

# High-flow nasal cannula therapy for initial oxygen administration in acute hypercapnic respiratory failure: study protocol of randomised controlled unblinded trial

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## ABSTRACT

**Introduction** Acute respiratory failure is a common clinical condition accounting for nearly 116 000 admissions in the UK hospitals. Acute type 2 respiratory failure is also called acute hypercapnic respiratory failure (AHRF) and characterised by an elevated arterial CO<sub>2</sub> level of >6 kPa due to pump failure. Acute exacerbation of chronic obstructive pulmonary disease is the most common cause of AHRF. High-flow nasal therapy (HFNT) is a new oxygen delivery system that uses an oxygen-air blender to deliver flow rates of up to 60 L/min. The gas is delivered humidified and heated to the patient via wide-bore nasal cannula.

**Methods and analysis** We hypothesised that HFNC as the initial oxygen administration method will reduce the number of patients with AHRF requiring non-invasive ventilation in patients at 6 hours post intervention when compared with low-flow nasal oxygen (LFO). A randomised single-centre unblinded controlled trial is designed to test our hypothesis. The trial will compare two oxygen administration methods, HFNT versus LFO. Patients will be randomised to one of the two arms if they fulfil the eligibility criteria. The sample size is 82 adult patients (41 HFNT and 41 LFO) presenting to the emergency department.

**Ethics and dissemination** Ethical approval was obtained from the Office for Research Ethics Committees Northern Ireland (REC reference: 20/NI/0049). Dissemination will be achieved in several ways: (1) the findings will be presented at national and international meetings with open-access abstracts online and (2) in accordance with the open-access policies proposed by the leading research funding bodies we aim to publish the findings in high-quality peer-reviewed open-access journals.

**Trial registration number** The trial was prospectively registered at the clinicaltrials.gov registry (NCT04640948) on 20 November 2020.

## INTRODUCTION

### Disease burden

Acute respiratory failure (ARF) is a common clinical condition accounting for nearly

## Key messages

- ▶ This randomised controlled trial will address an important knowledge gap in using high-flow nasal therapy for patients with acute hypercapnic respiratory failure.
- ▶ The study results will be analysed by an independent statistician, to avoid investigator bias.
- ▶ Due to the nature of the intervention, blinding of participants and clinicians is not possible.

116 000 of the UK hospital admissions for respiratory support per year and classified as type 1 or type 2.<sup>1</sup> Type 2 respiratory failure is also called acute hypercapnic respiratory failure (AHRF) and characterised by an elevated arterial CO<sub>2</sub> (PaCO<sub>2</sub>) level of >6 kPa due to pump failure.<sup>2</sup> The pump failure relates to the imbalance between the respiratory demand and the capacity of the muscle pump to match the demand. Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is the most common cause for AHRF with the rest accounted for by neuromyopathies, chest wall deformities and obesity.<sup>3</sup> Chronic obstructive pulmonary disease (COPD) is the most common chronic respiratory disease globally with approximately 328 million sufferers worldwide and expected to become the leading cause of death in the next 15 years.<sup>4,5</sup> AECOPD leads to 100 000 admissions in England annually. Approximately 20% of patients with AECOPD will present with or develop hypercapnia, an indicator of increased risk of death.<sup>6,7</sup> In-hospital mortality in patients with AECOPD is still high, up to 8%, that increases to up to 15% in the intensive care unit (ICU) patients. The

1-year mortality in these patients is up to 44%.<sup>8</sup> Adequate treatment of AHRF is essential to prevent mechanical ventilation in these patients to reduce mortality and the demand on critical care resources.

