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|  | ***ACUTE*** |
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|  | **The ACUTE (Ambulance CPAP: Use, Treatment effect and Economics) feasibility study:****A pilot randomised controlled trial of prehospital CPAP for acute respiratory failure** |
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Sheffield Clinical Trials Research Unit (CTRU)

**The ACUTE (Ambulance CPAP: Use, Treatment effect and economics) feasibility study: A pilot randomised controlled trial of prehospital CPAP for acute respiratory failure**

This document describes a clinical trial, and provides information about procedures for entering participants. The protocol is not intended for use as a guide to the treatment of other patients.

**Contents**

[General information 5](#_Toc458763456)

[Protocol amendments since Version 1.0: 6](#_Toc458763457)

[Scientific Summary 7](#_Toc458763458)

[Lay Summary 8](#_Toc458763459)

[1. Introduction 9](#_Toc458763460)

[2. Aims and objectives 12](#_Toc458763461)

[3. Trial Design 13](#_Toc458763462)

[4. Trial treatments 15](#_Toc458763463)

[5. Selection and withdrawal of participants 17](#_Toc458763464)

[6. Randomisation and enrolment 21](#_Toc458763465)

[7. Ancillary sub-studies 22](#_Toc458763466)

[8. Safety Reporting 24](#_Toc458763467)

[9. Assessments and procedures 28](#_Toc458763468)

[10. Statistics 32](#_Toc458763469)

[11. Trial supervision 34](#_Toc458763470)

[12. Data handling and record keeping 36](#_Toc458763471)

[13. Data access and quality assurance 37](#_Toc458763472)

[14. Publication and dissemination 38](#_Toc458763473)

[15. Finance 39](#_Toc458763474)

[16. Ethics approval 40](#_Toc458763475)

[17. Regulatory approval 41](#_Toc458763476)

[18. Indemnity / Compensation / Insurance 42](#_Toc458763477)

[19. References 43](#_Toc458763478)

### Abbreviations

|  |  |
| --- | --- |
| ACUTE | Ambulance CPAP: Use, Treatment effect and economics |
| AE | Adverse event |
| AHF | Acute heart failure |
| ARF | Acute respiratory failure |
| BTS | British Thoracic Society |
| CI | Chief Investigator |
| CPAP | Continuous positive airways pressure |
| CONSORT | Consolidated standards of reporting trials |
| COPD | Chronic obstructive pulmonary disease |
| CRF | Case report form |
| CTRU | Clinical Trials and Research Unit |
| DMEC  | Data Monitoring and Ethics Committee |
| ENBS | Expected net benefit of sampling |
| EQ-5D-5L | European Quality of Life Measure (5 levels) |
| EVSI | Expected Value of Sample Information |
| GCP | Good Clinical Practice |
| HRA | Health Research Authority |
| HTA | Health Technology Assessment |
| kPa | Kilopascals |
| LREC | Local Research Ethics Committee |
| MCA | Mental Capacity Act |
| MHRA | Medicines and Healthcare Products Regulatory Agency |
| NHS | National Health Service |
| NIHR | National Institute of Health Research |
| NRES | National Research Ethics Service |
| NIV | Non-invasive ventilation |
| PaCO2 | Partial pressure of carbon dioxide in arterial blood |
| PaO2 | Partial pressure of oxygen in arterial blood |
| QALY | Quality adjusted life year |
| R&D | Research and development |
| RCT | Randomised controlled trial |
| REC | Research Ethics Committee |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SOP | Standard Operating Procedure |
| SpO2 | Peripheral capillary oxygen saturations |
| SUSAR | Suspected unexpected serious adverse reaction |
| TMG | Trial Management Group |
| TSC | Trial Steering Committee |
| VAS | Visual analogue scale  |
| WMAS | West Midlands Ambulance Service |
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### Definition of terms

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| Acute respiratory failure | Low oxygen levels, and/or high carbon dioxide in the blood resulting from an acute disease process involving the lungs. Type 1 respiratory failure is defined by a PaO2 of <8 kPa with a normal or low PaCO2. Type 2 failure is defined by a PaO2 of <8 kPa and a PaCO2 of >6.1 kPa. |
| Ambulance hub | Central regional building where ambulances are prepared prior to travel to local ambulance stations to respond to emergency calls. |
| Chronic obstructive pulmonary disease | A disease where the lung’s airways become chronically inflamed (bronchitis) and the air sacs are damaged (emphysema). |
| Continuous Positive Airways Pressure | Oxygen enriched air is delivered to lungs at increased pressure through a tight fitting face mask. This splints open the lungs airways and pushes fluid and mucus out of the lung’s air sacs. |
| Hypercarbia | High levels of the waste product carbon dioxide in the body’s blood. Caused when diseases of the lung or heart prevent the lungs from excreting carbon dioxide. Defined as a PaCO2 of >6.1 kPa. |
|  |  |
| Hypoxia | Low oxygen levels in the blood delivered to the body’s tissues. Can be caused by diseases of the lung or heart which reduce the ability of the lungs to absorb oxygen. Defined by a PaO2 of <8 kPa. |
| Non-invasive ventilation | External method to support breathing by cyclically pushing air into the lungs (BIPAP) or delivering oxygen at a continually increased pressure (CPAP). |
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# Protocol amendments since Version 1.0:

Change to Section 6. Randomisation and enrolment

Method of randomisation changed from ambulance hub stratified randomisation to simple, unrestricted, randomisation.

Allocation concealment changed to reflect that the equipment boxes will now be prepared by Sheffield CTRU, not SP Services.

Method of implementation of allocation schedule further refined to allow Sheffield CTRU staff not directly involved in conduct of the Trial to aid in process of assembling equipment boxes.

Change to Section 8. Safety Reporting

Further refinement of policy so that AE’s related to ‘trial procedures’ will also be recorded.

‘Pressure area damage’ added to discrete list of related adverse events that will be reported.

# Scientific Summary

AIM: To determine whether a definitive pragmatic randomised controlled trial (RCT) comparing prehospital continuous positive airway pressure (CPAP) to standard oxygen therapy for acute respiratory failure is feasible, acceptable and cost-effective.

DESIGN: a) Individual patient randomised controlled external pilot trial b) Updated value of information analysis using existing HTA programme economic model.

SETTING: Four ambulance hubs in the West Midlands Ambulance Service.

PARTICIPANTS: Adults presenting to paramedics with acute respiratory failure and recruited using a hierarchical consent process complying with the 2005 Mental Capacity Act (MCA)

SAMPLE SIZE: A sample size of 1,518 is projected for the full trial (based on 5% absolute effect size, 88% baseline 30 day survival, 90% power, 2-sided significance of 5%, 5% attrition at 30 days). Recruitment of at least 120 participants to the pilot trial over 12 months will demonstrate that a definitive trial is feasible and cost-effective. It will also allow estimation of adherence, attrition, data completeness and event rates with sufficient precision to ensure validity of the definitive trial protocol.

INCLUSION CRITERIA: Respiratory distress with peripheral oxygen saturation below British Thoracic Society (BTS) target levels (88% for patients with chronic obstructive pulmonary disease (COPD), 94% for other conditions), despite supplemental oxygen (titrated low flow oxygen for COPD, titrated high flow oxygen for other conditions).

EXCLUSION CRITERIA: Hospital treatment available within 15 minutes of eligibility, age <18 years, terminal illness, not for resuscitation status, oxygen alert card, trauma aetiology, anticipated inability to apply CPAP, contraindication to CPAP (suspected pneumothorax, respiratory arrest, epistaxis, vomiting, hypotension), previous enrolment, pregnancy.

HEALTH TECHNOLOGIES ASSESSED: Prehospital CPAP (O\_two system) with supplemental oxygen versus standard oxygen therapy; both targeted to BTS recommendations for peripheral oxygen saturations. Interventions provided in identical sealed boxes to ensure allocation concealment.

FEASIBILITY OUTCOMES: 1. Incidence of recruited eligible patients; 2. Proportion recruited in error; 3. Adherence to the allocation schedule (i.e. initiation of allocated treatment); 4. Adherence to treatment (i.e. ability to tolerate CPAP); 5. Retention at 30 days; 6. Feasibility of data collection, based on proportion with missing or incomplete data; 7. Cost-effectiveness of conducting a definitive trial using value of information analysis of updated economic model.

EFFECTIVENESS OUTCOMES: Survival at 30 days (definitive trial primary endpoint); endotracheal intubation; admission to critical care; length of hospital stay; visual analogue scale (VAS) dyspnoea score; EQ-5D-5L and health-care resource use at 30 days.

ACCEPTABILITY OUTCOMES: Adverse events and side effects. Paramedic perceptions about, and satisfaction with, each intervention.

DATA COLLECTION: Efficient collection of baseline, outcome and adverse event data using ambulance service paper and electronic patient report forms, emergency department information systems, and NHS Summary Care Records. Quality of life and resource use from postal or telephone questionnaires. Assessment of paramedic acceptability using online survey.

