only the first-line mode of NRS will be randomly allocated. In line with current practice, and to safeguard patient safety, the treating clinical team will be allowed to switch the patient to the alternative mode of non-invasive respiratory support for non-response (based on pre-specified study criteria) or if the allocated mode is not being tolerated by the patient. Such switches will be monitored and recorded but will not be considered deviations provided they are undertaken in accordance with the protocol. Both CPAP and HFNC devices will be used for their intended purposes and are CE marked.

Similarly, the protocol will allow escalation to non-invasive ventilation (NIV) modes such as pressure support or bilevel positive airway pressure or to invasive mechanical ventilation (IMV) at the treating clinical team's discretion.
In order to standardise non-invasive respiratory support management in the two groups and across research sites, the study protocol will use current evidence to provide guidance relating to starting flow rates (HFNC) and pressure (CPAP) as well as when and how to wean HFNC and CPAP. Once the patient is escalated or switched to another mode of NIV or IMV, clinical management of the patient thereafter will be outside the study protocol and as per the clinicians' usual practice.

Consent will be sought from parents/legal guardians by a GCP-trained, delegated member of the local research team as soon as appropriate and practically possible after randomisation (this will usually be within 24-48 hours of randomisation).

Parents/legal guardians will be asked to complete a short-validated questionnaire assessing parental stress in hospital at time of consent (after their child started on the treatment).

Recruited children will continue to be monitored until 48 hours after liberation from all forms of respiratory support (in some cases this will be occur following discharge from critical care to the general ward).

At the six-month time point post randomisation, parents/legal guardians of recruited patients will be emailed or posted (as per their preference indicated at the time of consent) a follow-up questionnaire assessing health-related quality of life (consisting of three validated instruments). The questionnaire will be sent by a trained research team member at the ICNARC CTU, who will telephone the parent/legal guardian three weeks later (if no response is received).

In addition, data will be collected from routine national data sources (e.g. NHS Digital) on survival and these data will be used in the integrated economic evaluation.

Internal pilot
The 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. 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 RCTs. At the end of the internal pilot, the Trial Steering Committee (TSC) will make a recommendation the funder as to whether they feel that both RCTs should continue and the funder (NIHR) will take the final decision.

Oversight committees
Both a TSC and a Data Monitoring & Ethics Committee (DMEC) will be convened and will meet regularly during the trial. The DMEC will review available accruing trial data. A single interim analysis will be carried out in each RCT after

the recruitment and follow-up to 60 days of 300 patients to recommend early termination due to superiority of either intervention in time to liberation from respiratory support or evidence of harm from either intervention in mortality at 60 days.

Timeline
February 2019 to July 2019 - preparation for start of trial (site sign up and local approvals, production of materials for participating sites, conduct site initiation meetings)
July/August 2019 – start patient recruitment
December 2019/January 2020 - start six-month patient follow-up
March 2020 - Internal pilot stage completion
November 2020 - end patient recruitment for step-down RCT
January 2022 - end patient recruitment for step-up RCT
July 2022 - last patient, last follow-up (end of trial)

Each RCT will be analysed separately once follow-up is completed for the respective RCT. Articles will be prepared for publication. It will not be possible to identify any participants in any publications.

A14-1. In which aspects of the research process have you actively involved, or will you involve, patients, service users, and/or their carers, or members of the public?

- [x] Design of the research
- [x] Management of the research
- [ ] Undertaking the research
- [ ] Analysis of results
- [x] Dissemination of findings
- [ ] None of the above

Give details of involvement, or if none please justify the absence of involvement.
We had considerable PPI input into the FIRST-ABC Pilot Study (IRAS number: 185074) as well as the main FIRST-ABC RCTs described here. Two parents of children who received breathing support in paediatric critical care are co-applicants and members of the Trial Management Group and have actively contributed to the study design and procedures, including the use of deferred consent and the participant information materials.

Ahead of submitting the grant application, feedback was sought from the PPI research group at Great Ormond Street Hospital in 2017. Feedback from 5 parents included:
All parents confirmed the importance of this research to the NHS (Parent 1: “Yes, I think it is an important problem for the NHS to address as it has both cost implications [which in the current political climate is even more essential to address to try to make the most of the increasingly limited resources that are available] and patients and parents wellbeing implications…”). The ability for clinicians to switch from the first-line treatment to alternative treatments was considered important (Parent 2: “I'd like assurance that the team would always act in the child's best interests and hence switch to the other technique if it seemed clinically more appropriate or effective for them”). Deferred consent was found to be acceptable (Parent 1: “Although it's not ideal, but due to the fact of it being an emergency situation, I would imagine that it would be clear to most parents why deferred consent was necessary”; Parent 5: “The model of consent is practical but I think you need to be very careful how you approach the parents”). Parents provided feedback that preventing intubation and invasive ventilation and spending less time on a breathing support machine were the most important outcomes from their point of view. Patient comfort, ability to feed while on the treatment, hospital readmissions and long-term effects on breathing were other key outcomes highlighted as being important.

In addition, as part of the FIRST-ABC Pilot Study, 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.

4. RISKS AND ETHICAL ISSUES

RESEARCH PARTICIPANTS

A15. What is the sample group or cohort to be studied in this research?

Select all that apply:

- [ ] Blood
- [ ] Cancer
- [ ] Cardiovascular
- [ ] Congenital Disorders
- [ ] Dementias and Neurodegenerative Diseases
- [ ] Diabetes
- [ ] Ear
- [ ] Eye
- [ ] Generic Health Relevance
- [ ] Infection
- [ ] Inflammatory and Immune System
- [ ] Injuries and Accidents
- [ ] Mental Health
- [ ] Metabolic and Endocrine
- [ ] Musculoskeletal
- [ ] Neurological
- [ ] Oral and Gastrointestinal
- [x] Paediatrics
- [ ] Renal and Urogenital
- [ ] Reproductive Health and Childbirth
- [ ] Respiratory
- [ ] Skin
- [ ] Stroke

Gender:	Male and female participants
Lower age limit: 36	Weeks gestational age
Upper age limit: 16	Years

A17-1. Please list the principal inclusion criteria (list the most important, max 5000 characters).

1) 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).

A17-2. Please list the principal exclusion criteria (list the most important, max 5000 characters).

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, difficulty managing 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 critical care unit admission
5) Presence of untreated air-leak (pneumothorax and/or 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

RESEARCH PROCEDURES, RISKS AND BENEFITS

A18. Give details of all non-clinical intervention(s) or procedure(s) that will be received by participants as part of the research protocol. *These include seeking consent, interviews, non-clinical observations and use of questionnaires.*

Please complete the columns for each intervention/procedure as follows:

1. Total number of interventions/procedures to be received by each participant as part of the research protocol.
2. If this intervention/procedure would be routinely given to participants as part of their care outside the research, how many of the total would be routine?
3. Average time taken per intervention/procedure (minutes, hours or days)
4. Details of who will conduct the intervention/procedure, and where it will take place.

