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First-line support for assistance in breathing in children

Submission date 17/06/2019	**Recruitment status** No longer recruiting	[X] Prospectively registered [X] Protocol [X] Statistical analysis plan [X] Results [_] Individual participant data
Registration date 19/06/2019	**Overall study status** Completed	
Last Edited 07/05/2025	**Condition category** Respiratory	

Plain English summary of protocol

Background and study aims
Many of the 20,000 children admitted to NHS paediatric critical care units every year 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, but 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. The aim of this study is to find out whether HFNC is as effective as CPAP.

Who can participate?
Children from 25 paediatric critical care units who require non-invasive breathing support to either help prevent them from going onto a ventilator, or to prevent them from going back on a ventilator after having just come off one

What does the study involve?
Children assessed by the treating clinician to require non-invasive respiratory support will be randomly allocated to receive either CPAP or HFNC as the first method of non-invasive breathing support. Guidance on the initiation, maintenance and weaning of CPAP and HFNC will be provided but as per current clinical practice, clinicians will be able to switch, escalate or stop the allocated treated, if clinically deemed necessary. Time to liberation from breathing support is measured, defined as the start of a 48-hour period during which the child is free of all forms of breathing support.

What are the possible benefits and risks of participating?
This study will provide much-needed evidence and will have a large and immediate impact on

how sick children are cared for in the NHS. Both HFNC and CPAP are already used in standard NHS practice, but the benefits and risks of one method over the over are unclear at this time, which is why this study is needed.

Where is the study run from?
Great Ormond Street Hospital For Children NHS Foundation Trust

When is the study starting and how long is it expected to run for?
February 2019 to November 2022.

Who is funding the study?
National Institute for Health Research (NIHR) (UK)

Who is the main contact?
1. Dr Alvin Richards-Belle
alvin.richards-belle@icnarc.org
2. Dr Padmanabhan Ramnarayan
p.ramnarayan@gosh.nhs.uk

Study website
https://www.icnarc.org/Our-Research/Studies/First-Abc

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
CPMS: 42112

Study information

Scientific Title
FIRST-line support for Assistance in Breathing in Children (FIRST-ABC): a master protocol of two randomised trials to evaluate the non-inferiority of high flow nasal cannula (HFNC) versus continuous positive airway pressure (CPAP) for non-invasive respiratory support in paediatric critical care

Acronym
FIRST-ABC

Study objectives
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.

The researchers will study whether HFNC is as effective as CPAP by doing two randomised clinical trials (RCTs) under one framework (FIRST-ABC).

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.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 26/07/2019, East of England – Cambridge South (Tel: +44 (0)207 104 8097, +44 (0)207 104 8104; Email: NRESCommittee.EastofEngland-CambridgeSouth@nhs.net), ref: 19/EE/0185

Study design
Randomized; Interventional; Design type: Treatment, Prevention, Other

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details to request a patient information sheet

Health condition(s) or problem(s) studied
Non-invasive respiratory support in paediatric critical care

Interventions
Current interventions as of 17/07/2020:

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).

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

Each RCT will be analysed separately once follow-up is completed for the respective RCT.

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Previous interventions:

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).

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.
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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.

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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.

Each RCT will be analysed separately once follow-up is completed for the respective RCT.

Intervention Type
Procedure/Surgery

Primary outcome measure
Time to liberation from respiratory support, defined as the start of a 48-hour period during which the child was free of all forms of respiratory support

Secondary outcome measures
Current secondary outcome measures as of 02/03/2020:
1. Mortality at PICU/HDU discharge, day 60 and day 180, assessed through review of patient medical notes at the relevant timepoints and/or data-linkage with nationally held death registrations
2. Rate of (re)intubation at 48 hours assessed through review of patient medical notes
3. Duration of PICU/HDU and hospital stay assessed through review of patient medical notes at PICU/HDU discharge and hospital discharge
4. Patient comfort during randomised treatment and during non-invasive respiratory support (i.e. HFNC and/or CPAP) measured using the COMFORT-B score
5. Proportion of patients in whom sedation is used during non-invasive respiratory support, assessed through review of patient medical notes
6. Parental stress in hospital at the time of consent, measured using the Parental Stressor Scale: PICU (PSS:PICU)
7. Health-related quality of life measured using age-appropriate Pediatric Quality of Life Inventory (Peds-QL) and the Child Health Utility 9D (CHU-9D) at 6 months
8. Total costs at 6 months
9. Quality-Adjusted Life Years (QALYs) at 6 months
10. Net monetary benefit gained at a willingness-to-pay of £20,000 per QALY at six months associated with HFNC vs. CPAP

Previous secondary outcome measures:
1. Mortality at PICU/HDU discharge, day 60 and day 180, assessed through review of patient medical notes at the relevant timepoints and/or data-linkage with nationally held death registrations

2. Rate of (re)intubation at 48 hours assessed through review of patient medical notes
3. Duration of PICU/HDU and hospital stay assessed through review of patient medical notes at PICU/HDU discharge and hospital discharge
4. Patient comfort during randomised treatment measured using the COMFORT-B score
5. Proportion of patients in whom sedation is used during non-invasive respiratory support, assessed through review of patient medical notes
6. Parental stress in hospital at the time of consent, measured using the Parental Stressor Scale: PICU (PSS:PICU)
7. Health-related quality of life measured using age-appropriate Pediatric Quality of Life Inventory (Peds-QL) and the Child Health Utility 9D (CHU-9D) at 6 months