### Current management strategy

Treatment for AHRF includes medical therapy such as bronchodilators, diuretics, antibiotics and controlled oxygen therapy aimed at relieving the underlying pathological process such as fluid overload, bronchospasm and infection.<sup>3</sup> Patients will also require ventilatory support that may be non-invasive ventilation (NIV) or invasive mechanical ventilation (IMV). NIV is recommended in patients with modest respiratory acidosis, patients with severe respiratory acidosis as a trial prior to IMV or as a ceiling of therapy.<sup>9</sup> In a trial comparing NIV to IMV in patients with AECOPD, there was no survival benefit. However, in those patients in whom NIV was successful, duration of hospital stay was shorter, there were fewer complications, fewer patients required de novo oxygen supplementation and there were fewer readmissions to hospital in the following year.<sup>10</sup>

### Limitations of NIV

The failure rate of NIV is still up to 40% with a significant amount of late failure after initial success. The factors leading to NIV failure is multifactorial including ventilator asynchrony due to mask leak, trigger issues, non-compliance due to claustrophobia, delirium, sputum retention, reduced communication and skin compromise. Mask discomfort is seen in up to 50% of patients and skin compromise is seen in up to 20% of patients.<sup>11</sup> There are also relative medical contraindications including emesis, reduced mentation and reduced access to physiotherapy manoeuvres that limit its use. A study by Wood *et al* has suggested worse outcomes that may be secondary to an inadvertent delay in initiating IMV in patients who were failing NIV.<sup>12 13</sup> A similar observation was made in a large cohort study where NIV use was associated with a 29% mortality rate that was 60% higher than patients managed by immediate IMV.<sup>13</sup> These highlight the importance of vigilance and rapid escalation to IMV in patients failing NIV.

### High-flow nasal cannula therapy—beyond an oxygen delivery device

High-flow nasal therapy (HFNT) is a new oxygen delivery system that uses an oxygen-air blender to deliver flow rates of up to 60L/min. The gas is delivered humidified and heated to the patient via wide-bore nasal cannula. When compared with conventional oxygen via face mask and NIV, the benefits are considered to be multifactorial. The humidified system causes fewer side effects of nasal and throat dryness and or pain. Patients, therefore, tolerate the device for longer, leading to fewer episodes of interface dislodgement with associated desaturations.<sup>14</sup> The