ANALYSIS: Feasibility outcomes will be analysed descriptively (point estimates reported with 95% confidence intervals) and compared to pre-specified target values. Effectiveness outcomes will be reported descriptively. An existing meta-analysis and economic model will be updated and an expected net benefit of sampling analysis (ENBS) undertaken.

TIMETABLE: 28m project: 8m set-up; 1m training for paramedics; 12m recruitment; 1m follow-up; 6m close out, analysis and write-up.

# Lay Summary

**Background**

Acute respiratory failure (ARF) is a common and life-threatening medical emergency that often results in long hospital stays or expensive intensive care admissions. It occurs when heart or lung disease suddenly develops or worsens and leads to the patient being unable to maintain oxygen levels in their blood. When this happens the patient may be at high risk of death and needs emergency treatment.

Paramedics currently provide oxygen delivered at normal pressure by a loose fitting face mask. Continuous positive airway pressure (CPAP) is a potentially useful treatment that could be delivered by paramedics in an ambulance. It involves delivering oxygen under increased pressure through a close-fitting facemask. Its use in hospital can reduce the risk of death in people with lung disease and improve breathing in people with heart disease. Small studies undertaken outside the UK have suggested that using CPAP in an ambulance may save more lives than delaying its use until arrival at hospital. However, it is uncertain whether this treatment could work effectively in NHS ambulance services, and if it represents value for money.

**Aim**

The purpose of this study is to see whether it is possible and worthwhile to undertake a full-scale study comparing CPAP and standard oxygen treatment delivered by paramedics for acute respiratory failure, and if so, how we should do it.

**Methods**

Paramedics will identify adults with ARF when attending 999 emergency calls. One hundred and twenty such patients will be included in the study. Half will be randomly assigned to a group that will receive CPAP, while the other half will be treated with standard oxygen therapy. All the patients will then undergo normal hospital treatment and be followed up for a month to see if they survive. We will also measure each patient’s quality of life, need for admission to intensive care, length of stay in hospital, and health service use.

Additionally, we will look at how many adults are attended with ARF, how many are entered into study, the number who correctly receive CPAP treatment, and how many patients we can follow up to the end of the study. Paramedics will also be surveyed to understand their experience of delivering CPAP and being involved in the research. Together these results will tell us whether it is feasible and affordable to conduct a full -scale trial evaluating CPAP for acute respiratory failure, and will also inform us how to design such a study.

**Oversight**

The proposed study will be designed and conducted in accordance with Good Clinical Practice (GCP), an international standard that ensures medical research is safe and ethical. The main ethical issue is that the trial will involve patients who are severely ill and potentially unable to decide whether they wish to participate. In these circumstances patients can be recruited to the trial and their consent sought later, provided important legal safeguards are followed. All research procedures will be reviewed by an independent NHS ethics committee and overseen by committees of independent statisticians and clinical experts in the field. Additionally, the research will conform to University of Sheffield Clinical Trials and Research Unit (CTRU) standard operating procedures. We will publish our results in scientific journals and publicise our findings through the Study website and on social media.

# 1. Introduction

ARF is a serious acute illness which can occur secondary to common cardiac or respiratory conditions. Early prehospital administration of CPAP, a form of non-invasive ventilation (NIV), may improve survival and reduce the need for critical care admissions. The ACUTE study will determine the feasibility, acceptability and cost-effectiveness of a definitive trial to evaluate prehospital CPAP compared to standard oxygen therapy, for adults attended by paramedics with ARF.

**What is the problem being addressed?**

ARF is a common and life-threatening medical emergency which occurs when disease of the heart or lungs lead to failure to maintain adequate blood oxygen levels and/or increased blood carbon dioxide levels. It is caused by a number of common cardiac or respiratory diseases, including heart failure, pneumonia, and exacerbations of chronic obstructive pulmonary disease (COPD) and asthma. Current clinical practice guidelines (National Clinical Guideline Centre 2010, McMurray 2012) recommend a standard management approach of oxygen therapy for the treatment of acute respiratory failure; supplemented by specific management options directed at the underlying disease.

NIV involves delivering oxygen-enriched air to the lungs at increased pressure through a close-fitting face mask. NIV is widely used in hospital to treat ARF from a number of causes. Meta-analyses have shown that it improves outcomes in ARF due to COPD (Lightowler 2003) and acute cardiogenic pulmonary oedema (Vital 2013). Although the 3CPO trial showed that routine use of NIV for acute cardiogenic pulmonary oedema did not improve mortality compared to selective use (Gray 2009).

It has been suggested that NIV may be more effective if delivered earlier (Masip 2008), i.e. en-route to hospital (prehospital NIV). This is supported by data from a randomised trial comparing immediate to delayed prehospital NIV (Plaisance 2007), suggesting that a delay of only 15 minutes was associated with worse clinical breathlessness scores and blood gas measurements, and increased risk of intubation or death.

Practical considerations mean that prehospital NIV is usually delivered as CPAP, whereby airway pressure does not vary during inspiration and expiration. The difficulties of prehospital diagnosis mean that prehospital CPAP is likely to be applied generally to all cases of acute respiratory failure, rather than directed towards those due to a specific cause.

**Why is this research important?**

ARF is a common medical emergency with a high risk of death. Prehospital CPAP could markedly reduce the risk of death but requires substantial additional funding to be delivered across the ambulance service. A recent Health Technology Assessment (HTA) programme funded evidence synthesis of prehospital NIV for acute respiratory failure (HTA11/36/09) showed that prehospital CPAP reduced the risk of mortality and requirement for endotracheal intubation compared to standard treatment, but noted that the primary studies were relatively small and heterogeneous, and may not be applicable to the NHS (Goodacre 2014, Pandor 2015). A large pragmatic trial comparing prehospital CPAP to standard care in the NHS is therefore required.

The potential need for prehospital CPAP is likely to increase as the population ages and as acute hospital care becomes more centralised. The risk of death in patients with respiratory problems increases markedly with distance travelled to hospital, from 10% with distances below 10km, to 20% with distances over 20km (Nicholl 2007). Provision of prehospital CPAP could reduce the risk of death associated with long distances to hospital. However, all assumptions of benefit from prehospital CPAP depend upon the evidence of effectiveness from existing trials being reproduced in typical NHS practice and there being sufficient numbers of eligible patients treated.

**What is currently known about the effectiveness and cost-effectiveness of prehospital CPAP?**

Five previous systematic reviews (Simpson 2011, Rees 2011, Williams B 2013, Williams T 2013, Mal 2014) and three meta-analyses (Williams T 2013, Mal 2014, Pandor 2014) have examined the effectiveness of prehospital CPAP in ARF. The HTA-funded evidence synthesis review (Pandor 2014) was the most recent, valid, and comprehensive analysis. It identified 10 trials comparing prehospital NIV (including CPAP) with standard oxygen therapy. Network meta-analysis suggested that prehospital CPAP is an effective treatment for acute respiratory failure, with evidence that it reduces mortality (odds ratio 0.41; 95% CrI 0.20 to 0.77) and intubation rate (0.32; 95% CrI 0.17 to 0.62) compared to standard care. These findings were consistent with the two preceding meta-analyses (Williams T 2013, Mal 2014). However, some included studies were at risk of selection bias from lack of allocation concealment and information bias secondary to unblinded outcome assessment. Furthermore, the findings may also not be generalisable to the NHS. Only one trial included undifferentiated respiratory failure patients and most studies were small, suggesting recruitment of non-representative patients. None were undertaken in the UK and the methods used to deliver prehospital CPAP (physician or paramedics with online physician support) would not be usual NHS practice.

A de novo economic model was developed for the HTA evidence synthesis project (Pandor 2014), to explore the costs and health outcomes of implementing prehospital CPAP (Thokala 2015). This suggested that prehospital CPAP was more effective than standard care but was also more expensive, with an incremental cost-effectiveness ratio of £20,514/quality adjusted life year (QALY) and a 49.5% probability of being cost-effective at the £20,000/QALY threshold. Expected value of perfect information (EVPI) analyses suggested that further research costing up to £22.5 million could represent value for money, while expected value of sample information (EVSI) analyses suggested that a randomised trial recruiting 1000 patients per arm would be cost-effective if research costs were less than £18.1 million. However, these cost-effectiveness results were predicated on the accuracy of published effectiveness data and were very sensitive to estimates for the incidence of acute respiratory failure.

Estimates of the incidence of eligible patients with acute respiratory failure are uncertain, yet this parameter is a key determinant of cost-effectiveness and the value of information of a randomised trial. It is also clearly a key determinant of the feasibility of a randomised trial. Audit data relating to in-hospital NIV (British Thoracic Society 2012, Sheffield Teaching Hospitals audit data) suggest incidence rates of 36.1 and 40.8 per 100,000 population per year, which would be more than enough eligible patients to sustain a trial or a prehospital CPAP service. However, estimates from services that have implemented prehospital CPAP suggest a much lower incidence of 3.5 and 7.1 per 100,000 population per year (Spijker 2013, Aguilar 2013). Implementation was limited to selected providers and/or patients in these settings, so these are likely to be underestimates. Based on this incidence range, the annual cost of prehospital CPAP (initial equipment, implementation, and ongoing maintenance), to an ambulance service covering a 5 million population, could be anything from £235,683 to £582,300; while the potential number of lives saved could be anything from 11 to 124. These figures show that prehospital CPAP could save hundreds of lives each year across the NHS, but would be estimated to cost £2-6million each year to deliver.