Intervention or procedure	1	2	3	4
Seeking informed consent from parents/guardians	1	0	45	A trained member of the local research team recorded on the Delegation Log (e.g. a research nurse). The consent will be sought at the hospital or a letter will be sent to parents/guardians to their contact address in case patient was discharged from the hospital before the consent was sought.
Parental stress scale questionnaires	1	0	15	A trained member of the local research team recorded on the Delegation Log (e.g. a research nurse). The questionnaire will be given to parents/guardians at the hospital.
Assessment of COMFORT-B score	1	0	5	Clinical/Research nurses at participating sites
Six month follow-up questionnaire - assessing health related quality of life and health service resource use	1	0	15	Questionnaire centrally administered by a trained member of the FIRST-ABC Study team at ICNARC CTU

A19. Give details of any clinical intervention(s) or procedure(s) to be received by participants as part of the research protocol. *These include uses of medicinal products or devices, other medical treatments or assessments, mental health interventions, imaging investigations and taking samples of human biological material. Include procedures which might be received as routine clinical care outside of the research.*

Please complete the columns for each intervention/procedure as follows:

1. Total number of interventions/procedures to be received by each participant as part of the research protocol.
2. If this intervention/procedure would be routinely given to participants as part of their care outside the research, how many of the total would be routine?
3. Average time taken per intervention/procedure (minutes, hours or days).
4. Details of who will conduct the intervention/procedure, and where it will take place.

Intervention or procedure	1	2	3	4
Application of HFNC or CPAP	1	1	3 days on average	PICU clinicians (medical and nursing). HFNC or CPAP will be administered for as long as it is deemed to be needed by the local treating team - thus, the duration of the intervention is variable across participants. The primary outcome assesses time to liberation from respiratory support.

A20. Will you withhold an intervention or procedure, which would normally be considered a part of routine care?

○ Yes ◉ No

A21. How long do you expect each participant to be in the study in total?

Each participant will be followed up to a maximum of six months post-randomisation.

A22. What are the potential risks and burdens for research participants and how will you minimise them?

For all studies, describe any potential adverse effects, pain, discomfort, distress, intrusion, inconvenience or changes to lifestyle. Only describe risks or burdens that could occur as a result of participation in the research. Say what steps would be taken to minimise risks and burdens as far as possible.

Clinically, there are no additional risks over and above current clinical practice with regards to the intervention.

Using a deferred consent process is a potential risk, as children may be entered into a study which could be against the wishes of the parents/legal representatives. We have minimised these risks by following the procedures as specified after the FiSh Feasibility Study (REC: 15/NW/0913; IRAS: 191348) in order to incorporate the wishes of parents/legal representatives. This took guidance from previous work in the area (by Dr Kerry Woolfall) and interviews with 21 parents (7 bereaved) whose child had been admitted to PICUs. Using these approved procedures minimises this potential risk.

A23. Will interviews/ questionnaires or group discussions include topics that might be sensitive, embarrassing or upsetting, or is it possible that criminal or other disclosures requiring action could occur during the study?

◉ Yes ○ No

If Yes, please give details of procedures in place to deal with these issues:

Parents/legal guardians could potentially find some questions included in the Parental Stressor Scale (PSS: PICU) questionnaire upsetting. However, the questionnaire was used in the pilot study and was found to be acceptable by parents/legal guardians. Parents/legal guardians will not be pressured or coerced into completing the questionnaire and it will be their decision whether or not to complete it.

A24. What is the potential for benefit to research participants?

Since it is not clear whether HFNC is as effective as CPAP or not, although there is evidence that HFNC may be more comfortable for the children, it is not possible to state that there is a definite benefit for the patients in either group. However, the knowledge generated from the research will benefit future critically ill children treated in PICU.

A25. What arrangements are being made for continued provision of the intervention for participants, if appropriate, once the research has finished? *May apply to any clinical intervention, including a drug, medical device, mental health intervention, complementary therapy, physiotherapy, dietary manipulation, lifestyle change, etc.*

Both treatments being tested (HFNC and CPAP) are currently available at the study sites, so will continue to be offered beyond the study, if required. All other care and monitoring will be provided at the discretion of the treating clinician.

A26. What are the potential risks for the researchers themselves? *(if any)*

None.

RECRUITMENT AND INFORMED CONSENT

In this section we ask you to describe the recruitment procedures for the study. Please give separate details for different study groups where appropriate.

A27-1. How will potential participants, records or samples be identified? Who will carry this out and what resources will be used?*For example, identification may involve a disease register, computerised search of GP records, or review of medical records. Indicate whether this will be done by the direct healthcare team or by researchers acting under arrangements with the responsible care organisation(s).*

Clinical/Research staff working in the study sites will identify eligible patients using the eligibility criteria.

NHS support costs, as agreed with the funder (NIHR HTA), should be sought from the Local Clinical Research Network for costs associated with this part of the research.

A27-2. Will the identification of potential participants involve reviewing or screening the identifiable personal information of patients, service users or any other person?

◉ Yes ○ No

Please give details below:
Patient data which may be identifiable will be reviewed/screened by the local direct health care team working on the clinical trial (local research team). Eligibility includes the age of the patient.

A27-3. Describe what measures will be taken to ensure there is no breach of any duty of confidentiality owed to patients, service users or any other person in the process of identifying potential participants.*Indicate what steps have been or will be taken to inform patients and service users of the potential use of their records for this purpose. Describe the arrangements to ensure that the wishes of patients and service users regarding access to their records are respected. Please consult the guidance notes on this topic.*

Patient data which may be identifiable will only be reviewed/screened by the local direct healthcare team working on the trial (local FIRST-ABC team). No identifiable information will be passed to any individual outside of the direct health care team until participation is confirmed. All sites will undergo a site initiation meeting where the importance of confidentiality will be outlined.

A27-4. Will researchers or individuals other than the direct care team have access to identifiable personal information of any potential participants?

○ Yes ◉ No

A28. Will any participants be recruited by publicity through posters, leaflets, adverts or websites?

○ Yes ◉ No

A29. How and by whom will potential participants first be approached?

The clinical/research team will prospectively identify eligible patients based on the inclusion criteria and follow the consent procedures outlined in section A6-2.

Parents/legal guardians will only be approached by authorised staff members who have received training in FIRST-ABC processes and procedures and in Good Clinical Practice (GCP). The recruitment process will be done in such a way to mitigate any potential undue influence or coercion. No therapeutic promises will be made.

A30-1. Will you obtain informed consent from or on behalf of research participants?

◉ Yes ○ No

If you will be obtaining consent from adult participants, please give details of who will take consent and how it will be done, with details of any steps to provide information (a written information sheet, videos, or interactive material). Arrangements for adults unable to consent for themselves should be described separately in Part B Section 6, and for children in Part B Section 7.

If you plan to seek informed consent from vulnerable groups, say how you will ensure that consent is voluntary and fully informed.

We will obtain consent after randomisation, using a deferred consent model employed in a number of paediatric critical care clinical trials. We believe that this is the only appropriate model for consent in the face of the time pressure of initiating non-invasive respirotory support in critical care. Full details are provided in section A6-2.

If you are not obtaining consent, please explain why not.

Not applicable.

Please enclose a copy of the information sheet(s) and consent form(s).

A30-2. Will you record informed consent (or advice from consultees) in writing?

(●) Yes ( ) No

A31. How long will you allow potential participants to decide whether or not to take part?

Parents/guardians of critically ill children will be given as long as they require to read the information sheet and ask questions. Only after they have fully understood the study, would they be asked to sign the consent form.

The principal advantage of the 'deferred' or 'research without prior' consent approach is that families have able to time to consider the information and too discuss with wider family, friends and clinical and research staff without the immediate time pressure of the intervention awaiting their decision.

A32. Will you recruit any participants who are involved in current research or have recently been involved in any research prior to recruitment?