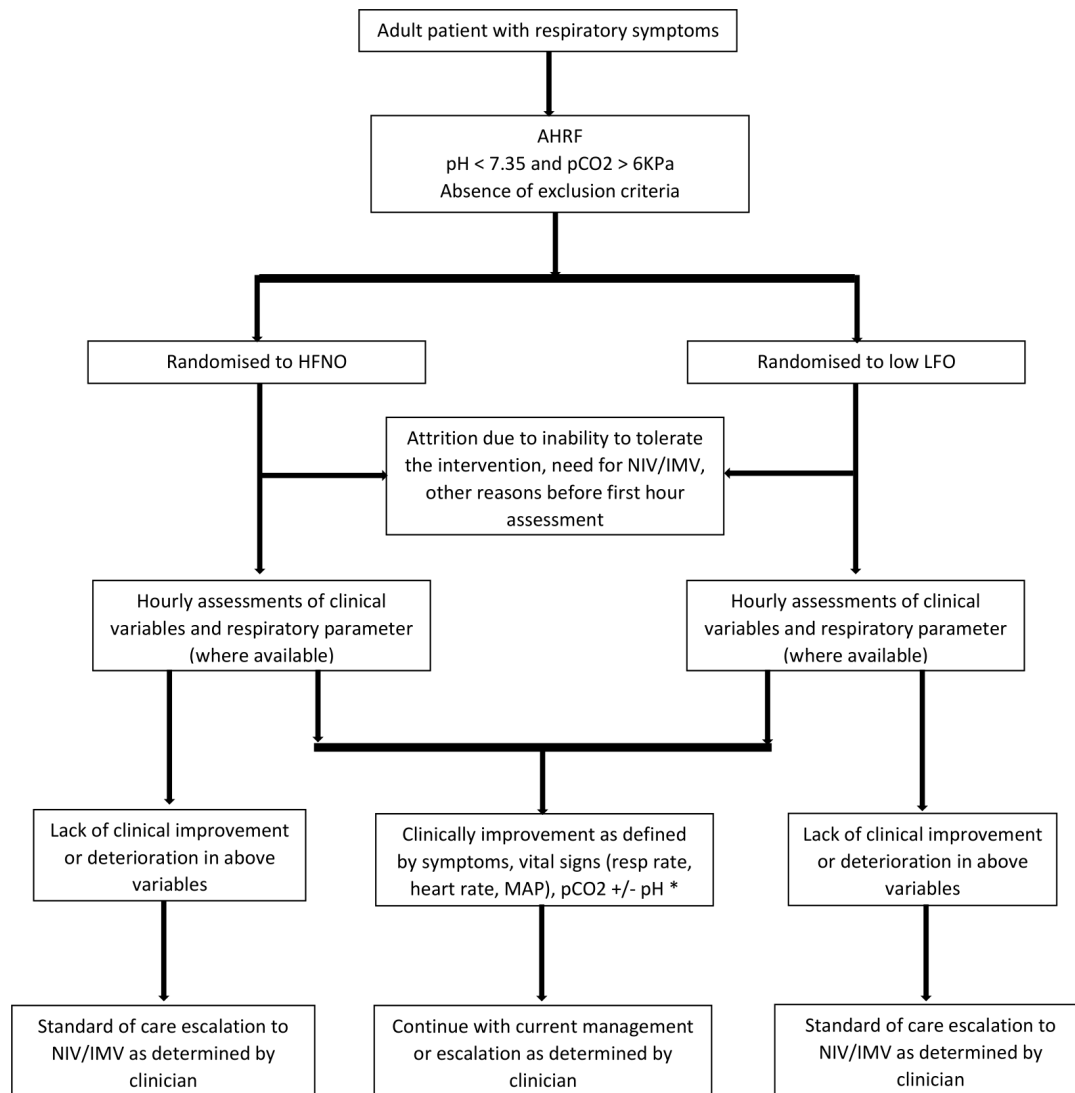
delivery of a constant fraction of inspired oxygen and ability to achieve high-flow rates above that possible with conventional oxygen (maximum 15L/min) allows the delivery flow rate to better match that of the patient in ARF, whose inspiratory flow can reach up to 100L/min.<sup>15</sup> A heating system and humidifier allow delivery of gases at temperatures of between 33°C and 43°C and 95%–100% humidity. During exercise or respiratory distress, flow rates of up to 120 L/min can be reached. This results in increased fluid losses and a higher metabolic oxygen requirement to achieve warmed gases. Flow rates such as this are achievable for only short periods and limited by fatigue. The application of cold, dry gases to patients with an increased oxygen requirement may exacerbate the heat loss and is associated with discomfort and reduced compliance with therapy. When this occurs, gas humidification decreases below 50% of relative humidity which can result in drying secretions, reduced ciliary function and poor mucous flow. This could promote mucus plugging and exacerbate airway obstruction and atelectasis.<sup>16</sup> HFNT circumvents the above problems by providing rates of flow up to 60L/min, warmed humidified gas delivery that improves patient comfort and supports mucous clearance.

The upper and lower airways from the nasal cavity to the conductive lower airways that do not take part in gas exchange constitute the anatomical dead space. HFNT clears the upper airways of expired air and reduces rebreathing thereby improving the efficiency of ventilation.<sup>17</sup> There is an associated increase in positive end-expiratory pressure (PEEP) that could be a potential benefit in patients with obstructive airways disease by increasing end-expiratory lung volume and offsetting intrinsic PEEP.<sup>15 18–20</sup> In a study of healthy human volunteers, HFNT in a dose and time-dependent manner was shown to decrease 81mKr gas clearance half-time.<sup>21</sup> There was a reduction in inspired CO<sub>2</sub> that correlated with an increase of inspired oxygen. In airway models, CO<sub>2</sub> clearance has been demonstrated even in apnoeic settings due to flow vortices created by the high-flow and cardiogenic oscillations.<sup>22 23</sup>

### Current evidence for high-flow nasal oxygen therapy in hypercapnic respiratory failure

We conducted a systematic review that included randomised controlled trials (RCTs) and cohort studies to synthesise the evidence for the efficacy of HFNT for adult patients with AHRF. The systematic review was published a priori in PROSPERO database (CRD42019148748).