**Why is this research needed now?**

Research is needed now, before pre-hospital CPAP is implemented on the basis of the limited evidence base and at potentially substantial cost. Our survey of English ambulance service clinical directors found that 3/10 had implemented pre-hospital CPAP in some form and 2/10 planned implementation. All 10 clinical directors were supportive of a trial to further evaluate prehospital CPAP, however concerns were expressed regarding the existing evidence base.

There is strong professional and public support for research investigating prehospital NIV. Asthma, COPD and heart failure advocacy bodies acknowledge the importance of the research question and have endorsed this pilot study. Patient and public involvement (PPI) groups consider this to be an important clinical problem requiring further investigation. Moreover, prehospital CPAP was identified as a research priority by the 999 EMS Research Forum. The Royal College of Emergency Medicine and College of Paramedics are also supportive of this pilot trial. Finally, previous systematic reviews examining prehospital CPAP have separately concluded that a large pragmatic clinical trial is required.

**Conclusion**

Taken together these findings suggest that although prehospital CPAP is a promising therapy, further research is clearly needed to examine whether the reported clinical and cost-effectiveness are confirmed in the UK setting. Prior to a large pragmatic trial and economic evaluation comparing prehospital CPAP to standard care, it is first necessary to estimate the incidence of eligible patients, to determine whether a trial would be feasible and cost-effective. We also need to determine whether prehospital CPAP can be delivered in the context of the NHS ambulance service. Prehospital trials also need to overcome a number of potential practical barriers if they are to deliver valid data. For these reasons a stand-alone feasibility study is necessary to estimate the incidence of eligible patients and test the feasibility and acceptability of potential definitive trial methods.

# 2. Aims and objectives

The ACUTE stand-alone external pilot study aims to determine the feasibility, acceptability and cost-effectiveness of a definitive trial to evaluate the clinical and cost-effectiveness of prehospital CPAP compared to standard oxygen therapy, for patients attended by paramedics with ARF.

A feasibility study comparing prehospital CPAP with standard oxygen therapy in one ambulance service is an essential preliminary step, prior to a definitive trial, which will address important uncertainties without incurring prohibitive risks or costs. Its primary aim is to ensure the design and methods of the definitive trial are sound, practicable, safe and feasible. A secondary aim is to update an existing HTA economic model, using an applicable effectiveness estimate and a more accurate incidence rate, to calculate credible ENBS for a range of sample sizes, to identify the optimal design of any future trial (Pandor 2014, Thokala 2015). If the feasibility and cost-effectiveness of further research can be demonstrated, a large pragmatic trial could then definitively test the hypothesis that prehospital CPAP reduces mortality, and is cost-effective, compared to standard oxygen therapy.

The primary objectives are to estimate the following feasibility outcomes:

1. The rate of eligible patients per 100,000 population per year
2. The proportion recruited and allocated to treatment appropriately
3. Adherence to allocated treatment
4. Retention and data completeness up to 30 days
5. ENBS for a range of trial sizes to identify optimal trial design

Secondary objectives are to estimate the following summary clinical outcome measures, across the whole trial population and per treatment group:

1. Proportion surviving to 30 days
2. Proportion undergoing endotracheal intubation by 30 days
3. Proportion admitted to critical care at any point up to 30 days
4. Mean and median length of hospital stay
5. Change in VAS dyspnoea score from presentation to immediately before ED arrival
6. Mean change in EQ-5D-5L
7. Key elements of health-care resource use up to 30 days

This clinical data will be used to update the existing HTA meta-analysis and economic model, to determine the cost-effectiveness of prehospital CPAP given current evidence. The summary clinical outcome measures will also inform the design of any future definitive trial.

# 3. Trial Design

The ACUTE study is a stand-alone, randomised, parallel group, external pilot trial. The study design is summarised in Figure 1. The study will examine whether the research design and methods are sound, practicable, safe and feasible to proceed to a large scale definitive trial. An applicable effectiveness estimate and a more accurate incidence rate will be used to update an existing economic model and calculate a credible ENBS for a future trial.

One hundred and twenty patients presenting to ambulance paramedics with ARF will be individually randomised in a 1:1 ratio to one of two treatment arms, either CPAP or standard oxygen therapy, using sequentially numbered opaque equipment boxes. All boxes will be tamper-proof, equal in weight, and identical in appearance to maintain allocation concealment. The study population is described in **Section 5: Selection and withdrawal of participants.** Further information on randomisation and allocation concealment is provided in **Section 6: Randomisation and enrolment.**

The intervention arm will be treated with CPAP and supplemental oxygen. The control arm will receive standard oxygen therapy. Treatment in both arms will be targeted to BTS guidelines for peripheral oxygen saturations. Ancillary condition-specific treatments will be administered in both trial arms. These interventions are described in further detail in **Section 4: Trial treatments.**

Recruitment rate, adherence to the allocation schedule, data completeness and loss to follow up will be examined to assess the feasibility of progressing to a large-scale definitive trial. Patients will also be followed up to 30 days post enrolment with clinical outcomes of survival, critical care admission, endotracheal intubation, length of stay, change in dyspnoea score, quality of life and health resource use recorded. These secondary endpoints will assist in planning of the definitive trial summary estimates of effectiveness outcomes. Further information on the trial outcomes is provided in **Section 10: Statistical analyses.**

Data from the study (incidence of ARF and relative effectiveness estimate) will also be used to update an existing economic model of the cost-effectiveness of prehospital CPAP and estimate the expected value of sample information (EVSI) and ENBS for a definitive pragmatic trial of effectiveness and cost-effectiveness (Pandor 2014). Further information on the cost-effectiveness analysis is detailed in **Section 7. Ancillary sub-studies.**

Due to the physical differences between the CPAP device and standard oxygen mask it is not possible to blind patients, paramedics or hospital clinicians to the treatment arms. Outcome assessors will also not be blinded. However, both primary and secondary endpoints comprise ‘hard’ objective measurements, minimising the possibility of information bias. The randomisation sequence will be generated by a Sheffield CTRU Statistician who is not directly involved in the conduct of the trial. The Trial Statistician will not have access to the randomisation sequence until after data lock.

**Figure 1. Flow chart of participants through the ACUTE study [CONSORT DIAGRAM]**

Adults with acute respiratory failure presenting to paramedics within 4 hubs of the West Midlands Ambulance Service (WMAS)

**Source population**

**Study population**

**Random allocation**

**Follow up**

**Analysis**

**Not eligible**

**Not enrolled**

•Patients assessed for eligibility and enrolled by paramedics in participating WMAS regions

•120 patients recruited according to provisions of the 2005 Mental Capacity Act

•1:1 permuted block randomisation using sequentially numbered treatment boxes

**Individual Allocation to Control cxv**

60 patients

Standard oxygen therapy

**Individual Allocation to Intervention**

60 patients

CPAP and oxygen therapy using O\_two system

**Lost to follow up**

• 30 day Mortality

**Early clinical follow up**

•Baseline EuroQol-5D-5L

**30-day Follow Up**

•Mortality

•Endotracheal intubation

•Intensive care admission

•Hospital length of stay

•EuroQol-5D-5L

•Health resource use

**Feasibility Outcomes**

•Incidence of acute respiratory failure

•Proportion of patients: meeting inclusion criteria; correctly receiving allocation; with complete data; lost to follow up.

**Clinical Outcomes**

•Summary estimates of clinical effectiveness outcomes

**Updated Health Economic Model**

•Revised cost-effectiveness estimate using pilot incidence and effectiveness estimates

•Value of information analysis with expected net benefit of sampling

# 4. Trial treatments

Patients in the intervention arm will be treated by CPAP with supplemental oxygen. Patients in the control arm will receive standard oxygen therapy. Treatment in both arms will be targeted to BTS guidelines for peripheral oxygen saturations. Ancillary condition-specific treatments will be administered in both trial arms. Paramedics, ambulance technicians, paramedic practitioners, or critical care paramedics will deliver trial treatments.

**Intervention arm:** CPAP is a form of non-invasive ventilation where oxygen or air is supplied to the upper airways at increased pressure. This pressure remains constant throughout the respiratory cycle, typically between 2.5 to 12.5 cmH2O.

CPAP requires a device to generate increased pressure, deliver oxygen or air, and an interface appliance to allow administration. Delivery of increased pressure has a number of effects including: improved ventilation of collapsed areas of lungs; unloading inspiratory muscles and thereby reducing the work of breathing; and lowering the pressures (preload and afterload) against which the heart has to pump.