Overall study start date
01/02/2019

Completion date
07/11/2022

Eligibility

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

Participant type(s)
Patient

Age group
Child

Upper age limit
16 Years

Sex
Both

Target number of participants
Planned Sample Size: 1200; UK Sample Size: 1200

Key exclusion criteria
Current participant exclusion criteria as of 02/03/2020:
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 PICU/HDU 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
9. Clinician decision to start other form of non-invasive respiratory support (i.e. not HFNC or CPAP)

Previous participant exclusion criteria:
1. Assessed by the treating clinician to require immediate intubation and invasive ventilation due to severe hypoxia, acidosis and/or respiratory distress, upper airway obstruction, 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 PICU/HDU 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

Date of first enrolment
06/08/2019

Date of final enrolment
07/11/2021

Locations

Countries of recruitment
England

Scotland

United Kingdom

Wales

Study participating centre
Great Ormond Street Hospital For Children NHS Foundation Trust
Great Ormond Street
London
United Kingdom
WC1N 3JH

Study participating centre
University Hospitals Bristol NHS Foundation Trust
Marlborough Street

Bristol
United Kingdom
BS1 3NU

Study participating centre
Birmingham Women's and Children's NHS Foundation Trust
Steelhouse Lane
Birmingham
United Kingdom
B4 6NH

Study participating centre
Imperial College Healthcare NHS Trust
St Marys Hospital
Praed Street
London
United Kingdom
W2 1NY

Study participating centre
Barts Health NHS Trust
The Royal London Hospital
Whitechapel Rd
London
United Kingdom
E1 1BB

Study participating centre
St George's University Hospitals NHS Foundation Trust
St George's Hospital
Blackshaw Road
Tooting
London
United Kingdom
SW17 0QT

Study participating centre
Cambridge University Hospitals NHS Trust
Addenbrooke’s Hospital
Hills Road
Cambridge

United Kingdom
CB2 0QQ

Study participating centre
Alder Hey Children's NHS Foundation Trust
Eaton Road
Liverpool
United Kingdom
L12 2AP

Study participating centre
University Hospitals Bristol NHS Foundation Trust
Bristol Royal Hospital for Children
Upper Maudlin Street
Bristol
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BS2 8BJ

Study participating centre
Chelsea and Westminster Hospital NHS Foundation Trust
369 Fulham Road
London
United Kingdom
SW10 9NH

Study participating centre
Guy's and St Thomas' NHS Foundation Trust
Evelina Hospital
Westminster Bridge Road
London
United Kingdom
SE1 7EH

Study participating centre
The Newcastle upon Tyne Hospitals NHS Foundation Trust
Royal Victoria Infirmary
Newcastle upon Tyne
United Kingdom
NE1 4LP

Study participating centre
Hull University Teaching Hospitals NHS Trust
Hull Royal Infirmary
Anlaby Road
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HU3 2JZ

Study participating centre
South Tees Hospital NHS Foundation Trust
James Cook Hospital
Marton Road
Middlesborough
United Kingdom
TS4 3BW

Study participating centre
Oxford University Hospitals NHS Foundation Trust
John Radcliffe Hospital
Headley Way
Oxford
United Kingdom
OX3 9DU

Study participating centre
King’s College Hospital NHS Foundation Trust
King's College Hospital
Denmark Hill
London
United Kingdom
SE5 9RS

Study participating centre
University Hospitals of Leicester NHS Trust
Leicester Royal Infirmary and Glenfield Hospital
Leicester
United Kingdom
LE3 9QP

Study participating centre

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CF14 4XW

Study participating centre
Nottingham University Hospitals NHS Trust
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NG7 2UH

Study participating centre
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Study participating centre
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Southampton Children's Hospital
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Southampton
United Kingdom
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Study participating centre
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Clarkson St
Sheffield
United Kingdom
S10 2TH

Sponsor information

Organisation
Great Ormond Street Hospital for Children NHS Foundation Trust

Sponsor details
Great Ormond Street
London
England
United Kingdom
WC1N 3JH
+44 (0)20 7905 2249
Research.Governance@gosh.nhs.uk

Sponsor type
Hospital/treatment centre

ROR
https://ror.org/03zydm450

Funder(s)

Funder type
Government

Funder Name
NIHR Evaluation, Trials and Studies Co-ordinating Centre (NETSCC); Grant Codes: 17/94/28

Results and Publications

Publication and dissemination plan
1. The protocol will be made publicly available on the ICNARC and the NIHR websites, once REC approval is received
2. Peer-reviewed scientific journals
3. Conference presentation
4. Publication on website

Intention to publish date
31/01/2024

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be available upon request from the Chief Investigator, Dr Padmanabhan Ramnarayan (P.Ramnarayan@gosh.nhs.uk). Non-patient identifiable data, for participants who consented to data sharing, will be made available one year after the publication of the main trial results. Application requests will be reviewed and approved by the Chief Investigator and the ICNARC CTU.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		04/08/2020	05/08/2020	Yes	No
Statistical Analysis Plan	Statistical and health economic analysis plan	31/10/2020	03/11/2020	Yes	No
Results article	Step-down RCT results	07/04/2022	08/04/2022	Yes	No
Results article	Step-up RCT results	16/06/2022	17/06/2022	Yes	No
HRA research summary			28/06/2023	No	No
Results article	Cost-effectiveness	07/06/2024	11/06/2024	Yes	No
Results article	Sub-group cost-effectiveness analysis	28/09/2024	02/10/2024	Yes	No
Results article		01/05/2025	07/05/2025	Yes	No