# RANDOMISED CONTROLLED TRIAL OF HOME MECHANICAL VENTILATION IN HYPERCAPNIC CHRONIC OBSTRUCTIVE PULMONARY DISEASE PATIENTS POST ACUTE HYPERCAPNIC EXACERBATION

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## Study Funding
The project is a true industry–academic collaboration with funding from two commercial partners (Phillips-Respironics & ResMed) as well as charitable sources (Guy’s and St Thomas’ Charity and the ResMed Foundation).

## Clinical Trials database registration
UKCRN – 8059  
Clinicaltrials.gov - NCT00990132  
ISRCTN28058693

## Summary
The study is designed to test the hypothesis that domiciliary non-invasive ventilation in patients who remain persistently hypercapnic following an acute exacerbation of COPD can delay time to readmission in the following 12 months. The trial is a randomised controlled trial of home mechanical ventilation versus home oxygen therapy in patients who remain persistently hypercapnic following an acute exacerbation of COPD. The primary outcome is admission free survival and the trial duration is 12 months. Secondary outcomes include exacerbation frequency, disease progression as measured by pulmonary function testing, arterial blood gases, exercise capacity, respiratory muscle strength and health related quality of life. The trial was conceived by the GMEC for COPD and is funded by commercial and charitable sources. The study aims to build on previous trial data in this important area and answer an important clinical question. The trial was deemed of sufficient importance to be accepted on to the UKCRN portfolio.

## Background
By 2020, chronic obstructive pulmonary disease (COPD) is expected to be the 3rd leading cause of
death in the world. COPD exacerbations are now the most common cause of medical hospital
admission in the UK (15.9% of hospital admissions) accounting for 707,488 bed days at a cost the
NHS of £253 million a year. Despite the improvements in survival by using non-invasive ventilation
(NIV) to treat patients with exacerbations of COPD complicated by acute hypercapnic respiratory
failure (AHRF), these patients are at high risk of re-admission and further life-threatening events. In
the United Kingdom, 5.9% of admissions to intensive care are the result of respiratory failure due to
COPD and this account for around 13,000 admissions per year with an in-hospital mortality of 49.4%.
Furthermore, in a recent study of 110 patients who had AHRF requiring NIV, at one year after
discharge 63% had another life-threatening event, and 49% had died. This is similar to the
applicants’ unpublished data from the South London area showing a 50% mortality rate at 339 days,
but with a re-admission rate of only 35%. Finally, severe acute exacerbations of COPD are now
recognised as an independent negative prognostic factor with mortality increasing with the frequency
of severe exacerbations. There is an urgent need to develop strategies to reduce the number and
severity of exacerbations of COPD.

In the 1970s a number of uncontrolled trials suggested benefits from domiciliary long term oxygen
therapy (LTOT) in patients with hypercapnic COPD. This led to the MRC LTOT trial, which reported that
LTOT improves 3 year survival from 30% to approximately 50%. However, benefits of LTOT were only
evident after 500 days from the start of the study and the early mortality observed was related to the
severity of patients’ baseline hypercapnia. This suggests that early intervention with long term
ventilatory support to reduce hypoventilation and hypercapnia may improve prognosis. Hypercapnia
may worsen with administration of LTOT and this may contribute to some of the early mortality in the
MRC LTOT trial.

In patients with chest wall disease and neuromuscular disease, home mechanical ventilation (HMV)
through a nasal or face mask has been found clinically to correct blood gases and improve survival. In
COPD, the data is less clear-cut. There have been a number of uncontrolled studies as well as 2 short
term cross-over trials and 1 short-term randomised controlled trial of the combination of NIV with LTOT,
compared to LTOT with and without sham ventilation in patients with hypercapnic COPD. These
studies are encouraging in that they have generally shown improvements in gas exchange, sleep
quality, exercise capacity and also quality of life, which does not improve with LTOT alone. A small
uncontrolled study of HMV in COPD patients, where follow-up was continued for two years after start of
ventilation, showed reductions in hospital admissions and general practitioner consultations with HMV.
Another study showed reductions in intensive care admissions. However, these benefits have not been
reproduced in all studies. One cross-over trial showed no benefit of NIV over LTOT, though patients
were only treated for two weeks with each intervention. This early data also suggested that patients
who showed benefit with respect to blood gases, were those with chronic hypercapnia, while
normocapnic patients showed no benefit.