The ACUTE trial will use the O\_two unit, a lightweight, open, single use, low flow CPAP system. The device consists of an oxygen pipe, which is connected to an oxygen source (either a portable oxygen cylinder or the usual ambulance oxygen flow regulator), and an in-line CPAP unit connecting to a close-fitting face mask. The CPAP unit entrains ambient air to increase local mask pressure, providing resistance for the patient to breathe against. The level of CPAP is varied by altering the incoming oxygen flow rate. Thus the inspired concentration of oxygen varies according to desired degree of CPAP, as the flow rate is altered. As an open system, with access to ambient air, the device allows unrestricted inspiratory flows and is unaffected by respiratory rate.

CPAP will be administered to patients by paramedics after clinical assessment has confirmed acute respiratory failure and the absence of any contraindications to CPAP or exclusion criteria. Treatment may be commenced at the site of initial clinical contact or after transfer to an ambulance. An appropriately sized mask will be used. CPAP will then be commenced at 5cm H2O and then incrementally increased by 1cm H2O every 2-5 minutes to a maximum of 15cm H2O according to BTS peripheral oxygen saturation limits, measured by standard pulse oximetry. Target peripheral capillary oxygen saturations (SpO2) will be 88-92% for patients with known/suspected COPD and 94-98% for patients with other suspected causes of acute respiratory failure. If necessary, nebulizer treatments can be positioned between the facemask and the O\_two CPAP unit.

CPAP will be continued until arrival at hospital unless: not tolerated (e.g. patient request, claustrophobia, anxiety, significant agitation); patient unable to maintain own airway; decrease in systolic blood pressure to <90mmHg; vomiting; epistaxis; conscious level decreases and patient does not respond to voice; or suspected pneumothorax. Following use, the O\_two CPAP device will be discarded by standard waste disposal procedures for used clinical products.

**Control arm:** Oxygen will be delivered at normal atmospheric pressure from a compressed gas tank (or portable oxygen cylinder), via a flow regulator, to the patient using nasal cannula, an air entrainment ‘Venturi’ mask, a simple face mask, or a non-rebreathing reservoir face mask. Breathing higher inspired concentrations of oxygen increases the amount of oxygen carried in the blood and delivered to tissues, ameliorating the effects of respiratory failure. The exact choice of flow rate and oxygen delivery device will be determined according to the patient’s condition and is targeted to peripheral oxygen saturation levels. Target oxygen saturations will be 88-92% for patients with COPD, and 94-98% for other suspected causes of acute respiratory failure.

**Treatment common to both trial arms:** All patients will be placed on a cardiac monitor. Heart rate and SpO2 will be monitored continuously, respiratory rate and blood pressure will be monitored every five minutes consistent with current clinical practice

Paramedic guidelines (Fisher 2013) currently recommend additional specific management options for patients with suspected asthma or COPD including nebulisation of salbutamol and ipratropium bromide, intramuscular adrenaline and intravenous steroids. Sub-lingual glyceryl trinitrate and intravenous furosemide are recommended for acute heart failure.

On arrival at hospital emergency department staff will be informed of the study and current treatment. Patient care will then be transferred from paramedics to hospital clinicians according to normal practice. Care will subsequently continue according to hospital guidelines as implemented by the hospital clinician. In the intervention group the hospital clinician will determine whether to continue NIV using the O\_two unit, switch to an in-hospital system, or discontinue NIV altogether. Patients in the control group will be able to receive in-hospital NIV if indicated, according to assessment by the hospital clinician.

**Treatment compliance monitoring:** The following information will be recorded by research paramedics from ambulance service patient report forms:

* Level of CPAP and concentration of inspired oxygen
* Time of commencement, and duration of intervention and control therapies
* Treatment complications
* Use of ancillary treatments

**Training**

The West Midlands Ambulance Service (WMAS), O\_two representatives, and two research paramedics will provide training and support for all paramedics based at the participating ambulance hubs. This will involve training in identification of eligible patients, application of the inclusion criteria, providing appropriate information and seeking consent, randomisation, delivery of CPAP, monitoring for adverse events and data collection. Training will specifically focus on study exclusion criteria, particularly the identification of clinical conditions, e.g. pneumothorax or vomiting, where administration of CPAP could be harmful.

Training may include small group teaching; demonstration; hands-on familiarisation and scenario-based practice. In addition, an online video training tool demonstrating the use of the CPAP equipment will be made available to all paramedics. Only once a paramedic has received this training and has been assessed to be competent, will they be permitted to apply CPAP to patients as part of the study. Research paramedics will provide ongoing support and training as necessary, including training of new paramedics starting at ambulance hubs after recruitment to the study has begun.

# 5. Selection and withdrawal of participants

**Setting**

The study will take place in WMAS, which serves a mixed urban and rural population of 5.6 million. It employs approximately 4,000 staff across 5 divisions and operates from 15 'super-hubs', each covering 5-10 Community Ambulance Stations. Recruitment will take place across 4 super-hubs in 2 divisions covering a population of 1.5 million.

**Target population**

The target population will be adults transported to hospital by emergency ambulance with ARF. ARF may be caused by a number of different pathologies, the most common being exacerbation of COPD, asthma, acute heart failure and pneumonia. These pathologies may be difficult to distinguish in the prehospital setting, especially in older people with multiple comorbidities, and may co-exist. There is also no strong rationale for expecting that prehospital CPAP will be effective in one pathology, but ineffective in others. We therefore plan to recruit any patient with acute respiratory failure and only exclude those at significant risk of complications, such as pneumothorax, that could be worsened by prehospital CPAP. We will also not attempt to differentiate between type I (hypoxia alone) and type II (hypoxia and hypercapnia) respiratory failure since reliable identification of hypercapnia is not routine practice in the UK prehospital setting.

Potential participants will not be recruited if the anticipated time difference between being able to start prehospital CPAP on scene and being able to start in-hospital CPAP (in an acute hospital emergency department) is less than 15 minutes. In these circumstances the potential time saving from prehospital administration of CPAP is likely to be too small to produce meaningful benefit. It should be noted that this time difference includes time required for on scene management of the patient, transfer into the ambulance and transport to hospital, so it is only expected to be less than 15 minutes in exceptional cases.

We will place no upper age limit on eligibility but will not recruit those in whom critical care interventions may be inappropriate, such as those with terminal illness, advanced dementia or who have documented not for resuscitation status. Patients acutely incapacitated by ARF are likely to represent the most seriously ill patients with the greatest chance of benefit from pre-hospital CPAP. This subgroup will therefore be recruited in accordance with the UK Mental Capacity Act 2005.

**Inclusion/Exclusion Criteria:**

Inclusion and exclusion criteria will be based on paramedic judgement at the scene of incident. Acute respiratory failure will be defined as respiratory distress with peripheral oxygen saturation below BTS target levels (88% for patients with COPD, 94% for other conditions), despite supplemental oxygen (titrated low flow oxygen for COPD, or titrated high flow oxygen in other conditions).

Potential participants will be excluded if any of the following criteria are met:

1. Hospital CPAP treatment available within 15 minutes of eligibility.
2. Age < 18 years
3. Known to have terminal illness
4. Known pre-existing lack of capacity (confirmed by relatives, carers or documentary evidence, such as Lasting Power of Attorney)
5. Documented not for resuscitation status
6. Acutely incapacitated patients with known valid advanced directive declining non-invasive ventilation or participation in research
7. The patient has an oxygen alert card
8. Anticipated inability to apply CPAP (e.g. facial deformity)
9. Respiratory failure due to chest trauma
10. Contraindication to CPAP (suspected pneumothorax, respiratory arrest, epistaxis, vomiting, hypotension)
11. Previous enrolment in the ACUTE trial
12. Pregnancy
13. Patients unable to communicate with paramedics

**Consent procedures**

In accordance with the Declaration of Helsinki, UK Mental Capacity Act 2005, and GCP guidelines we plan to seek verbal consent if the treating paramedic determines that the patient is able to provide informed consent; and to proceed without consent if the treating paramedic determines that the patient is not able to provide consent. In either case a research paramedic will review the participant in hospital as soon as possible after enrolment, provide verbal and written information regarding the study, and seek written informed consent as soon as the participant has capacity. Each patient’s clinical care team will be initially approached by research paramedics shortly after admission (target within 24-48 hours) to ensure that it is an appropriate time to discuss consent. If the patient does not regain capacity we will seek advice from a Personal Consultee for enrolment in the trial. When a Personal Consultee is unavailable, a Nominated Consultee will be approached for a consent waiver. Paramedics are trained in the implication of the UK Mental Capacity Act 2005 and routinely assess capacity in their usual working roles. Research paramedics will receive additional training in obtaining informed consent for participation in research. We will confirm these consent arrangements with an independent NHS Research Ethics Committee (REC) prior to commencement of the trial. The consent arrangements for the ACUTE trial are summarised in Figure 2.

**Patients unable to communicate with paramedics**

Patients who are alert and may be expected to have capacity, but whom are unable to communicate with paramedics due to language or other barriers, will not be enrolled.

**Patients withholding verbal consent for inclusion**

Patients who decline to provide verbal consent to paramedics will not be enrolled.

**Patients withdrawing verbal consent for intervention**

If patients indicate that they no longer wish to receive pre-hospital CPAP the treatment will be stopped, standard oxygen therapy commenced, and the reason for discontinuation from intervention recorded. The patient would then be approached by a research paramedic for written consent for follow up at the earliest opportunity in hospital.

