ISRCTN78297040 https://doi.org/10.1186/ISRCTN78297040

The HiFlo Study: a feasibility trial of using high flow humidified oxygen in acute asthma

Submission date
17/02/2020

Recruitment status
No longer recruiting

Registration date
16/04/2020

Overall study status
Completed

Last Edited
10/10/2024

Condition category
Respiratory

[_] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Asthma affects 1 in 11 British children. Attacks of Acute Severe Asthma (ASA) are among the commonest reasons for children to attend hospital emergency departments. Many children do not respond to initial treatment, and need to stay in hospital for rescue therapy. Current rescue therapy is unsatisfactory and has unpleasant side effects. High flow humidified oxygen (HiFlo) is a new treatment which helps children breathe by delivering moist air enriched with oxygen down into the airways of the lungs, through short soft tubes that fit snugly into the nostrils. It is more comfortable than other methods of breathing support and has a good safety record. HiFlo is already being used in premature babies with breathing problems, babies with virus lung infections, and ASA later on when rescue therapy has failed. The researchers believe that starting HiFlo early on in ASA will speed up recovery and reduce the need for unpleasant rescue therapy. They therefore aim to run a feasibility study (a small test version of the full trial) before starting a large national trial to decide whether early HiFlo is effective. They have designed this together with children and parents.

Who can participate?
Children (aged 2–11 years) with ASA who attend the emergency department

What does the study involve?
Participants will be randomly allocated to standard care or early Hi-Flo. The study involves comparing, between the two groups: how quickly they improve and are ready to go home, how many have side effects, how many end up needing rescue treatment, and what children, parents and staff think about being involved in the study. Things need to move quickly during emergency treatment, and children and parents are often very distressed. Because of this, the researchers will delay asking for consent for the research until the emergency has passed, but they will let families know the research is taking place.

What are the possible benefits and risks of participating?
The researchers cannot promise that participants will benefit directly from participating in this study and this is made clear when providing the patient information sheet and explaining the study to parents and participants. There is a potential for children in the intervention group to benefit from early HiFlo. Children in both groups may benefit from a more detailed assessment

than is standard practice. The two treatment options used in this trial have potential side effects. Side effects of the intravenous option include the known adverse effects of intravenous bronchodilators: pain from placing the needle in a vein, rapid and sometimes irregular heartbeat, nausea or vomiting and alteration in blood chemistry such as low potassium levels. Side effects of the HiFlo option include discomfort to the nose and a small risk of leakage of air from the lungs (pneumothorax, pneumomediastinum or subcutaneous emphysema). Both treatment options are already widely used in hospitals in the UK, including those taking part in this study. Children involved in the study would therefore potentially have been exposed to these risks as a result of treatment for their condition, rather than specifically due to participation in the study. No treatment option is denied to participants as a result of taking part in the study. In order to minimise risks and burdens to patients, it will be ensured that clinical staff are properly trained to apply both treatments, monitor their side effects and record them in a standard way as part of the clinical trial.

Where is the study run from?
1. Royal Alexandra Children's Hospital (UK)
2. King's College Hospital (UK)
3. Southampton Children's Hospital (UK)

When is the study starting and how long is it expected to run for?
September 2019 to June 2023

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

Who is the main contact?
Prof. Paul Seddon
seddop@gmail.com

Contact information

Type(s)
Scientific

Contact name
Dr Hector Rojas

Contact details
Academic Department of Paediatrics
Room 601
Level 6
Royal Alexandra Children's Hospital
Eastern Rd
Brighton
United Kingdom
BN2 5BE
+44 (0)1273 696955 x62401
h.rojas@nhs.net

Type(s)
Scientific

Contact name
Prof Paul Seddon

ORCID ID
https://orcid.org/0000-0003-2136-958X

Contact details
Respiratory Care
Level 4
Royal Alexandra Children's Hospital
Eastern Rd
Brighton
United Kingdom
BN2 5BE
+44 (0)1273 696955 x62320
seddop@gmail.com

Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
261627

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
CPMS 42761, IRAS 261627

Study information

Scientific Title
High Flow humidified oxygen as an early intervention in children with acute severe asthma. A feasibility study (HiFlo ASA)

Acronym
HiFlo ASA

Study objectives
The researchers believe that starting high flow humidified oxygen (HiFlo) early on in ASA will speed up recovery and reduce the need for unpleasant rescue therapy. Before starting a large national trial to decide whether early HiFlo is effective, they need to run a feasibility study. They have designed this together with children and parents.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 25/07/2019, West Midlands - Solihull Research Ethics Committee (The Old Chapel, Royal Standard Place, Nottingham, NG1 6FS, UK; +44 (0)2071 048019 NRESCommittee. WestMidlands-Solihull@nhs.net), REC ref: 19/WM/0219

Study design
Randomized; Interventional; Design type: Treatment, Physical

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Acute severe asthma

Interventions
This is a feasibility randomised controlled trial (RCT) of early HiFlo versus standard care, in children aged 2 to 11 years with ASA which has not responded to first-line therapy in the emergency department. The aim of this feasibility study is to determine whether a full RCT of early HiFlo in ASA is feasible, and to determine how large such a study needs to be.