(●) Yes
( ) No
( ) Not Known

If Yes, please give details and justify their inclusion. If Not Known, what steps will you take to find out?

We will include children who may be part of research protocols as a result of acute or chronic diseases that are not directly related to the need for intensive care. With respect to PICU studies, the research team will consider co-enrolment of FIRST-ABC participants onto other interventional studies where the management does not conflict with the FIRST-ABC objectives on a case-by-case basis. Participants will be permitted to co-enrol in studies that do not involve an intervention (e.g. observational studies). We will follow the "CO-ENROLMENT TO CRITICAL CARE STUDIES AND TRIALS IN THE UNITED KINGDOM" - a guidance document from 2012 produced by the Intensive Care Society. Details of any co-enrolment will be documented on the FIRST-ABC study Case Report Form.

In practice this is not an issue because of the highly coordinated approach to paediatric intensive care research, we are aware of the other protocols that may be relevant. All such studies are delivered in each centre by a common team of research doctors and nurses.

A33-1. What arrangements have been made for persons who might not adequately understand verbal explanations or written information given in English, or who have special communication needs?*(e.g. translation, use of interpreters)*

If the parent/guardian is unable to adequately understand verbal explanations, detailed written information will be provided. If the parents/guardians do not understand oral or written information in English, translation services will be used as per routine practice at each of the participating centres. PICU clinical staff are therefore very experienced at using interpreters frequently, depending on location and case mix.

A33-2. What arrangements will you make to comply with the principles of the Welsh Language Act in the provision of information to participants in Wales?

All participating hospitals in Wales will have access to a Welsh interpreter.

A34. What arrangements will you make to ensure participants receive any information that becomes available during the course of the research that may be relevant to their continued participation?

We are aware of the relevant studies in progress from clinical trial databases and none are currently recruiting (or to our knowledge planned) that are addressing this question. The Chief Investigator will inform both the Trial Steering Committee and the Data Monitoring & Ethics Committee of any relevant new data if it appears.

A35. What steps would you take if a participant, who has given informed consent, loses capacity to consent during the study? *Tick one option only.*

- ○ The participant and all identifiable data or tissue collected would be withdrawn from the study. Data or tissue which is not identifiable to the research team may be retained.
- ○ The participant would be withdrawn from the study. Identifiable data or tissue already collected with consent would be retained and used in the study. No further data or tissue would be collected or any other research procedures carried out on or in relation to the participant.
- ○ The participant would continue to be included in the study.
- ◉ Not applicable – informed consent will not be sought from any participants in this research.
- ○ Not applicable – it is not practicable for the research team to monitor capacity and continued capacity will be assumed.

Further details:

As per the consent procedures outlined in A6-2, parents/legal guardian will provide consent on behalf of the child.

CONFIDENTIALITY

In this section, personal data means any data relating to a participant who could potentially be identified. It includes pseudonymised data capable of being linked to a participant through a unique code number.

Storage and use of personal data during the study

A36. Will you be undertaking any of the following activities at any stage (including in the identification of potential participants)?*(Tick as appropriate)*

- ☑ Access to medical records by those outside the direct healthcare team
- ☐ Access to social care records by those outside the direct social care team
- ☑ Electronic transfer by magnetic or optical media, email or computer networks
- ☑ Sharing of personal data with other organisations
- ☐ Export of personal data outside the EEA
- ☑ Use of personal addresses, postcodes, faxes, emails or telephone numbers
- ☐ Publication of direct quotations from respondents
- ☐ Publication of data that might allow identification of individuals
- ☐ Use of audio/visual recording devices
- ☑ Storage of personal data on any of the following:
  - ☑ Manual files (includes paper or film)
  - ☑ NHS computers
  - ☐ Social Care Service computers
  - ☐ Home or other personal computers
  - ☐ University computers
  - ☑ Private company computers

☐ Laptop computers

Further details:
Members of the FIRST-ABC study team from the ICNARC CTU will require access to patient's medical notes during routine trial monitoring visits conducted at the hospital to ensure the quality of the data collection and consenting procedures.

Identifiable data (e.g. name and contact details) will need to be sent to and stored at ICNARC CTU to enable a follow-up questionnaire to be sent to the parents/legal representatives of recruited patients. In additional, further patient identifiable data (e.g. name, date of birth, NHS number and post code) will be required to enable linkage with NHS Digital (or equivalent) for important trial outcome data. All data will be encrypted to an appropriate standard prior to sending from the hospital.

The PI and authorised delegated members of the local research team at each site will have access to the link code to the identifying data. ICNARC will also hold the link code for participants in whom consent for follow-up (i.e. questionnaires and data linkage to NHS Digital) is in place.

A37. Please describe the physical security arrangements for storage of personal data during the study?

Personal data (e.g. name of child, NHS number, date of birth, name of parent/legal guardian) will need to be sent to and stored at ICNARC CTU to enable a follow-up questionnaire to be sent to the parents/legal guardian and to obtain data from NHS Digital (or their equivalent).

At the ICNARC CTU, personal data is collected on a secure web-based data entry system housed at Red Technology (a third party contractor providing services to ICNARC). ICNARC has assessed this supplier as low risk and this is acceptable to ICNARC. This is a specialist hosting provider and all data centre buildings include proximity access control and digital CCTV to control physical access to equipment.

With regards to the ICNARC office based in London, England - physical office security includes a Grade 3 Red Care intruder detection system that has been supplied, installed and is maintained by ADT Fire and Security Plc. All visitors are notified to building security by ICNARC staff in advance.

Data destruction will be carried out in compliance with the UK Policy Framework for Health and Social Care Research and we work with suitably qualified contractors for both electronic and paper record destruction.

A38. How will you ensure the confidentiality of personal data?*Please provide a general statement of the policy and procedures for ensuring confidentiality, e.g. anonymisation or pseudonymisation of data.*

To minimise the use of personal identifiers, participants will be allocated a unique FIRST-ABC Trial Number and this will be used by the FIRST-ABC study team in communications with the local research teams at participating sites. ICNARC and the local NHS Trust will hold the link code.

Personal data will only be processed in physical form where absolutely necessary (e.g. when posting a letter to a parent/guardian).

ICNARC is registered under the Data Protection Act (Registration number: Z6289325). Confidentiality forms the basics of ICNARC's Information Security Policy. All staff employed by ICNARC sign a contract, which incorporates a confidentiality clause and the consequences of breaching confidentiality are covered in our Disciplinary Procedure. External researchers, temporary staff and contractors are all required to sign a formal confidentiality agreement with ICNARC. Data security and confidentiality are a fixed agenda item at staff meetings for all staff at ICNARC.

A40. Who will have access to participants' personal data during the study? *Where access is by individuals outside the direct care team, please justify and say whether consent will be sought.*

Participant data will be held on a secure web-based data entry system. Access to the secure web-based data entry system in the hospitals will be restricted (by username and password) to trained staff in the hospital, authorised by the site Principal Investigator.

Patients' identification data, including full name, date of birth, full address and NHS number will be required at ICNARC. It is necessary to collect this identifiable information as the follow-up questionnaires need to be sent directly to the parent/legal representative. ICNARC will act to preserve patient confidentiality and will not disclose or reproduce

any information by which patients or their parent/legal representative could be identified to a third party.