**Patients withholding written consent for follow up**

Patients providing verbal consent, or who are incapacitated, will undergo randomisation and will be enrolled in the study. Research paramedics will approach patients (or a personal or nominated consultee if the patient is incapacitated) for delayed written consent for further data collection shortly after admission to hospital. If patients (or their consultee) decline consent, all non-identifiable data up to the point of refusal will be retained. No further data collection will be conducted from this point onwards, except for anonymised 30 day mortality data.

**Patients withdrawing written consent for follow up**

Participants may withdraw from participation in the study at any time before their final follow up. In the unlikely event that a patient wishes to withdraw from follow up we will discuss any issues with the patient and explore their reasons for withdrawal. If they still wish to withdraw, non-identifiable data up to the point of withdrawal will be retained. No further data collection will be conducted from this point onwards, except for anonymised 30 day mortality data.

**Patients where obtaining written consent is not possible**

If it is not possible to obtain delayed written consent from a patient due to death prior to approach from paramedics we will collect anonymised 30 day mortality and clinical outcome data; and all non-identifiable data collected up to this point will be retained.

For patients discharged from hospital prior to an approach from research paramedics, we will attempt to contact patients by post and/or telephone asking for their permission to discuss the study and obtain written consent. We will then proceed according to the patient’s (or identified personal consultee’s) wishes. If we do not receive a reply, or are unable to contact the patient, we will collect anonymised 30 day mortality data and all non-identifiable data collected up to this point will be retained. To avoid distress to relatives we will check clinical records to ensure patients are still alive, prior to attempting contact.

**Patients with fluctuating capacity**

Participants may deteriorate after providing verbal and/or written consent, and subsequently lose capacity; or may regain capacity after being previously incapacitated:

* For patients who provide verbal consent and then lose capacity before giving written consent, nominated or personal consultees will be approached, as described above.

* In the contingency that a patient loses capacity after giving written consent, the existing consent will be considered to remain effective. Data collected up to the point of losing capacity will be retained and further follow up will continue as initially planned. If a personal or nominated consultee indicates that such an incapacitated patient should be withdrawn from the study in the 30 days post-randomisation, non-identifiable data up to the point of withdrawal will be retained. No further data collection will be conducted from this point onwards, except for anonymised 30 day mortality.
* Incapacitated patients enrolled by paramedics, and retained in the study after a consultee provides written consent, may later regain capacity within the 30 day follow up period. In this event research paramedics will contact the patient directly to obtain written consent to continue in the trial. Data collection will then proceed as per the patients’ wishes and details described above.

**Advanced directives**

Paramedics and research paramedics will adhere to the instructions of valid advanced directives in incapacitated patients.

**Lasting Power of attorney**

Paramedics and research paramedics will abide by the decisions of an attorney, where the donor has expressly stated in a valid Lasting Power of Attorney that they have the authority to make decisions about life-sustaining treatment. Research paramedics will identify personal consultees who have been appointed Lasting Power of Attorney where possible.

**Figure 2. Flow chart detailing consent procedures for the ACUTE study**



# 6. Randomisation and enrolment

**Randomisation method**

The Acute study will allocate patients with ARF to CPAP or standard oxygen therapy in a 1:1 ratio using simple, unrestricted, randomisation.

**Sequence generation**

The randomisation sequence will be computer generated by a Sheffield CTRU Statistician who is not directly involved in the conduct of the trial. The allocation sequence will be held centrally on a password-protected, access-restricted University of Sheffield network drive. The Trial Statistician will not have access to the randomisation sequence until after data lock.

**Allocation concealment**

CPAP devices and high concentration oxygen therapy masks will be packaged in identical equipment boxes measuring approximately 170mm x 170mm x 70mm. The boxes will be tamper-proof and equal in weight and appearance to maintain allocation concealment. Boxes can only be opened after a patient is definitively enrolled in the trial. Once a box is opened when attending a patient, that patient will be included in the study as per allocated treatment. It will not be possible to re-seal the box. Research paramedics and Sheffield CTRU will periodically check containers to ensure that seals have not been broken and that boxes have not been damaged.

**Implementation of allocation schedule**

Equipment boxes will be assembled, numbered and sealed centrally at Sheffield CTRU in accordance with the allocation sequence. The equipment boxes will be prepared by CTRU staff not directly involved in the conduct of the Trial, under the supervision of the Trial manager.

Boxes will then be transferred to the central WMAS storage and distribution centre where they will be held in an access restricted research store. Boxes will subsequently be supplied to participating ambulance hubs as required by the WMAS internal distribution team and held locally in a designated storage area. Logistic support technicians will then distribute equipment boxes to ambulances and first responder vehicles at the beginning of each clinical shift. At the end of the shift boxes will be returned to the ambulance hub equipment store. Boxes will be signed in and out for each shift with paramedic, ambulance, and equipment box details recorded in a distribution log. Together these processes will ensure concealment of the allocation sequence until treatment assignment occurs.

Research Paramedics will monitor the location of boxes, allocation concealment (i.e. boxes have not been tampered with), and adherence to the allocation schedule on a regular basis.

**Enrolment**

Paramedics will identify patients with ARF when attending 999 ambulance calls. Patients meeting trial inclusion criteria will be approached for enrolment in the trial, guided by a standardised script. If possible, verbal consent will be obtained for participation. Patients lacking capacity will be enrolled according to a hierarchical consent process complying with MCA 2005 and detailed in Section 5 and summarised in Figure 2. Immediately after inclusion, paramedics will open the trial equipment box and provide treatment according to whether a CPAP device or high concentration oxygen mask is supplied.

# 7. Ancillary sub-studies

**Health economics model**

A previously published meta-analysis and decision analysis model evaluating the cost-effectiveness of prehospital CPAP for acute respiratory failure will be updated (Pandor 2014, Thokala 2015). The key variable incorporated in the updated model will be the incidence of patients eligible for prehospital CPAP. This was shown to be a key determinant of the cost-effectiveness of prehospital CPAP, and the expected value of sample information for a definitive randomised trial.

The decision analysis model simulates the management, outcomes and costs of a hypothetical cohort of patients transported to hospital by emergency ambulance with acute respiratory failure. Full details are available at [http://www.journalslibrary.nihr.ac.uk/hta/volume-19/issue-42](http://www.journalslibrary.nihr.ac.uk/hta/volume-19/issue-42#abstract). Effectiveness is estimated in terms of short term mortality, using odds ratios from the meta-analysis, and valued as QALYs. Costs are estimated from a health service perspective and include all costs related to delivering prehospital CPAP and subsequent treatment of acute respiratory failure. The cost of providing prehospital CPAP is estimated by dividing the total cost of establishing and running the service across an ambulance service by the total number of patients treated.

The incidence of ARF patients proved difficult to accurately estimate and a wide range of values were identified. These were high (probably overestimates) when routine data were used to estimate the number with acute respiratory failure, and low (probably underestimates) when data from studies reporting actual use of prehospital CPAP were used. The ACUTE feasibility study offers an ideal opportunity to estimate the incidence of patients eligible for prehospital CPAP and to update the model with an estimate that is representative and applicable to the NHS. A literature search will also be conducted for new randomised controlled trials comparing prehospital CPAP to standard care; and if any are found, the meta-analysis will be updated along with effectiveness data from the ACUTE study.

The outputs of the model will be updated estimates of the cost-effectiveness of prehospital CPAP, expressed as the incremental cost per QALY gained by CPAP compared to standard care and the probability of CPAP being cost-effective at £20,000/QALY and £30,000/QALY thresholds for willingness to pay. Expected value of sample information (EVSI) and expected net benefit of sampling (ENBS) for a range of future randomised trial sample sizes will also be calculated. Extensive sensitivity analyses will be performed to explore decision uncertainty including examination of future scenarios where CPAP technology changes in cost or efficacy.

**Incidence of ARF**

The incidence of ARF will be estimated for the geographical areas served by the participating ambulance hubs. Ambulance service electronic patient report forms and computer aided dispatch records will be searched for presentations consistent with ARF over the trial recruitment period. Research paramedics will then judge whether the patient met trial inclusion criteria. Incidence rates will then be calculated from adult population figures according to national statistics e.g. Office for National Statistics census data.

**Accuracy of paramedic assessment of ARF**

Prehospital diagnosis of acute respiratory failure by paramedics will also be investigated in a diagnostic accuracy study. The index test will be paramedics’ initial recorded clinical impression of aetiology. The reference standard will be the final hospital discharge diagnosis. Sensitivity and specificity will be calculated with 95% confidence intervals.

**Acceptability of prehospital CPAP to paramedics**

Paramedics from participating ambulance hubs will be invited to complete a short, anonymous, web-based questionnaire to examine their experience of providing prehospital CPAP. Closed Likert scale questions will rate ease of use, satisfaction, and acceptability. Open questions will then explore barriers and enablers to providing pre-hospital CPAP, in more detail. The survey will be analysed using simple descriptive statistics and qualitative approaches. Ordinal Likert responses will be summarized using medians and relative frequency histograms. Text answers will be processed and coded, with subsequent identification of important themes.