The researchers will recruit 70 patients (35 in each arm) over 18 months in three centres (Royal Alexandra Children's Hospital Brighton, Southampton Children's Hospital and King’s College Hospital, London). Children aged 2-11 years will be eligible if they present to hospital with ASA and fail to respond to standard first-line therapy (high-dose inhaled bronchodilators). Failure to respond means having a Paediatric Respiratory Assessment Measure (PRAM) score of 5 or more, between 1 and 4 hours after starting first-line therapy. Screening, recruitment and randomisation will take place in the relevant emergency paediatric care department (ED).

The researchers will use a deferred consent model to avoid delay in treatment and minimise distress to families who present to the ED with acutely unwell children. Informed consent will not be sought prior to randomisation, but parents will be approached for informed consent within 24-72 hours of randomisation, once their child's condition is more stable. If consent is declined, the child will then exit the study and their data will not be analysed. Eligible children will be randomised to intervention (HiFlo) or control (standard care) arms.

Randomisation will be stratified by site, age (less than 5, 5 and over) and severity of acute asthma (PRAM score at study entry: less than 8, 8 and above), and will be implemented using 'Sealed Envelope' online randomisation software. Progress will be monitored with PRAM scores hourly in the ED and 4-hourly after admission to an inpatient ward.

This study will be pragmatic, and HiFlo will be an add-on to existing therapy in those randomised to the intervention arm. Children will not be denied access to existing standard second-line interventions (e.g. intravenous bronchodilators) as a result of participation in the study. The treating clinical team will be allowed to initiate intravenous bronchodilators as clinically indicated in either treatment arm. In children randomised to the early HiFlo arm, HiFlo will be commenced as soon as possible after randomisation, and should be the next treatment initiated rather than IV bronchodilator. If equipment is not available to allow HiFlo to be commenced within 30 minutes of randomisation, the child will not be recruited to the study.

If a child randomised to conventional therapy is failing to respond, as defined by preset criteria, the clinical team can opt to initiate HiFlo as rescue therapy - the child would remain in the study on an intention to treat basis. Equally, if a child randomised to HiFlo is failing to respond, the clinical team can opt to initiate intravenous bronchodilators. Reasons for discontinuing the intervention prematurely or other protocol violations will be clearly recorded.

The researchers will be assessing two candidate primary outcomes for a full RCT:
1. Need for escalation of therapy due to treatment failure and
2. Time to meeting hospital discharge criteria

The researchers will also be assessing a range of candidate secondary outcomes. The acceptability of both early HiFlo and deferred consent to participants and staff will be assessed by a) questionnaires administered just prior to discharge from hospital and b) semi-structured qualitative telephone interviews with participants and staff.

Intervention Type
Procedure/Surgery

Primary outcome(s)
Primary feasibility outcome measures:
1. Proportion of recruited children amongst eligible patients with ASA, measured using counts from screening and eligibility forms and logs at enrolment
2. Proportion of children with signed deferred consent amongst those recruited into the study, measured using counts from consent tracking forms and logs at deferred consent
3. Proportion of data collection complete per participant, measured using counts from validated MACRO database after discharge
4. Summary statistics for candidate primary outcomes, measured using counts from validated MACRO database after discharge
5. Proposed design, sample size and number of centres for a definitive study, evaluated from final study report at end of study
6. Satisfaction measured using end of study questionnaire (Likert or visual analogue scale for parents/pictographic tools for children) at discharge

Two candidate primary outcome measures are to be recorded and evaluated as part of feasibility objectives 3 and 4:
1. Treatment failure needing escalation of therapy is measured by monitoring PRAM score, respiratory rate, heart rate, FiO2 and pCO2 at the following timepoints: randomisation (T0), hourly during the first four hours after randomisation (T1-T4) and four-hourly afterwards until discharge from hospital (T8, T12, T16, ...)
2. Time between presentation to the Emergency Department and meeting hospital discharge criteria is measured in hours using hospital records at hospital discharge. Actual hospital discharge criteria measured by monitoring SpO2, FiO2, respiratory support and frequency of inhaled bronchodilators from the time a patient is stable/improving at the timepoints mentioned above