Data will be stored in a secure manner and ICNARC are registered in accordance with the Data Protection Act 2018. Access to participant's personal data will be limited to authorised staff members at the ICNARC CTU (the FIRST-ABC trial team). The site Principal Investigators will take responsibility for ensuring that study data stored on paper at the site is restricted to authorised personnel only (as per the Delegation Log).

Storage and use of data after the end of the study

A41. Where will the data generated by the study be analysed and by whom?

The data generated by the FIRST-ABC study will be analysed by appropriately qualified members of the FIRST-ABC study team within the ICNARC office in London, England. The economic evaluation will be conducted by appropriately qualified members of the FIRST-ABC study team based at the London School of Hygiene & Tropical Medicine.

A42. Who will have control of and act as the custodian for the data generated by the study?

	Title Forename/Initials Surname
	Dr Padmanabhan Ramnarayan
Post	Consultant in Paediatric Intensive Care and Retrieval
Qualifications	MBBS - Medicine, MD - Medical Informatics Applications, Fellow - Paediatrics, Global Clinical Scholar - Research, Member - Paediatrics, Fellow - Intensive Care Medicine
Work Address	Children's Acute Transport Service, Great Ormond Street Hospital for Children NHS Foundation Trust
	26-27 Boswell Street
	London
Post Code	WC1N 3JZ
Work Email	P.Ramnarayan@gosh.nhs.uk
Work Telephone	020 74305850
Fax	

A43. How long will personal data be stored or accessed after the study has ended?

- ○ Less than 3 months
- ○ 3 – 6 months
- ○ 6 – 12 months
- ○ 12 months – 3 years
- ◉ Over 3 years

If longer than 12 months, please justify:
Identifiable data will be kept for up to one year after the study has ended. If parents/legal guardians agree to be contacted about future research studies (the final point on the Consent Forms), then their identifiable data will be kept for five years after the end of the study, for this purpose.

A44. For how long will you store research data generated by the study?

Years: 15
Months:

A45. Please give details of the long term arrangements for storage of research data after the study has ended.*Say*

where data will be stored, who will have access and the arrangements to ensure security.

In line with Standard Operating Procedures (SOPs) from the Sponsor (GOSH) and the ICNARC CTU, all central essential documents will be archived for 15 years after the end of the trial. Once this period has passed, arrangements will be made for its confidential destruction.

INCENTIVES AND PAYMENTS

A46. Will research participants receive any payments, reimbursement of expenses or any other benefits or incentives for taking part in this research?

○ Yes ◉ No

A47. Will individual researchers receive any personal payment over and above normal salary, or any other benefits or incentives, for taking part in this research?

○ Yes ◉ No

A48. Does the Chief Investigator or any other investigator/collaborator have any direct personal involvement (e.g. financial, share holding, personal relationship etc.) in the organisations sponsoring or funding the research that may give rise to a possible conflict of interest?

○ Yes ◉ No

NOTIFICATION OF OTHER PROFESSIONALS

A49-1. Will you inform the participants' General Practitioners (and/or any other health or care professional responsible for their care) that they are taking part in the study?

○ Yes ◉ No

If Yes, please enclose a copy of the information sheet/letter for the GP/health professional with a version number and date.

PUBLICATION AND DISSEMINATION

A50. Will the research be registered on a public database?

The UK Policy Framework for Health and Social Care Research sets out the principle of making information about research publicly available. Furthermore: Article 19 of the World Medical Association Declaration of Helsinki adopted in 2008 states that "every clinical trial must be registered on a publicly accessible database before recruitment of the first subject"; and the International Committee of Medical Journal Editors (ICMJE) will consider a clinical trial for publication only if it has been registered in an appropriate registry. Please see guidance for more information.

◉ Yes ○ No

Please give details, or justify if not registering the research.
The research will be registered with the ISRCTN Registry.

Please ensure that you have entered registry reference number(s) in question A5-1.

A51. How do you intend to report and disseminate the results of the study?*Tick as appropriate:*

☑ Peer reviewed scientific journals

- [ ] Internal report
- [x] Conference presentation
- [x] Publication on website
- [ ] Other publication
- [ ] Submission to regulatory authorities
- [ ] Access to raw data and right to publish freely by all investigators in study or by Independent Steering Committee on behalf of all investigators
- [ ] No plans to report or disseminate the results
- [ ] Other (please specify)

A52. If you will be using identifiable personal data, how will you ensure that anonymity will be maintained when publishing the results?

It will not be possible to identify any person who has taken part in the FIRST-ABC study in any reports or articles. All identifiable personal data will be anonymised following completion of the trial.

A53. Will you inform participants of the results?

(●) Yes ( ) No

Please give details of how you will inform participants or justify if not doing so.
Results will be disseminated to those hospitals who participated in the study, and summarised on the ICNARC website. Participants and their parents/legal guardians will be informed in the information sheet as to where they can access results of the study.

5. Scientific and Statistical Review

A54. How has the scientific quality of the research been assessed?*Tick as appropriate:*

- [x] Independent external review
- [ ] Review within a company
- [x] Review within a multi−centre research group
- [x] Review within the Chief Investigator's institution or host organisation
- [x] Review within the research team
- [ ] Review by educational supervisor
- [ ] Other

Justify and describe the review process and outcome. If the review has been undertaken but not seen by the researcher, give details of the body which has undertaken the review:
The FIRST-ABC study has been reviewed by the NIHR Health Technology Assessment (HTA) programme which commissioned the trial. The review included anonymous review by an independent statistician.

For all studies except non-doctoral student research, please enclose a copy of any available scientific critique reports, together with any related correspondence.

For non-doctoral student research, please enclose a copy of the assessment from your educational supervisor/ institution.

A56. How have the statistical aspects of the research been reviewed?*Tick as appropriate:*

- [x] Review by independent statistician commissioned by funder or sponsor
- [ ] Other review by independent statistician
- [ ] Review by company statistician

☐ Review by a statistician within the Chief Investigator's institution

☑ Review by a statistician within the research team or multi−centre group

☐ Review by educational supervisor

☐ Other review by individual with relevant statistical expertise

☐ No review necessary as only frequencies and associations will be assessed – details of statistical input not required

In all cases please give details below of the individual responsible for reviewing the statistical aspects. If advice has been provided in confidence, give details of the department and institution concerned.

	Title	Forename/Initials	Surname
		Anonymous	reviewer
Department	Health Technology Assessment (HTA) programme		
Institution	National Institute for Health Research (NIHR)		
Work Address			
Post Code			
Telephone			
Fax			
Mobile			
E-mail			

Please enclose a copy of any available comments or reports from a statistician.

A57. What is the primary outcome measure for the study?

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.

A58. What are the secondary outcome measures?*(if any)*

•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 time of consent using a validated Parental Stressor Scale: PICU (PSS: PICU)
•Health-related quality of life and use of health services at 6 months using age-appropriate Peds-QL,HUI2 questionnaire and health services questionnaire

Cost-effectiveness analysis outcomes:
•Total costs at 6 months
•quality-adjusted life years (QALYs) at 6 months
•Incremental net monetary benefit gained at a willingness-to-pay of £20,000 per QALY at 6 months associated with HFNC versus CPAP

A59. What is the sample size for the research? *How many participants/samples/data records do you plan to study in total? If there is more than one group, please give further details below.*

Total UK sample size: 1200

Total international sample size (including UK):

Total in European Economic Area:

Further details:
We aim to recruit around 600 patients in each of the two RCTs at the 25 participating sites.