# 8. Safety Reporting

**Background**

Adverse changes in the health of ACUTE participants will be defined, monitored, recorded and reported according to CTRU SOP PM004 and Health Research Authority guidance for non-CTIMP studies. Table 1 details the definitions used in the ACUTE study. Only adverse events (AEs) and serious adverse events (SAEs) related to trial interventions or procedures will be recorded and reported in the ACUTE study.

**Identification**

Adverse health changes that are related to the intervention, or trial procedures, will be identified by paramedics during delivery of trial treatments, by research paramedics’ review of medical records at 30 days, or by the study manager from the 30 day follow up questionnaire. Furthermore trial participants will be encouraged to inform the research team if they experience any adverse health changes until 30 days after joining the study; and local investigators will report any additionally identified adverse health changes. Adverse health changes will be identified and reported to the research team as AEs if there is any doubt as to whether they are related to trial treatments.

**Management**

All adverse health changes will be assessed and classified by an appropriately qualified member of the ACUTE research team, or local clinician, and reported to the CI. It is their responsibility to review all documentation (e.g. hospital notes, laboratory and diagnostic reports) related to the event and determine seriousness according to the definitions stated in Table 1. If the AE is classed as serious, an SAE report form must be completed by the ACUTE investigator and sent to the CTRU within 24 hours of its discovery. The CI will then review causality, severity and expectedness to determine whether the AE is related and/or is unexpected. The CI may not downgrade an event that has been assessed by a member of the research team as a SAE but can upgrade an AE to a SAE if appropriate. Additional information may be requested from local research team members, research site staff, or GP, at a later date.

**Documentation**

All identified related adverse health changes will be documented in the participant’s source medical records (if relevant), recorded in the relevant section of the patient case report forms (CRF), entered into the study database, and followed up until resolution. A SAE form will be completed for each identified SAE and signed by the CI. This will be kept in the trial master file and a copy sent to the research site for filing in the investigator site file. If further information is obtained at a later date regarding a SAE the SAE report form will be updated.

**Reporting**

Reporting requirements are dependent on the seriousness of the adverse health change and categorisation as expected or unexpected:

* Related AEs will be regularly reported in aggregate to the Trial Management Group (TMG), Trial Steering Committee (TSC) and Data Monitoring and Ethics Committee (DMEC) prior to each meeting; to the sponsor every 3 months; and to the REC in the Annual Progress Report, for instances where the AE has led to treatment failure. The following related AEs would be expected to occur and will not be reported: standard disease progression (e.g. reduced exercise tolerance, increased shortness of breath, infective exacerbation of COPD, exacerbation of congestive heart failure) or normal symptoms of underlying disease (e.g. wheeze, productive cough). Other related adverse events that would be reported include vomiting, nausea, pressure area damage, or claustrophobia.
* Related SAEs, will be reported in aggregate to the TMG, TSC and DMEC prior to each meeting; to the sponsor every 3 months; and to the REC in the Annual Progress Report for instances where the SAE has led to treatment failure. Possible expected related SAEs from CPAP administration could include: pneumothorax, aspiration, hypercapnia, progressive respiratory failure, or hypotension. The following SAEs would be expected to occur following ARF, and are being recorded as outcomes: death, hospitalisation, intubation and ventilation, admission to critical care.
* Unexpected SAEs related to trial interventions or procedures require expedited reporting. The trial manager will inform the sponsor and relevant NHS R&D department; and will also inform the REC and DMEC within 15 days of notification using the Health Research Authority (HRA) serious adverse event form.

Figure 3 summarises the safety reporting procedures. AE and SAE data will be reported to the trial governance groups and the Sponsor as aggregated data periodically. This will be monitored at management meetings and, if required, action in regards to safety will be decided. A DMEC will also monitor adverse event data and make recommendations to the Trial Steering Committee (TSC) on whether there are any ethical or safety reasons why the trial should not continue. As the study is ‘open label’, with all participants knowing which treatment is being administered, emergency un-blinding procedures are not required.

|  |  |
| --- | --- |
| **Adverse Health Change Terminology\*** | **Definition** |
| **Seriousness** |  |
| **Adverse Event (AE)** | An adverse change in health that occurs while a patient is taking part in a study |
|  |  |
| **Serious Adverse Event (SAE)** | Any adverse event occurring while a patient is taking part in a study, that results in:• Death• Life Threatening Illness• Hospitalisation • Prolongation of Hospitalisation• Disability or Incapacity• Congenital abnormality or birth defect• Other adverse health change resulting in inability to perform routine activities or significant medical event |
| **Causality** |  |
| **Unrelated** | An adverse change in health that occurs while a patient is taking part in a study which is not caused by or related to trial treatments.  |
| **Related** | An adverse change in health that occurs while a patient is taking part in a study, which is caused by or related to trial treatments. An AE or SAE is considered related if the relationship between the event and trial treatments is:• Possible - There is some evidence to suggest a causal relationship. However, the influence of other factors may have contributed to the event (e.g. the participant’s clinical condition, other concomitant treatments).• Probable - There is evidence to suggest a causal relationship and the influence of other factors is unlikely, or• Definite - There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.  |
| **Expectedness** |  |
| **Unexpected**  | Any adverse health change that is **NOT** consistent with the known and expected adverse events of trial treatments i.e. it is not listed in the protocol or related documents/literature as an expected occurrence. |
| **Expected** | Any adverse health change that **IS** consistent with the known and expected adverse events of trial treatments |
| **Severity\*** |  |
| **Mild** | An adverse health change that does not interfere with routine activities |
| **Moderate** | An adverse health change that interferes with routine activities |
| **Severe** | An adverse health change that makes it impossible to perform routine activities  |

**Table 1. Classification of adverse events** \*The term ‘severity’, is used to describe the intensity, and should not be confused with ‘serious’ which is based on participant/event outcome or action criteria. For example, a headache may be severe but not serious, while a minor stroke is serious but may not be severe.

**Figure 3. Flow chart detailing safety reporting procedures for the ACUTE study**

**ADVERSE CHANGE IN HEALTH OF ACUTE PARTICIPANT**

• Adverse change in health of ACUTE trial participant **related** to trial interventions/procedures

**IDENTIFICATION AND RECORDING**

• Identified by paramedics (pre-hospital), research paramedics (in-patient), or study manager (follow up questionnaire)

• Details recorded in:

•The patient’s medical notes

•The study CRFs

• The study database

**MANAGEMENT**

• All adverse health changes assessed and classified for relatedness and seriousness by an appropriately qualified member of the ACUTE research team.

•All AEs reported to the CI; SAEs recorded on SAE from and reported to CTRU within 24 hours.

• CI reviews causality, severity and expectedness.

**Related Adverse Event**

Reported in aggregate to:

 •REC (Annual Progress Report)\*

 •DMEC (Prior to meetings)

 •TSC (Prior to meetings)

 •Sponsor (3 monthly)

**Related Serious Adverse Event**

Reported in aggregate to:

 •REC (Annual Progress Report)\*

 •DMEC (Prior to meetings)

 •TSC (Prior to meetings)

 •Sponsor (3 monthly)

**Unexpected Related Serious Adverse Event**

Expedited reporting of individual SAEs within 15 days, using HRA SAE form, to:

 •Sponsor

 •WMAS or hospital R&D

 •REC

 •DMEC

**REPORTING**

• CI reviews causality, severity and expectedness.

\*Related AEs/SAEs resulting in treatment failure

**9. Assessments and procedures**

Ambulance service electronic patient report forms, emergency department information systems, and NHS Summary Care Records will be used where possible to ensure efficient data collection.

**Recruitment**

Paramedics and ambulance technicians at participating ambulance stations will encounter patients with ARF during routine practice and will be asked to consider them for enrolment in the ACUTE study. They will be trained on the study protocol and will also be provided with information indicating study inclusion and exclusion criteria. A standardised script, briefly describing the study and how to request verbal consent for inclusion, will be provided to guide recruitment of patients. A recruitment form (Case report form (CRF) A), contained within each equipment box, will be completed every time a patient is enrolled in the trial (or an electronic version of CRF A will be completed over the phone). This will record basic demographic details (non-identifiable), eligibility criteria, suspected pre-hospital diagnosis, study number, consent details, and limited clinical and treatment data not routinely recorded, including a patient and paramedic completed VAS dyspnoea scale (1-10) recorded on initial assessment and immediately before ED arrival.

**Feasibility, efficacy and safety parameters**

For recruited patients, routinely collected baseline characteristics, details of treatments provided and observations en-route to hospital will be extracted from the ambulance service patient report forms/electronic patient records into ACUTE case report form B (CRF B) by research paramedics. At 30 days, research paramedics will also review the hospital records to record details of subsequent progress, treatments provided (including time to receiving hospital NIV, if provided), length of hospital stay, use of critical care, any adverse events and status at 30 days. Any related AEs or SAEs will be recorded on the study case report form (CRF B).