Four articles were eligible for qualitative and quantitative synthesis. Three RCTs and one observational study involved 345 patients with acute-moderate hypercapnic respiratory failure or AECOPD or COPD. The results showed that HFNT significantly improves PaCO<sub>2</sub> at 4 hours in comparison to NIV. Furthermore, patients in the HFNT group were more comfortable than the NIV group. Secondary outcomes including, arterial oxygen



**Figure 1** Study design summarising patient screening, randomisation and clinical care of a patient. Postrandomisation care will follow the current standard of care including peripheral oxygenation saturation target, 88%–92%. Continuation of treatment strategy is at the discretion of the treating clinician and established BTS guidelines of managing a patient with acute type 2 respiratory failure should guide clinical care. This includes symptom assessment, trends in Glasgow Coma Scale, respiratory rate, heart rate, monitoring of changes in pH, PaO<sub>2</sub> and PaCO<sub>2</sub>. AHRF, acute hypercapnic respiratory failure; IMV, invasive mechanical ventilation; NIV, non-invasive ventilation; LFO, low-flow nasal oxygen.

(PaO<sub>2</sub>), pH, dyspnoea score, intubation rate, mortality rate and hospital stay showed no significant differences between HFNT and NIV or low-flow nasal oxygen (LFO).

Despite the clinical benefits found in improving PaCO<sub>2</sub> at 4 hour and patient comfort by HFNT, the review found that the quality of evidence was low and their certainty was affected by the high risk of bias, non-RCT study design and serious imprecision. Therefore, no recommendation could be made regarding the use of HFNT for AHRF. The review highlighted an important knowledge gap in the evidence for the use of HFNT for AHRF. Despite the increasing evidence for the benefit of HFNT in managing AHRF from mechanistic and physiological studies in airway models, healthy volunteers and patients with COPD, urgent high-quality RCTs are recommended to assess HFNT efficacy for patients with AHRF as an initial management strategy.

### Current practice

Current guidelines for the management of patients include medical therapy and controlled oxygen administration in patients with AHRF as the initial management strategy. Twenty per cent of patients are expected to improve with this conservative management strategy with LFO.<sup>24</sup> NIV is recommended for patients who do not improve where the pH is 7.25–7.35 secondary to hypercapnia with no contraindications for NIV.

## METHODS AND ANALYSIS

### Hypothesis

HFNT as the initial oxygen administration method reduces PaCO<sub>2</sub> and reduces the number of patients

requiring NIV in patients with AHRF when compared with LFO.

### Study design

RCT. The trial design is defined in [figure 1](#).

### Population

Patients will be eligible to participate in the study if they fulfil the following criteria:

#### Inclusion criteria

1. Adult patients >18 years of age.
2. Acute hypercapnic respiratory failure with pH <7.35 and PaCO<sub>2</sub> >6 kPa.

#### Exclusion criteria

1. Age <18 years.
2. Pregnant or breast feeding.
3. A patient cannot read and understand English.
4. Hypercapnia secondary to drug toxicity or non-pulmonary aetiology.
5. Hypercapnia secondary to exacerbation of asthma.
6. Contraindication to NIV.
7. Contraindication to HFNT.
8. Not for escalation to NIV.
9. pH <7.15.
10. Glasgow Coma Scale (GCS) of 8 or less.
11. Shock defined as systolic <90 mm Hg or a reduction by 20 mm Hg from usual systolic blood pressure despite volume resuscitation.
12. Respiratory or cardiorespiratory arrest.
13. Any other indication that requires immediate invasive/non-invasive mechanical ventilation.

### Screening assessment

The following will be performed at screening:

1. Participant demographics (date of birth, gender, height and weight, any medical history, recreational and prescribed medication history).
2. Electronic cigarette and tobacco smoking history.
3. Vital signs—heart rate, blood pressure, respiratory rate, oxygen saturation.
4. Laboratory assessments: haematological parameters, arterial blood gas.
5. Pulmonary function—FEV<sub>1</sub>, FVC, FEV<sub>1</sub>/FVC ratio (if available).
6. Check inclusion and exclusion criteria.