A60. How was the sample size decided upon? *If a formal sample size calculation was used, indicate how this was done, giving sufficient information to justify and reproduce the calculation.*

A sample size of 600 patients in each of the two RCTs provides 90% power with a type I error rate of 2.5% (one-sided) to exclude the pre-specified non-inferiority margin of HR=0.75 (corresponding to approximately a 16-hour increase in median time to liberation), allowing for censoring due to death or transfer, withdrawal/refusal of deferred consent and exclusion due to non-adherence in the per-protocol population.

A61. Will participants be allocated to groups at random?

(●) Yes ( ) No

If yes, please give details of the intended method of randomisation:
Eligible patients will be randomised on a 1:1 basis to either CPAP or HFNC using a central telephone/web-based randomisation service called Sealed Envelope managed by ICNARC. Randomisation will be stratified by site and age (<12 months versus >/=12 months). The randomisation sequence will be computer generated and variable block sizes will be used to strengthen allocation concealment.

A62. Please describe the methods of analysis (statistical or other appropriate methods, e.g. for qualitative research) by which the data will be evaluated to meet the study objectives.

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 in detail.

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 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 health-related quality of life 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.

6. MANAGEMENT OF THE RESEARCH

A63. Other key investigators/collaborators. *Please include all grant co−applicants, protocol co−authors and other key members of the Chief Investigator's team, including non-doctoral student researchers.*

	Title	Forename/Initials	Surname
	Honorary Professor	Kevin Paul	Morris
Post	Consultant in Paediatric Intensive Care		
Qualifications	MBBS - Medicine, Member - Medicine, MD - Medicine, Fellow - College, Fellow - Intensive Care Medicine		
Employer	Birmingham Women's and Children's NHS Foundation Trust		
Work Address	Steelhouse Lane Birmingham		
Post Code	B4 6NH		
Telephone	0121 333 8739		
Fax			
Mobile			
Work Email	kevin.morris3@nhs.net		

	Title	Forename/Initials	Surname
	Mr	Paul	Mouncey
Post	Head of Research		
Qualifications	MSc - Epidemiology		
Employer	Intensive Care National Audit & Research Centre (ICNARC)		
Work Address	Napier House 24 High Holborn London		
Post Code	WC1V 6AZ		
Telephone	020 7269 9277		
Fax	020 7831 6879		
Mobile			
Work Email	paul.mouncey@icnarc.org		

	Title	Forename/Initials	Surname
	Professor	Kathryn	Rowan
Post	Director of Scientific and Strategic Development/Clinical Trials Unit Director		
Qualifications	PhD - Epidemiology, MSc - Experimental Pathology (Toxicology), BSc - Biochemistry/Toxicology		
Employer	Intensive Care National Audit & Research Centre (ICNARC)		
Work Address	Napier House 24 High Holborn London		
Post Code	WC1V 6AZ		
Telephone	020 7269 9277		
Fax	020 7831 6879		

Mobile	
Work Email	kathy.rowan@icnarc.org

Title	Forename/Initials	Surname
Associate Professor	Lyvonne Nicole	Tume

Post	Associate Professor in Child Health
Qualifications	PhD - Nursing, PGDE Healthcare Education, MSc - Clinical MSc in Critical care Nursing, BN - Bachelor of Nursing,Diploma - Dip Applied Science (Pre-registration Nursing)
Employer	University of the West of England
Work Address	Coldharbour Lane Stoke Gifford Bristol
Post Code	BS16 1QY
Telephone	0117 32 86828
Fax	
Mobile	
Work Email	lyvonne.tume@uwe.ac.uk

Title	Forename/Initials	Surname
Professor	Mark	Peters

Post	Professor of Paediatric Intensive Care
Qualifications	PhD - Immunobiology, Fellow - Paediatrics and Child Health, Member - Physicians, MB ChB - Medicine and Surgery
Employer	University College London
Work Address	UCL Great Ormond Street Institute of Child Health 30 Guilford Street London
Post Code	WC1N 1EH
Telephone	020 7242 9789
Fax	
Mobile	
Work Email	mark.peters@ucl.ac.uk

Title	Forename/Initials	Surname
Mrs	Julie	Lester

Post	Patient and Public Involvement (PPI) representative
Qualifications	BA (Hons) - Applied Psychology
Employer	
Work Address	
Post Code	
Telephone	
Fax	
Mobile	
Work Email	

Title	Forename/Initials	Surname
Dr	Zia	Sadique

Post	Assistant Professor in Health Economics

Qualifications	PhD - Economics
Employer	London School of Hygiene & Tropical Medicine
Work Address	15-17 Tavistock Place London
Post Code	WC1H 9SH
Telephone	020 79272619
Fax	
Mobile	
Work Email	zia.sadique@lshtm.ac.uk

Title	Forename/Initials	Surname
Dr	Peter	Davis

Post	Consultant Paediatric Intensivist
Qualifications	Member - Medicine, MB ChB - Medicine
Employer	University Hospitals Bristol NHS Foundation Trust
Work Address	Bristol Royal Hospital for Children Upper Maudlin Street Bristol
Post Code	BS2 8BJ
Telephone	0117 923 0000
Fax	
Mobile	
Work Email	peter.davis@uhbristol.nhs.uk

Title	Forename/Initials	Surname
Professor	Richard	Grieve

Post	Professor of Health Economics Methodology
Qualifications	PhD - Health Economics
Employer	London School of Hygiene & Tropical Medicine
Work Address	15-17 Tavistock Place London
Post Code	WC1H 9SH
Telephone	020 7927 2255
Fax	
Mobile	
Work Email	richard.grieve@lshtm.ac.uk

Title	Forename/Initials	Surname
Professor	David	Harrison

Post	Head Statistician
Qualifications	Fellow - Fellow of the Royal Statistical Society, PhD - Medical Statistics, MA, Certificate - Certificate of Advanced Study in Mathematics, BA (Hons) - Mathematics
Employer	Intensive Care National Audit & Research Centre (ICNARC)
Work Address	Napier House 24 High Holborn London
Post Code	WC1V 6AZ

Telephone	020 7269 9277
Fax	020 7831 6879
Mobile	
Work Email	david.harrison@icnarc.org

Title	Forename/Initials	Surname
Mr	Alvin	Richards-Belle

Post	Trial Manager
Qualifications	BSc (Hons)
Employer	Intensive Care National Audit & Research Centre (ICNARC)
Work Address	Napier House 24 High Holborn London
Post Code	WC1V 6AZ
Telephone	020 7269 9277
Fax	020 7831 6879
Mobile	
Work Email	Alvin.Richards-Belle@icnarc.org

Title	Forename/Initials	Surname
Miss	Laura	Drikite

Post	Research Assistant
Qualifications	MSc - Epidemiology, BSc (Hons)
Employer	Intensive Care National Audit & Research Centre (ICNARC)
Work Address	Napier House 24 High Holborn London
Post Code	WC1V 6AZ
Telephone	020 7269 9277
Fax	020 7831 6879
Mobile	
Work Email	laura.drikite@icnarc.org

Title	Forename/Initials	Surname
Dr	Richard	Feltbower

Post	Senior Lecturer in Epidemiology
Qualifications	PhD - Epidemiology MSc - Medical Statistics BSc - Mathematics
Employer	University of Leeds
Work Address	Worsley Building Clarendon Way Leeds
Post Code	LS2 9LU
Telephone	0113 343 4841
Fax	
Mobile	
Work Email	R.G.Feltbower@leeds.ac.uk

A64. Details of research sponsor(s)

A64-1. Sponsor

Lead Sponsor

Status:
- (●) NHS or HSC care organisation
- ( ) Academic
- ( ) Pharmaceutical industry
- ( ) Medical device industry
- ( ) Local Authority
- ( ) Other social care provider (including voluntary sector or private organisation)
- ( ) Other

Commercial status: Non-Commercial

If Other, please specify:

Contact person

Name of organisation	Great Ormond Street Hospital for Children NHS Foundation Trust
Given name	Jenny
Family name	Rivers
Address	30 Guilford Street
Town/city	London
Post code	WC1N 1EH
Country	UNITED KINGDOM
Telephone	020 7905 2249
Fax	
E-mail	Research.Governance@gosh.nhs.uk

A65. Has external funding for the research been secured?