Baseline quality of life assessments will be performed by research paramedics shortly after hospital admission, following confirmation of patient consent for participation in the trial. Patients, or their representatives, will be asked to estimate their current health status, using the EQ-5D-5L. This data will be recorded in the study case report form (CRF B). Quality of life and resource use will also be assessed remotely by questionnaire at 30 days following presentation. Participants will be asked for their preferred method for data collection; either telephone or postal mail. Initial non-responders will be contacted again after a further 2 weeks by telephone or mail. Key elements of health-care resource use to be recorded will include hospital services and GP or community services. Participants will also be asked to report any adverse events in the 30 day follow-up questionnaire.

For patients’ declining consent for follow up, or where it is not possible to contact the patient for consent, anonymised 30 day mortality will be recorded. Where a patient dies prior to confirming consent for follow up, anonymised 30 day mortality and clinical outcome data will be recorded.

**Ancillary studies data collection**

Research paramedics will screen routine data collected at regular intervals in ambulance service computer aided dispatch systems, ambulance patient report forms and routine emergency department data to identify potentially eligible patients that were not considered for recruitment. Paramedics will also be encouraged to contact the research team with the incident number of patients who decline verbal consent for enrolment in the trial. Anonymised details of age, sex, time, date, prehospital vital signs and respiratory support will be recorded on a missed recruitment form. No patient identifiable information will be recorded. This data collection will attempt to focus particularly on non-recruited patients who subsequently required NIV in the Emergency Department.

The final clinical diagnosis for each patient enrolled in the trial will be recorded in the case report form (CRF B) based on discharge summaries and clinical records.

Paramedics from participating ambulance hubs will be invited to complete a short, anonymous, web-based questionnaire, to examine their experience of providing prehospital CPAP. Closed Likert scale questions will rate ease of use, satisfaction, and acceptability. Open questions will then explore barriers and enablers in detail.

The assessments and follow up for the ACUTE trial are summarised in Table 2 and Figure 4.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **What** | **Where** | **Who** | **How** |  | **When** |  |
|  |  |  |  | **Baseline** | **Hospital admission** | **30 days** |
| **Consent Form** |  |  |  |  |  |  |
| •Verbal consent | Scene of incident | Paramedics | Verbal | X |  |  |
| •Written informed consent | Hospital | Research paramedic | Paper |  | X |  |
| **case report form A** |  |  |  |  |  |  |
| •Patient demographics | Scene of incident/ Emergency department | Paramedics | Paper  | X |  |  |
| •Patient characteristics |  |  | Telephone |  |  |  |
| •Prehospital treatments •Adverse events |  |  |  |  |  |  |
| **missed recruitment form** |  |  |  |  |  |  |
| •Patient demographics | Ambulance hub | Research paramedic | Paper |  |  | X |
| •Patient characteristics |  |  |  |  |  |  |
| **case report form B** |  |  |  |  |  |  |
| •Patient demographics | Hospital | Research paramedic | Paper |  | X | X |
| •Baseline quality of life  |  |  |  |  |  |  |
| •Inpatient treatments |  |  |  |  |  |  |
| •30 day mortality |  |  |  |  |  |  |
| •Intubation |  |  |  |  |  |  |
| •Critical care admission |  |  |  |  |  |  |
| •Length of stay•Adverse events |  |  |  |  |  |  |
| **Patient questionnaire** |  |  |  |  |  |  |
| •Quality of life | Home | Patient | Paper |  |  | X |
| •Resource use |  | Research paramedic | Telephone |  |  |  |
| •Adverse events |  |  |  |  |  |  |
| **Paramedic questionnaire** |  |  |  |  |  |  |
| •Acceptability of CPAP | Home / work | Paramedics | Electronic |  |  | X |
| **HRA SAFTEY REPORT FORM** |  |  |  |  |  |  |
| •Unexpected related serious adverse events | CTRU | Chief Investigator | Electronic | X | X | X |
| **SAE FORM** |  |  |  |  |  |  |
| •Other serious adverse events | CTRU | Chief Investigator | Paper | X | X | X |

**Table 2. Summary of data collection and trial documentation**



**Figure 4. Data collection processes**

\*Anonymised clinical outcomes also recorded for patients who die prior to confirmation of consent for follow up.

# 10. Statistics

**Sample size calculation**

The ACUTE feasibility study aims to recruit n=120 over 12 months. A minimum sample size of 120 was proposed by Teare (Teare 2014) for pilot studies with dichotomous outcomes, based on the precision to which binary parameters are estimated for use in the sample size calculation of the full trial. Mortality under standard care is estimated at 12% and for the full trial a 5% absolute reduction is postulated (i.e. to 7%) in the intervention arm. With n=120 we will therefore be estimated to within a standard error of 2.7% and used in the sample size calculation for the eventual trial. Given the short follow up period loss to follow up of <5% at 30 days is envisaged.

A previous evidence synthesis study produced estimates of the incidence of eligible cases ranging from 3.5 to 40.8 per 100,000 population per year. The lowest estimates were based upon actual patients treated with CPAP, in services with limited ability to deliver treatment for all eligible patients, and are likely to be underestimates. The highest estimates were based upon audit data for in-hospital NIV use among emergency admissions, and are likely to be overestimates. Assuming that there are 20 eligible cases per 100,000 population per year and 40% are recruited 120 patients will be recruited from the study’s source population of 1.5 million, over one year.

The sample size of n=120 will allow a determination of feasibility in the following ways:

1. Feasibility of recruitment: Recruiting 120 patients over 12 months from a population would show that a full trial recruiting n=1,508 could be achieved by recruiting over 30 months from a population of 7.5 million.
2. Inappropriate recruitment and allocation: Cases that were recruited in error will be identified and classified as major non-compliances if they represents a significant threat to trial validity or patient safety (e.g. recruitment of a patient with a pneumothorax) and a minor non-compliance if not. How often the allocated treatment was incorrectly given will also be recorded. Assuming the prevalence of each is ≤5% these parameters will be estimated with a precision of +/-2%.
3. Adherence to treatment (i.e. ability to tolerate CPAP): It is anticipated that 48/57 (84%) allocated to and initiated on CPAP will adhere to treatment, based on data from in-hospital CPAP use (Gray 2009). This will allow estimation of adherence to treatment with precision of <5%.
4. 30-day retention and data completeness: The 3CPO trial recruited patients with similar illness severity using a similar consent process and reported that 13/1069 withdrew by 30 days and 39/1069 refused retrospective consent, leaving 1017/1069 (95%) available for analysis. If this is reproduced in the ACUTE feasibility study, 30-day outcome data would be available for 114/120, again estimated to a precision of +/-2%.

The sample size will also allow determination of the cost-effectiveness of conducting a definitive trial. Recruiting 120 patients over one year from a population of 1.5 million would show that at least 8 per 100,000 population per year were eligible for prehospital CPAP. If this estimate of incidence of eligible patients is used in the existing CPAP economic model (Thokala 2015) the population EVSI for a trial enrolling 1500 patients is £3.6 million. If trial factors meant that only 40% of those likely to receive prehospital CPAP were recruited and the incidence of patients eligible for treatment was 20 per 100,000 population per year, then the population EVSI is £9.1 million.

**Statistical analyses**

Full details of planned analyses will be contained in an ACUTE trial statistical analysis plan (SAP), which will conform to Sheffield CTRU SOP ST001. Participant recruitment and retention will be presented with a CONSORT flow diagram. The following feasibility outcomes will then be reported descriptively for the whole trial population, together with their 95% confidence interval (calculated using the Wilson score method, Newcombe 1998):

1. Recruitment rate per 100,000 population per year (target 8, i.e. 120 across the 1.5 million population of the 4 WMAS hubs)
2. Proportion recruited in error and classified as minor or major non-compliances (target 0% and ≤10%)
3. Adherence to the allocation schedule (target ≥90%)
4. Adherence to treatment in the CPAP arm (target ≥75%)
5. Retention at 30 days (target ≥90%)
6. Data completeness (target ≥90%)

Summary estimates of effectiveness outcomes will also be reported, for the whole trial population and separately per treatment group, with 95% confidence intervals using an as randomised analysis:

1. Proportion surviving to 30 days
2. Proportion undergoing endotracheal intubation by 30 days
3. Proportion admitted to critical care at any point up to 30 days
4. Mean and median length of hospital stay
5. Change in VAS dyspnoea score from initial presentation versus immediately before ED arrival
6. Mean EQ-5D-5L
7. Key elements of health-care resource use up to 30 days

Anonymised data from eligible but non-recruited patients will be analysed descriptively and presented alongside data from those recruited, to explore whether a representative sample was recruited. If the study fails to meet the feasibility target for recruitment, the anonymised data will be analysed to determine whether failure reflected a lack of eligible patients or a failure of paramedics to recruit eligible patients.

The proportion of patients with COPD, asthma, cardiac failure, lower respiratory tract infection, or other diagnosis, together with the clinical outcomes, will be reported descriptively. These results will inform DMEC meetings, influence definitive trial inclusion criteria, and determine whether a future large scale trial should be powered for subgroup analyses.