### Intervention

Controlled oxygen administration using HFNT as the initial oxygen administration method with a starting flow rate of 30 L/min and titrated to up as tolerated within 15 min of initiation dependent on patient comfort. Titration of supplemental oxygen to an arterial saturation

between 88% and 92%. All other aspects of clinical management will be at the discretion of the clinician.

### Comparator

Controlled oxygen administration using LFO (venturi mask or nasal cannula) titrated to an arterial saturation between 88% and 92% as the initial oxygen administration method. All other aspects of clinical management will be at the discretion of the clinician.

### Outcomes

This is a study of the physiological effects of two current methods of controlled oxygen administration, HFNT versus LFO, in patients with AHRF. The primary outcome is the proportion of patients requiring NIV in each cohort up to 6 hours after initial controlled oxygen therapy and medical optimisation. Various secondary outcomes will also be evaluated as stated follows:

1. Gas exchange/acid-base parameters—PaCO<sub>2</sub>, PaO<sub>2</sub>, pH at 1 hour, 6 hours and 24 hours post-HFNT/LFO initiation.
2. Respiratory parameters—respiratory rate, heart rate, mean arterial pressure at 1 hour, 6 hours and 24 hours post HFNT/LFO initiation.
3. Clinical outcomes—rate of intubation and ICU admission, in-hospital mortality, ICU length of stay, hospital length of stay.
4. Patient-centred outcomes—dyspnoea and comfort will be assessed using a visual analogue scale (score range 0–10, higher values represent a better outcome) if the patient has capacity or the Likert scale (score range 1–5; higher values represent a better outcome) to be completed by the clinical team (doctor/nurse/physio) if the patient lacks capacity.<sup>25</sup>

### Study procedures

[Table 1](#) demonstrates the assessments to be performed at given time periods.

### Recruitment

This study will be conducted in the emergency medicine department (ED) of the Royal Victoria Hospital. The ED is the largest in Northern Ireland and provides emergency care to the Belfast and surrounding areas that have the largest population density in Northern Ireland.

### Randomisation and blinding

After patients assessed for eligibility, they will be randomised to either HFNT (experimental arm) or LFO (control arm) therapy. Permuted block randomisation using computer-generated random numbers will be used to produce randomization sequence. Sealed, sequentially numbered envelopes will be used to provide a 1:1 randomisation ratio for the study. The treatment arm (HFNT or LFO) will be decided by opening the randomisation



**Table 1** Timing of assessments

Time	Screening	1 hour*	6 hours*	24 hours*	24 hours*† (till discharge)
Inclusion criteria	*				
Exclusion criteria	*				
Informed consent	*				
Demographics/medical history	*				
Arterial blood gas (ABG*)	*	*	*	*	*
NIV rate		*	*	*	*
Intubation rate		*	*	*	*
Dyspnoea score	*	*	*	*	*
Comfort score		*			
Physiological variables	*	*	*	*	*
Adverse event assessment		*	*	*	*

\*Or the nearest time-point when ABG is available. Any additional available ABG result will also be collected and imputed to the nearest hourly time-point. Additional blood sampling will be avoided to reduce patient discomfort.

†The 24 hours variables will be collected till death or discharge, whichever is earlier. ABG will be collected where available.  
NIV, non-invasive ventilation.

envelope at the time of care. Due to the nature of the intervention, participants and clinicians cannot be blinded. The results will be analysed by a statistician who will be independent of the research team.

### Clinical management of patients in the study

There will be no change to standard care treatment apart from the initial oxygen administration method (figure 1).

### Informed consent

#### Consenting process

Consent will be obtained by an appropriately trained doctor or nurse, who must be good clinical practice trained. Given the low-risk nature of the intervention and because the trial compares two established standards of care, a deferred consent process will be followed. The patient will be randomised once eligibility is confirmed.