Please tick at least one check box.

- [x] Funding secured from one or more funders
- [ ] External funding application to one or more funders in progress
- [ ] No application for external funding will be made

What type of research project is this?

- (●) Standalone project
- ( ) Project that is part of a programme grant
- ( ) Project that is part of a Centre grant
- ( ) Project that is part of a fellowship/ personal award/ research training award
- ( ) Other

Other – please state:

Please give details of funding applications.

Organisation	National Institutes for Health Research (NIHR)
Address	Evaluation, Trials and Studies Coordinating Centre
	University of Southampton
	Alpha House, Enterprise Road, Southampton
Post Code	SO16 7NS
Telephone	023 8059 5586
Fax	023 8059 5639
Mobile	
Email	hta.funding@nihr.ac.uk

Funding Application Status: (●) Secured ( ) In progress

Amount: 1,499,215.19

Duration
Years:
Months: 48

If applicable, please specify the programme/ funding stream:

What is the funding stream/ programme for this research project?
National Institutes for Health Research (NIHR) - Health Technology Assessment (HTA) Programme

A66. Has responsibility for any specific research activities or procedures been delegated to a subcontractor (other than a co-sponsor listed in A64-1) ? *Please give details of subcontractors if applicable.*

(●) Yes ( ) No

Name: Intensive Care National Audit & Research Centre (ICNARC)

Type of organisation:
( ) NHS ( ) Academic ( ) Commercial (●) Other

Please give further details of sub-contractor and main areas of delegated responsibility: Trial management (including set-up, day to day management, close down and dissemination)

Name: Intensive Care National Audit & Research Centre (ICNARC)

Type of organisation:
( ) NHS ( ) Academic ( ) Commercial (●) Other

Please give further details of sub-contractor and main areas of delegated responsibility: Management of randomisation system

A67. Has this or a similar application been previously rejected by a Research Ethics Committee in the UK or another country?

( ) Yes (●) No

Please provide a copy of the unfavourable opinion letter(s). You should explain in your answer to question A6-2 how the reasons for the unfavourable opinion have been addressed in this application.

A68-1. Give details of the lead NHS R&D contact for this research:

	Title	Forename/Initials	Surname
	Miss	Stephanie	De Sa Marques Basset
Organisation	Great Ormond Street Hospital for Children NHS Foundation Trust		
Address	30 Guilford Street London		
Post Code	WC1N 1EH		
Work Email	Research.Governance@gosh.nhs.uk		
Telephone	020 7905 2669		
Fax			
Mobile			

Details can be obtained from the NHS R&D Forum website: http://www.rdforum.nhs.uk

A68-2. Select Local Clinical Research Network for NHS Organisation identified in A68-1:

North Thames

For more information, please refer to the question specific guidance.

A69-1. How long do you expect the study to last in the UK?

Planned start date: 01/02/2019
Planned end date: 31/01/2023
Total duration:
Years: 3 Months: 11 Days: 31

A71-1. Is this study?

- ○ Single centre
- ◉ Multicentre

A71-2. Where will the research take place? *(Tick as appropriate)*

- ☑ England
- ☑ Scotland
- ☑ Wales
- ☐ Northern Ireland
- ☐ Other countries in European Economic Area

Total UK sites in study 25

Does this trial involve countries outside the EU?

○ Yes ◉ No

A72. Which organisations in the UK will host the research? *Please indicate the type of organisation by ticking the box and give approximate numbers if known:*

☑ NHS organisations in England	22
☑ NHS organisations in Wales	1
☑ NHS organisations in Scotland	2
☐ HSC organisations in Northern Ireland	
☐ GP practices in England	
☐ GP practices in Wales	
☐ GP practices in Scotland	
☐ GP practices in Northern Ireland	
☐ Joint health and social care agencies (eg community mental health teams)	
☐ Local authorities	
☐ Phase 1 trial units	
☐ Prison establishments	
☐ Probation areas	
☐ Independent (private or voluntary sector) organisations	
☐ Educational establishments	
☐ Independent research units	
☐ Other (give details)	
Total UK sites in study:	25

A73-1. Will potential participants be identified through any organisations other than the research sites listed above?

○ Yes ◉ No

A74. What arrangements are in place for monitoring and auditing the conduct of the research?

Central monitoring

The study team at the ICNARC Clinical Trials Unit will communicate regularly with sites via email, telephone, teleconferences and newsletters. Data recorded in the central, secured data entry system will undergo checks for accuracy, completeness and consistency. The local Principal Investigator will be responsible for ensuring all data queries area addressed and for the overall quality of local data. A particular emphasis will be put on adherence to the trial protocol.

Site monitoring

The site monitoring plan will be based on a risk assessment, including an assessment of the sites and local research team (e.g. experience of multi-centre research, RCTs, etc.). Sites will be visited based on a risk assessment model 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.

A75-1. What arrangements will be made to review interim safety and efficacy data from the trial? Will a formal data monitoring committee or equivalent body be convened?

In line with Standard Operating Procedures at the ICNARC CTU, a Data Monitoring and Ethics Committee (DMEC) will be convened and will include experienced critical care clinicians and at least one statistician. All members of the DMEC will be independent of both the trial and the Trial Steering Committee (TSC), and will operate under the DAMOCLES Charter. The DMEC will report to the TSC, making recommendations on the continuation, or not, of the study. Adherence to the intervention and safety will be monitored by the DMEC throughout the study period.

If a formal DMC is to be convened, please forward details of the membership and standard operating procedures to the Research Ethics Committee when available. The REC should also be notified of DMC recommendations and receive summary reports of interim analyses.

A75-2. What are the criteria for electively stopping the trial or other research prematurely?

Internal pilot phase

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. Both RCTs will use a traffic light system to assess progression from pilot stage. The RCTs will progress from the pilot stage to full trial based on the progression criteria. Where any of the progression criteria are given an 'Amber light', a management plan will be put in place by the Trial Management Group and discussed with the Trial Steering Committee. 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 Trial Steering Committee.

Interim analysis

A single interim analysis at 50% recruitment in each RCT will test for superiority of either HFNC or CPAP to recommend termination on efficacy. The DMEC will review the interim analysis and will report to the TSC, making recommendations on the continuation, or not, of the study.

A76. Insurance/ indemnity to meet potential legal liabilities

***Note:** in this question to NHS indemnity schemes include equivalent schemes provided by Health and Social Care (HSC) in Northern Ireland*

A76-1. What arrangements will be made for insurance and/or indemnity to meet the potential legal liability of the sponsor(s) for harm to participants arising from the management of the research? *Please tick box(es) as applicable.*

Note: Where a NHS organisation has agreed to act as sponsor or co-sponsor, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For all other sponsors, please describe the arrangements and provide evidence.