# 11. Trial supervision

**Trial Steering Committee**

A Trial Steering Committee will be convened during study set up. This group will provide overall supervision of the ACUTE trial on behalf of the trial sponsor (University of Sheffield) and funder (National Institute of Health Research, NIHR). The TSC will ensure that the study is conducted according to principles of Good Clinical Practice (GCP), with specific tasks including:

* Approval of the study protocol
* Review of study progress
* Monitoring adherence to trial protocol
* Ensuring patient safety
* Consideration of new information relevant to the research question
* Scrutiny of protocol amendments and extension requests
* Recommend appropriate actions such as changes to the protocol, additional patient information, stopping or extending the trial.

The composition of the TSC is detailed in Table 3. The TSC will receive information from the Trial Management Group and the DMEC. TSC meetings will be convened by the CI approximately annually. Representatives of the trial sponsor and funder may also be invited to participate. The TSC chairperson will provide advice to the CI, sponsor (University of Sheffield), host institution (WMAS), and funder (NIHR). The TSC will have the power to prematurely close the trial if necessary due to safety concerns, futility, or convincing clinical effectiveness.

**Table 3. Composition of Trial Steering Committee**

|  |  |
| --- | --- |
| **TSC roles** | **DMEC roles** |
| **Members:** | **Members:** |
| Independent chair | Independent chair |
| Lay representative | Independent clinician |
| Independent trialist/statistician | Independent trialist/statistician |
| Independent paramedic |  |
| Independent clinician |  |
| Chief Investigators |  |
|  |  |

**Trial Management Group**

A Trial Management Group (TMG) will oversee day-to-day management of the ACUTE study, in accordance with CTRU SOP GOV001. Specific roles will include:

* Ensuring adherence with the trial protocol
* Ensuring ethical and GCP standards are met
* Monitoring data quality
* Developing and reviewing paperwork e.g. case report forms, patient information
* Responding to queries from the host institution
* Developing the trial protocol in response to operational challenges
* Review of results
* Dissemination of trial findings

The TMG will comprise the CI, study manager, co-investigators, trial statistician, research paramedics, data manager and lay representatives. The TMG will meet frequently during trial set up and approximately quarterly thereafter.

**Data Monitoring and Ethics Committee**

An independent DMEC will be organised during the study set up period in accordance with CTRU SOPs. The DMEC will review un-blinded comparative data and adverse event reports and will ensure that the safety, rights and well-being of trial participants are upheld throughout the ACUTE study. Specific roles will include:

* Approval of the study protocol
* Review and approval of the SAP
* Evaluate interim effectiveness data
* Review recruitment, compliance and loss to follow up rates
* Consider emerging evidence from relevant studies
* Advise the TSC on whether there are any ethical or safety reasons why the trial should not continue or protocol should be amended
* Advise the TSC on release of interim data

DMEC composition (Table 3) and conduct will be in accordance with CTRU SOP GOV003. An initial meeting will be held prior to the start of the trial and then approximately 6 monthly thereafter. No formal interim analyses are planned.

**Public and patient advisory group**

A public and patient advisory group will be enlisted for collaboration throughout the project. This group will be consulted on all aspects of study conduct, and help with specific tasks such as developing research materials and follow up questionnaires. The CI will liaise and mediate between the advisory group and the trial oversight groups, providing support where needed.

# 12. Data handling and record keeping

Pre-hospital information from CRF A may be reported by paramedics telephonically to the WMAS clinical operations centre after patient recruitment and treatment. This information may then be directly entered into the secure web-based CTRU study database (Prospect). A paper copy of CRF A will also be available inside each trial equipment box. GCP trained Research Paramedics will be responsible for local collection of consent, paper recruitment forms and questionnaires; and for completion of missed recruitment and case report forms. Research paramedics will also be responsible for ensuring records are stored appropriately and the information is transferred to the CTRU as necessary. Trial documents will be retained in a locked filing cabinet in a secure WMAS location during the trial. All study documents will be archived for a period of 5 years following the end of the trial. Copies of consent forms will also be stored securely at the University of Sheffield CTRU, by the Trial Manager.

Trial data will be extracted from source documents and CRF’s and entered onto the CTRU’s in-house data management system (Prospect). Prospect stores data in a PostgreSQL database on virtual servers hosted by Corporate Information and Computing Services (CiCS) at the University of Sheffield. The database uses industry standard techniques to provide security, including password authentication and encryption using SSL/TLS. Access to Prospect is controlled by usernames and encrypted passwords. A comprehensive privilege management feature ensures only the minimum amount of data required is revealed to complete tasks. The system has a full electronic audit trail and is regularly backed up. Validation reports will be run regularly to check the study data for completeness, accuracy and consistency. Discrepancies will be generated and managed to resolution. Output for analysis will be generated in a format and at intervals to be agreed between Sheffield CTRU and the CI.

Patient identifiable data (names, date of birth, and contact details) will only be collected and entered on the Prospect database when written informed consent has been confirmed. Access to these personal details will be restricted to users with appropriate privileges only. All users who do not require access to patient identifiable data will only access data by a unique participant ID number/study number, and no patient identifiable data will be transferred from the database to the statistician. All data will be collected and retained in accordance with the Data Protection Act 1998 and University of Sheffield CTRU SOPs.

Paramedic survey responses will be collected online using a quality-assured United Kingdom based survey company, utilising an encrypted internet server and registered with the Information Commissioner’s Office. Further information is available from: <http://www.smart-survey.co.uk/security>. Access to online responses is password protected, and will be available only to the research team. Additionally subjects will be provided with a unique participant number to use when completing the web-based survey, so no personal data is stored online. Results will be downloaded to a secure, password-protected and access-restricted area of the University of Sheffield network drive to allow analysis by the research team. This computer will contain a separate, additionally password protected file, matching each subjects name to their unique participant number. Data will be stored for the duration of the research project only and then deleted. Participants will be able to access submitted information according to UK data protection laws.

# 13. Data access and quality assurance

The study manager, data managers, CI, research paramedics and administrators will have access to anonymised data on the study database, through the use of usernames and encrypted passwords.

The Sponsor will permit monitoring and audits by the relevant authorities, including the Research Ethics Committee. The CI will also allow monitoring and audits by these bodies and the Sponsor, providing direct access to source data, CRF’s and all trial documents.

The CTRU data management system incorporates quality control to validate study data. Error reports, to be investigated by research paramedics to resolution, will be generated where data clarification is required.

The CTRU, Trial Manager, research assistant and the Data Management Team will work with research paramedics to ensure the quality of data provided. Data monitoring and audit will be conducted in accordance with the University of Sheffield CTRU SOP QU001 and DM009.

Anonymised data from the study will be made available to other researchers. Secondary use of the data for other research projects will be actively encouraged. The study consent form will include a statement affirming agreement with sharing anonymised data.

# 14. Publication and dissemination

The trial protocol will be submitted for open access publication and presented at relevant conferences. Results of the study and the updated economic model will be disseminated in high profile peer reviewed scientific journals and relevant academic conferences. Authorship will include funding co-applicants, research paramedics and the study manager, according to International Committee of Medical Journal Editors (ICMJE) guidelines.

Details of the trial, including regularly updated progress reports, will be available on a dedicated study website hosted by the CTRU. Plain English study progress reports will be provided to participants, patient advocacy groups, local PPI panels and our service user advisory group. Study developments will also be communicated through social media including twitter. The lay TMG member and service user advisory group will contribute to writing any scientific publications, particularly plain English summaries and conference presentations.

At the end of the study a report will be submitted to the trial funders with full details of study progress and study findings. It is anticipated that this report will be independently peer reviewed and the final accepted report published as a “gold” open access monograph in the *Health Technology Assessment* journal.

# 15. Finance

The study is funded by the NIHR Health Technology Assessment Programme (grant number 15/08/40). Details have been drawn up in a separate agreement.

# 16. Ethics approval

The trial will be conducted subject to a favourable opinion from a Local Research Ethics Committee (LREC), organised through the central National Research Ethics Service allocation system. An approval letter from the ethics committee, and approved copies of patient facing questionnaires, patient information and consent forms, will be registered with the CTRU before initiation of the study. Local research governance approvals will be sought from all participating research sites. This clinical trial will be conducted in accordance with Good Clinical Practice Guidelines and CTRU SOPs.

# 17. Regulatory approval

The O\_two CPAP device is CE-marked (CE0120) and will be used for its intended purpose, so prior approval from the Medicines and Healthcare products Regulatory Authority (MHRA) is not required. The ACUTE trial will be conducted in compliance with a predefined protocol, HRA approval, REC approval, Good Clinical Practice, CTRU SOPs, and the NHS research framework. Local research governance approvals will be sought from all participating research sites.

# 18. Indemnity / Compensation / Insurance

The ACUTE study is sponsored by the University of Sheffield. The University holds insurance covering liabilities arising from negligent harm caused by poor protocol design by the Chief Investigator and researchers employed by the University. The West Midlands Ambulance Service is covered by NHS indemnity for liabilities arising from clinical negligence, or other negligent harm to individuals taking part in the study where a duty of care is owed.

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