For a patient with capacity, consent will be obtained as soon as it is deemed clinically safe to do so. If the patient lacks capacity, the legal requirements to recruit and give informed consent for patients without capacity will be followed. The personal consultee of the patient will be approached for their approval for the involvement of the patient in the study either in person or through telephone agreement. In the event a personal consultee is not available, a registered medical practitioner who is not part of the research team will be approached for their agreement.

Patient and public involvement (PPI) included a review of study design, outcomes, review of patient-related documents. Ongoing engagement from PPI will be sought for any substantial amendments to the study and provision of a lay summary to charities and patient support groups.

### Withdrawal from the study

In the event, the agreement for patient participation is not obtained or the regulations for recruitment of patient without capacity is not met within five working days, the patient will be withdrawn and all data destroyed.

Participants may be withdrawn from the study at any time without prejudice. In the event of a request to withdraw, the option to withdraw from part or all of the study, including the destruction of any collected data will be given.

### Statistical considerations

#### Sample size calculation

The success rate in the LFO care arm is 20% in conjunction with other medical optimisation.<sup>24</sup> The success rate in the LFO arm is based on previous evidence that suggests the resolution of AHRF in 20% of patients with medical optimisation including LFO. We assume that the success rate in the HFNT arm is 50%. The success rate in the HFNT arm is based on previous evidence that has shown a failure rate requiring mechanically ventilatory support was 25% of patients.<sup>26</sup> In another study, the failure rate was still lower at 13%.<sup>27</sup> The sample size calculation is based on a more conservative 50% failure rate. A two-group  $\chi^2$  test, with a two-sided significance level of 0.05, will have 80% power to detect the difference between the proportions when the sample size is 39 per arm. A total of 41 per arm be recruited after accounting for 5% drop out rate. Recruitment will continue until 41 patients in each arm in the study have stayed in the study for 24 hours post recruitment.



## Statistical analysis

The primary outcome measure will be compared between the two treatment groups using the  $\chi^2$  test or Fisher's exact test. A secondary analysis will involve a logistic regression model, with the dependent variable as NIV within 24 hours, treatment group as the independent variable and age, admission PaCO<sub>2</sub>, admission PaO<sub>2</sub>, raised WCCs, chest X-ray changes (Y/N) and admission GCS, type of nebuliser as covariates. An OR measuring the treatment effect and its 95% CI will be reported. Other categorical variables will be analysed using a logistic regression model, with treatment group as the independent variable and age, admission PaCO<sub>2</sub>, admission PaO<sub>2</sub>, raised WCCs, chest X-ray changes (Y/N), admission GCS, type of nebuliser as covariates. Continuous outcomes will be analysed using linear regression models, with treatment group as an independent variable with age, admission PaCO<sub>2</sub>, admission PaO<sub>2</sub>, raised WCCs, chest X-ray changes (Y/N) admission GCS, type of nebuliser in the model.

## ETHICS AND DISSEMINATIONS

### Ethics

The study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. This study has been approved by the Office for Research Ethics Committees (REC) Northern Ireland (REC reference: 20/NI/0049).

This study will involve patients with AHRF. However, the research question cannot be answered without undertaking the study in these subjects. Following a detailed discussion of the study, written, informed consent will be obtained from the participant. Consenting processes are standardised and are reinforced via training prior to study start-up.

### Safety reporting

#### Adverse event reporting

The chief investigator (CI) or their delegated investigator is responsible for recording adverse events observed during the study period. The investigator should attempt, if possible, to establish a diagnosis based on the subject's signs and symptoms. When a diagnosis for the reported signs or symptoms is known, the investigator should report the diagnosis as the adverse event, rather than reporting the individual symptoms.

Patients with AHRF are critically ill and will be expected to develop various complications as part of the natural course of their illness. Events that are directly related to their pre-existing medical condition including the primary outcome, need for mechanical ventilation, escalation of therapy and development of infective complications will be captured but not reported as adverse events or serious adverse events (SAEs).