- [x] NHS indemnity scheme will apply (NHS sponsors only)
- [ ] Other insurance or indemnity arrangements will apply (give details below)

Please enclose a copy of relevant documents.

A76-2. What arrangements will be made for insurance and/ or indemnity to meet the potential legal liability of the sponsor(s) or employer(s) for harm to participants arising from the design of the research? *Please tick box(es) as applicable.*

Note: Where researchers with substantive NHS employment contracts have designed the research, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For other protocol authors (e.g. company employees, university members), please describe the arrangements and provide evidence.

- [x] NHS indemnity scheme will apply (protocol authors with NHS contracts only)

☐ Other insurance or indemnity arrangements will apply (give details below)

Please enclose a copy of relevant documents.

A76-3. What arrangements will be made for insurance and/ or indemnity to meet the potential legal liability of investigators/collaborators arising from harm to participants in the conduct of the research?

Note: Where the participants are NHS patients, indemnity is provided through the NHS schemes or through professional indemnity. Indicate if this applies to the whole study (there is no need to provide documentary evidence). Where non-NHS sites are to be included in the research, including private practices, please describe the arrangements which will be made at these sites and provide evidence.

☑ NHS indemnity scheme or professional indemnity will apply (participants recruited at NHS sites only)

☐ Research includes non-NHS sites (give details of insurance/ indemnity arrangements for these sites below)

Please enclose a copy of relevant documents.

A77. Has the sponsor(s) made arrangements for payment of compensation in the event of harm to the research participants where no legal liability arises?

○ Yes ◉ No

Please enclose a copy of relevant documents.

A78. Could the research lead to the development of a new product/process or the generation of intellectual property?

○ Yes ◉ No ○ Not sure

PART B: Section 7 - Children

1. Please specify the potential age range of children under 16 who will be included and give reasons for carrying out the research in this age group.

Age range: over 36 weeks corrected gestational age and less than 16 years of age.
The research concerns evaluating two commonly used treatment modalities within paediatric intensive care units.

2. Indicate whether any children under 16 will be recruited as controls and give further details.

All participants will be children under the age of 16. Participants will be randomised in a 1:1 ratio to either HFNC or CPAP.

3-2. Please describe the arrangements for seeking informed consent from a person with parental responsibility and/or from children able to give consent for themselves.

Please describe the arrangements for seeking informed consent from a person with parental responsibility and/or from children able to give consent for themselves.

Children who are eligible for FIRST-ABC become so during a period of critical illness. This is a profoundly stressful time for parents/legal guardians during which time there are ethical concerns both about their ability to provide informed consent during a time of great distress and the burden placed of trying to understand the trial and make a quick decision. The decision to initiate non-invasive respiratory support is most often made under a time-sensitive emergency situation, where any delay in commencing treatment could be detrimental to the patient (and to the

scientific validity of the trial). In addition, the two modes of non-invasive respiratory support are already used in usual clinical practice with the choice determined only by clinician preference.

Considering these reasons, we will utilise a deferred consent model ('research without prior consent') in the FIRST-ABC RCTs, a model that has been found to be acceptable to parents/guardians as well as clinicians in several previous RCTs conducted in the PICU setting. This consent model has been informed by extensive patient and public involvement (PPI) work conducted by our group and others in this area. Once a patient is identified and screened 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 applied as soon as possible.

This model has been found to be acceptable to parents/legal guardians, as well as to clinicians, in several recent RCTs conducted in the PICU setting and is also informed by experience and feedback gained directly from conducing the FIRST-ABC Pilot Study. 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.

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 guardian will be approached at a later point (see Discharge prior to consent being sought and Death prior to consent being sought).

A Participant Information Sheet (PIS) for parents/legal guardian 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. The shorter Patient Information Leaflet may be given initially before following up with the PIS with full details 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 permit data linkage with national routine sources (e.g. NHS Digital or equivalent) and to receive a follow-up questionnaire at six months. Parents/legal guardian 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 guardian to sign the Consent Form and will then add their own name and countersign it. A copy will be given to the parent/legal guardian to keep, a copy placed in the child's medical notes and the original kept in the Investigator Site File.

Due to severity of illness and its impact on 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. Parents/legal guardian will be involved in this discussion. In all other respects, the assenting procedures will follow the consenting procedures as described above. If the participant is likely to regain capacity following hospital discharge, then an age-appropriate PIS will be provided to parents/legal guardian to discuss with the participant following recovery.

In the rare situation where the patient is discharged from hospital or dies prior to consent has been obtained, the most appropriate member of the site research team will attempt at least one phone call to the parents/legal guardian 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 guardian 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 [an adapted version of the PIS will be used for bereaved parents]. The letter will direct the parents/legal guardian to the PIS for detailed information on the study and provide telephone contact details if the parents/legal guardian wish to discuss the trial with a member of the site research team. The letter will ask the parents/legal guardian to return the Consent Form (postal version) 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 version), 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 trial 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.

4. If you intend to provide children under 16 with information about the research and seek their consent or agreement, please outline how this process will vary according to their age and level of understanding.

Patient information sheets will be provided to study participants according to their age group:
- 8-10 years
- 11+

Copies of written information sheet(s) for parents and children, consent/assent form(s) and any other explanatory material should be enclosed with the application.

PART C: Overview of research sites

Please enter details of the host organisations (Local Authority, NHS or other) in the UK that will be responsible for the research sites. *For further information please refer to guidance.*

Investigator identifier	Research site		Investigator Name	
IN1	◉ NHS/HSC Site ○ Non-NHS/HSC Site		Forename Middle name Family name Email	Mark Peters Mark.Peters@gosh.nhs.uk
	Organisation name	GREAT ORMOND STREET HOSPITAL FOR CHILDREN NHS FOUNDATION TRUST	Qualification (MD...)	MB ChB PhD
	Address	GREAT ORMOND STREET LONDON GREATER LONDON	Country	UNITED KINGDOM
	Post Code	WC1N 3JH		
	Country	ENGLAND		
IN2	◉ NHS/HSC Site ○ Non-NHS/HSC Site		Forename Middle name Family name Email	Peter Davis Peter.Davis@UHBristol.nhs.uk
	Organisation name	UNIVERSITY HOSPITALS BRISTOL NHS FOUNDATION TRUST	Qualification (MD...)	MB ChB
	Address	MARLBOROUGH STREET BRISTOL AVON	Country	UNITED KINGDOM
	Post Code	BS1 3NU		
	Country	ENGLAND		
IN3	◉ NHS/HSC Site ○ Non-NHS/HSC Site		Forename Middle name Family name Email	Kevin Morris kevin.morris3@nhs.net
	Organisation name	BIRMINGHAM WOMEN'S AND CHILDREN'S NHS FOUNDATION TRUST	Qualification (MD...)	MBBS MD
	Address	STEELHOUSE LANE	Country	UNITED KINGDOM

	BIRMINGHAM WEST MIDLANDS
Post Code	B4 6NH
Country	ENGLAND

IN4

◉ NHS/HSC Site
○ Non-NHS/HSC Site

Forename	David
Middle name	
Family name	Inwald
Email	d.inwald@imperial.ac.uk
Qualification (MD...)	
Country	UNITED KINGDOM