Key secondary outcome(s))
The following candidate secondary outcome measures are to be evaluated:
1. Time (hours) between presentation to ED and actual hospital discharge, measured from data in hospital records at discharge
2. Time (hours) between presentation to ED and achieving a Paediatric Respiratory Assessment Measure (PRAM) score ≤ 3, measured from data in validated MACRO database from PRAM

measurements at the established study timepoints: randomisation (T0), hourly during the first four hours after randomisation (T1-T4) and four-hourly afterwards until discharge from hospital (T8, T12, T16, ...)
3. Time (hours) between presentation to ED and ability to maintain SaO2 ≥ 92% without supplemental oxygen or respiratory support, measured from data in validated MACRO database from oxygen-related measurements at the established study timepoints as stated above
4. Need for intravenous (IV) bronchodilator therapy, measured using counts from validated MACRO database from therapy records at the established study timepoints as stated above
5. Duration of IV bronchodilator therapy, measured from data in validated MACRO database from therapy records at the established study timepoints as stated above
6. Requirement for non-invasive ventilation, measured using counts from validated MACRO database from therapy records at the established study timepoints as stated above
7. Requirement for invasive ventilation (intubation), measured using counts from validated MACRO database from therapy records at the established study timepoints as stated above
8. Treatment-related adverse effects, measured using counts from validated MACRO database from safety reporting records at the established study timepoints as stated above
9. Hospital readmission within 48 hours of discharge, measured using counts from hospital records and patient research logs at 48 hours after discharge
10. Acceptability and comfort score for treatment during the episode, recorded by end of study questionnaire (Likert or visual analogue scale for parents/pictographic tools for children) and by qualitative interview following the episode (thematic content analysis conducted on anonymised interview transcripts) at and after discharge

Completion date
30/06/2023

Eligibility

Key inclusion criteria
1. Age 2-11 years
2. Acute severe asthma ASA, defined as respiratory distress combined with wheeze on auscultation (a formal preceding diagnosis of asthma is not necessary)
3. Failure to respond to standard initial emergency management with 'burst' therapy (back-to-back 3 consecutive inhaled or nebulised doses of salbutamol with or without the addition of ipratropium bromide over a 1-hour period) plus systemic corticosteroids, with or without subsequent intravenous bronchodilator therapy as deemed appropriate by the treating physician. Failure to respond will be defined as PRAM score of 5 or more, between 1 and 4 hours after starting burst therapy. PRAM score has been shown to be a good predictor of need for admission and escalation of therapy. A child with PRAM score = 5 would typically have moderately increased work of breathing, audible wheeze and oxygen saturation below 92% but above 90%.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Child

Lower age limit
2 years

Upper age limit
11 years

Sex
All

Total final enrolment
56

Key exclusion criteria
1. Clinical/radiological evidence of bacterial pneumonia: fever > 38.5°C PLUS focal signs on auscultation or chest X-ray
2. Signs of impending respiratory failure mandating imminent intubation. These will be at the discretion of the treating clinical team, but would include elevated pCO2, refractory hypoxaemia and exhaustion
3. Contraindications to use of HiFlo:
3.1. Air leak (pneumothorax, pneumomediastinum or subcutaneous emphysema)
3.2. Decreased level of consciousness - AVPU score P or worse
3.3. Recent (within 6 weeks) bowel surgery
3.4. Intractable vomiting
4. Other major respiratory, cardiovascular or neurological condition.
5. Previous participation in the HiFlo ASA study, during a prior hospital episode

Date of first enrolment
17/02/2020

Date of final enrolment
30/04/2023

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Brighton And Sussex University Hospitals NHS Trust
Royal Sussex County Hospital
Eastern Road
Brighton
United Kingdom
BN2 5BE

Study participating centre
University Hospital Southampton NHS Foundation Trust
Mailpoint 18
Southampton General Hospital
Tremona Road
Southampton
United Kingdom
SO16 6YD

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

Study participating centre
University Hospitals of Leicester NHS Trust
The Research Space - Level 0 Balmoral
Leicester Royal infirmary
Leicester
United Kingdom
LE1 5WW

Sponsor information

Organisation
Brighton and Sussex University Hospitals NHS Trust

Funder(s)

Funder type
Government

Funder Name
NIHR Central Commissioning Facility (CCF); Grant Codes: PB-PG-1217-20024

Results and Publications

Individual participant data (IPD) sharing plan

The data sharing plans for the current study are unknown and will be made available at a later date

IPD sharing plan summary

Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		07/10/2024	10/10/2024	Yes	No
Protocol article		28/03/2024	02/04/2024	Yes	No
HRA research summary			28/06/2023	No	No
Participant information sheet	version v2	06/08/2019	16/04/2020	No	Yes