The investigator should follow all adverse events observed during the study until they are resolved or stabilised, or the events are otherwise explained. All adverse

events should be treated appropriately. Treatment may include one or more of the following: no action is taken (ie, further observation only); non-drug therapy given; subject hospitalised. The action taken to treat the adverse event will be recorded in the case report form (CRF). The CI will report all related and unexpected SAEs to the REC within 15 days.

For both adverse events and SAEs, the adverse event report page in the CRF will be completed.

The CI must assess seriousness and causality for any adverse events in keeping with regulatory requirements. The investigator must record the adverse events, seriousness as well as duration (start and end dates). Adverse events are recorded at each study time point and tabulated for inclusion in an annual safety report to the sponsor and REC.

### End of study

The study will end when the completed number of patients have been recruited and completed follow-up.

The trial will be stopped prematurely if:

1. Mandated by the ethics committee.
2. Mandated by the sponsor, for example, following recommendations from the data monitoring and ethical committee (DMEC).
3. Funding for the trial ceases.

The REC that originally gave a favourable opinion of the trial will be notified in writing if the trial has been concluded or terminated early.

### Patient confidentiality

Patient confidentiality will be maintained at every stage and compliance with the Data Protection Act (2018).

### Good clinical practice

The study will be carried out in accordance with the principles of the International Conference on Harmonisation Good Clinical Practice (ICH-GCP) guidelines ([www.ich.org](http://www.ich.org)).

### Sponsorship

Belfast Health and Social Care Trust will act as a sponsor and will provide indemnity for the study.

### Data collection management

#### Data collection and recording

All data for individual subjects will be collected by the CI or by a delegated investigator and recorded in the CRF. Due care will be taken to ensure data safety and compliance with the Data Protection Act 2018. Quality control is implemented by adherence to standard operating procedures, which are defined to encompass aspects of the clinical data management process and to ensure standardisation and adherence to ICH-GCP guidelines and regulatory requirements.

All data for an individual patient will be collected by the CI or designee and recorded in source documents/electronic CRF for the study. Patient identification on the CRF will be through their unique study identifier, allocated at the time of recruitment. Data will be stored in a fully anonymised format with all links to patient identifying information broken. A separate list of patients and their unique identifiers will be stored in a password protected national health service computer.

## Trial committees

### Data monitoring and ethics committee

A DMEC will be appointed. The committee will be independent of the study team and will comprise two clinicians with experience in undertaking clinical trials.

The DMEC will meet to agree to conduct and remit. The DMEC will meet after the first 5 subjects have completed the study and meet annually thereafter. In the event of an occurrence of an unexpected severe adverse reaction, an additional unplanned DMEC meeting may be convened.

An interim analysis of efficacy is not planned although this issue can be discussed by the DMEC as required. The DMEC will function primarily as a check for safety, reviewing adverse events. They will report any issues pertaining to safety to the CI. It will be the responsibility of the CI to inform the sponsor who will take appropriate action to halt the trial if concerns exist about patient safety.

## Dissemination

The trial will be reported in accordance with the Consolidated Standards of Reporting Trials guidelines ([www.consort-statement.org](http://www.consort-statement.org)). Dissemination will be achieved in several ways: (1) the findings will be presented at national and international meetings with open access abstracts online, for example, the American Thoracic Society annual meeting; and (2) in accordance with the open-access policies proposed by the leading research funding bodies we aim to publish the findings in high quality peer-reviewed open access (via PubMed) journals. This will secure a searchable compendium of these publications and make the results readily accessible to the public, healthcare professionals and scientists. Where appropriate, research details will also be posted on institutional websites available to the general public. In addition, the most significant results will be communicated to the public through press releases.

## Trial status and summary

The study is a UK single-centre randomised trial comparing HFNT and LFO in reducing the need for NIV in patients with AHRF. The current protocol version is V.2.0 dated 22 April 2020. The recruitment to this trial is expected to commence in December 2020 for 12 months.

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**Contributors** AA and MS conceived the idea for the clinical trial. MS wrote the protocol. AA and MS drafted the manuscript. AA, AM and BB commented on the intellectual content and reviewed the manuscript.

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**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

**Patient consent for publication** Not required.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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