Organisation name	IMPERIAL COLLEGE HEALTHCARE NHS TRUST
Address	ST. MARYS HOSPITAL
	PRAED STREET
	LONDON GREATER LONDON
Post Code	W2 1NY
Country	ENGLAND

IN5

◉ NHS/HSC Site
○ Non-NHS/HSC Site

Forename	Naomi
Middle name	
Family name	Edmonds
Email	naomi.edmonds@bartshealth.nhs.uk
Qualification (MD...)	
Country	UNITED KINGDOM

Organisation name	BARTS HEALTH NHS TRUST
Address	THE ROYAL LONDON HOSPITAL
	WHITECHAPEL
	LONDON GREATER LONDON
Post Code	E1 1BB
Country	ENGLAND

IN6

◉ NHS/HSC Site
○ Non-NHS/HSC Site

Forename	Jon
Middle name	
Family name	Lillie
Email	jonathan.lillie@gstt.nhs.uk
Qualification (MD...)	
Country	UNITED KINGDOM

Organisation name	GUY'S AND ST THOMAS' NHS FOUNDATION TRUST
Address	TRUST OFFICES
	GUY'S HOSPITAL
	GREAT MAZE POND LONDON GREATER LONDON

Post Code	SE1 9RT
Country	ENGLAND

IN7

- (●) NHS/HSC Site
- ( ) Non-NHS/HSC Site

Forename	Nicholas
Middle name	
Family name	Prince
Email	nprince@nhs.net
Qualification (MD...)	
Country	UNITED KINGDOM

Organisation name	ST GEORGE'S UNIVERSITY HOSPITALS NHS FOUNDATION TRUST
Address	ST GEORGE'S HOSPITAL BLACKSHAW ROAD TOOTING LONDON GREATER LONDON
Post Code	SW17 0QT
Country	ENGLAND

PART D: Declarations

D1. Declaration by Chief Investigator

1. The information in this form is accurate to the best of my knowledge and belief and I take full responsibility for it.

2. I undertake to fulfil the responsibilities of the chief investigator for this study as set out in the UK Policy Framework for Health and Social Care Research.

3. I undertake to abide by the ethical principles underlying the Declaration of Helsinki and good practice guidelines on the proper conduct of research.

4. If the research is approved I undertake to adhere to the study protocol, the terms of the full application as approved and any conditions set out by review bodies in giving approval.

5. I undertake to notify review bodies of substantial amendments to the protocol or the terms of the approved application, and to seek a favourable opinion from the main REC before implementing the amendment.

6. I undertake to submit annual progress reports setting out the progress of the research, as required by review bodies.

7. I am aware of my responsibility to be up to date and comply with the requirements of the law and relevant guidelines relating to security and confidentiality of patient or other personal data, including the need to register when necessary with the appropriate Data Protection Officer. I understand that I am not permitted to disclose identifiable data to third parties unless the disclosure has the consent of the data subject or, in the case of patient data in England and Wales, the disclosure is covered by the terms of an approval under Section 251 of the NHS Act 2006.

8. I understand that research records/data may be subject to inspection by review bodies for audit purposes if required.

9. I understand that any personal data in this application will be held by review bodies and their operational managers and that this will be managed according to the principles established in the Data Protection Act 2018.

10. I understand that the information contained in this application, any supporting documentation and all correspondence with review bodies or their operational managers relating to the application:

    - Will be held by the REC (where applicable) until at least 3 years after the end of the study; and by NHS R&D offices (where the research requires NHS management permission) in accordance with the NHS Code of Practice on Records Management.
    - May be disclosed to the operational managers of review bodies, or the appointing authority for the REC (where applicable), in order to check that the application has been processed correctly or to investigate any complaint.
    - May be seen by auditors appointed to undertake accreditation of RECs (where applicable).
    - Will be subject to the provisions of the Freedom of Information Acts and may be disclosed in response to requests made under the Acts except where statutory exemptions apply.
    - May be sent by email to REC members.

11. I understand that information relating to this research, including the contact details on this application, may be held on national research information systems, and that this will be managed according to the principles established in the Data Protection Act 2018.

12. I understand that the main REC or its operational managers may share information in this application or supporting documentation with the Medicines and Healthcare products Regulatory Agency (MHRA) where it is relevant to the Agency's statutory responsibilities.

13. Where the research is reviewed by a REC within the UK Health Departments Research Ethics Service, I understand that the summary of this study will be published on the website of the Health Research Authority (HRA) together with the contact point for enquiries named below. Publication will take place no earlier than 3 months after the issue of the ethics committee's final opinion or the withdrawal of the application.

Contact point for publication*(Not applicable for R&D Forms)*

HRA would like to include a contact point with the published summary of the study for those wishing to seek further information. We would be grateful if you would indicate one of the contact points below.

- ◯ Chief Investigator
- ◯ Sponsor
- ◯ Study co-ordinator
- ◯ Student
- ◯ Other – please give details
- ◯ None

Access to application for training purposes *(Not applicable for R&D Forms)*

Optional – please tick as appropriate:

☐ I would be content for members of other RECs to have access to the information in the application in confidence for training purposes. All personal identifiers and references to sponsors, funders and research units would be removed.

This section was signed electronically by Dr Padmanabhan Ramnarayan on 26/04/2019 16:12.

Job Title/Post:	Consultant
Organisation:	Great Ormond Street Hospital
Email:	p.ramnarayan@gosh.nhs.uk

D2. Declaration by the sponsor's representative

If there is more than one sponsor, this declaration should be signed on behalf of the co−sponsors by a representative of the lead sponsor named at A64-1.

I confirm that:

1. This research proposal has been discussed with the Chief Investigator and agreement in principle to sponsor the research is in place.

2. An appropriate process of scientific critique has demonstrated that this research proposal is worthwhile and of high scientific quality.

3. Any necessary indemnity or insurance arrangements, as described in question A76, will be in place before this research starts. Insurance or indemnity policies will be renewed for the duration of the study where necessary.

4. Arrangements will be in place before the study starts for the research team to access resources and support to deliver the research as proposed.

5. Arrangements to allocate responsibilities for the management, monitoring and reporting of the research will be in place before the research starts.

6. The responsibilities of sponsors set out in the UK Policy Framework for Health and Social Care Research will be fulfilled in relation to this research.

   Please note: *The declarations below do not form part of the application for approval above. They will not be considered by the Research Ethics Committee.*

7. Where the research is reviewed by a REC within the UK Health Departments Research Ethics Service, I understand that the summary of this study will be published on the website of the National Research Ethics Service (NRES), together with the contact point for enquiries named in this application. Publication will take place no earlier than 3 months after issue of the ethics committee's final opinion or the withdrawal of the application.

8. Specifically, for submissions to the Research Ethics Committees (RECs) I declare that any and all clinical trials approved by the HRA since 30th September 2013 (as defined on IRAS categories as clinical trials of medicines, devices, combination of medicines and devices or other clinical trials) have been registered on a publically accessible register in compliance with the HRA registration requirements for the UK, or that any deferral granted by the HRA still applies.

This section was signed electronically by Dr Vanshree Patel on 26/04/2019 14:47.

Job Title/Post:	Deputy Director of R & I
Organisation:	Great Ormond Street Hospital for Children NHS Foundation Trust
Email:	Stephanie.DeSaMarquesBasset@gosh.nhs.uk