There has only been one attempt at a large study to define outcome with HMV in COPD. An
international study was set up to investigate the longer term effects of NIV with LTOT in patients with
hypercapnic COPD. This study involved patients in various centres in 10 European countries with
erratic follow-up and no formal monitoring. Reports suggest no benefit after 3 years of therapy;
however, the study design had inadequate power for mortality as an end point, and there is generally
limited clarity in the dataset related to data collection and storage methods. Furthermore the levels of
pressure delivered by the ventilators in this study would be deemed low compared to our current
practice. Finally, the ventilatory companies have produced major technological advances in these now
portable lightweight ventilators, especially in terms of triggering system and pressure delivery. This
combined with the advance in interfaces has led to enhanced compliance with HMV.

Mechanism evaluation work also supports efficacy from HMV in COPD. We have recently shown that
HMV resets the central drive in COPD patients, and thus there is a greater ventilatory response for a
given level of carbon dioxide. Furthermore, in severe COPD a significant proportion (up to 60%) have
an increase in partial pressure of carbon dioxide (Paco2) of >1.3kPa and/or a pH decrease to <7.33
during LTOT. Patients with advanced COPD are prone to exacerbations and the more frequent and
severe the exacerbation history, the more likely the patient will require hospital admissions. Recent
research has shown that exacerbations not only promote decline in forced expiratory volume in one
second (FEV1), but also are a major driver of health status and mortality in COPD. HMV could
potentially reduce the frequency and severity of exacerbations by decreasing the associated
deterioration in gas exchange that occurs. Health related quality of life (HRQL) has been shown to

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correlate with exacerbation frequency in COPD, and it is likely that HRQL changes observed in the early studies with HMV are due to reduction of exacerbation and its consequences. There is no evidence that LTOT alone can reduce exacerbation or hospital admission. Therefore, treatment with HMV would aim to reduce frequency and severity of exacerbations leading to major health economic benefits.

**Hypothesis**

This study has an event-related outcome design and the primary outcome will be admission-free survival. The hypothesis of this study is that the HMV and home oxygen therapy (HOT) compared to HOT alone will reduce re-admission to hospital in COPD patients who remain persistently hypercapnic following an exacerbation requiring NIV.

**Importance of the Trial**

There is a need for a long term study of the effects of HMV in patients with hypercapnic COPD, as there is a considerable morbidity, and mortality with frequent hospital admissions associated with this condition. There are also an increasing number of referrals of patients with hypercapnic COPD to units specialising in ventilatory support for consideration of HMV, yet there is no good evidence for the long term effectiveness of this therapy. Data from the Eurovent study showed that over 20% of patients receiving HMV in the UK had COPD and this rises to over 50% in Italy. The overall percentage across Europe was above 30% which is in line with the data from the Lane Fox Respiratory Unit in South London and other UK units. Information is required on any predictive factors for improvement with HMV and on the relation between hours of use of HMV and outcome. There are currently over 86,630 patients on LTOT in the England and Wales, of which 61.8% (53,537) have COPD. Data has shown that up to 45% of patients on LTOT have a PaCO₂ above >6.5 kPa; thus it is estimated that up to 24,091 patients in the UK with COPD have hypercapnic respiratory failure.

**Trial Investigators & Centres**

The trial was initially devised with the support of the Global Medical Excellence Cluster for COPD and the trial was initiated in centres with established experience of both domiciliary NIV and clinical trials. The initial trial centres have been expanded in order to improve recruitment and ensure trial success.

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<tr>
<th>Hospital</th>
<th>Collaborators &amp; Local Principal Investigators</th>
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<tr>
<td><strong>Initial Trial Centres</strong></td>
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<tr>
<td>Guys &amp; St Thomas' Foundation Trust, King's College Hospital, King's College London</td>
<td>Dr Nicholas Hart, Professor John Moxham, Dr Rebecca Lyall, Professor John Weinman</td>
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<tr>
<td>Royal Brompton Hospital, Imperial College London</td>
<td>Professor Michael Polkey</td>
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<tr>
<td>Royal Free University Hospital, University College London</td>
<td>Professor Wisia Wedzicha, Dr John Hurst</td>
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<tr>
<td>Papworth Hospital, Cambridge University</td>
<td>Dr Ian Smith, Dr Nick Oscroft</td>
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<tr>
<td>John Radcliffe Hospital, Respiratory Clinical Trials Unit, University of Oxford</td>
<td>Professor John Stradling, Dr Annabel Nickol</td>
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<tr>
<td>St James' University Hospital, Leeds</td>
<td>Dr Mark Elliot, Mr Craig Armstrong</td>
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<tr>
<td>Aintree University Hospital NHS Foundation Trust, Liverpool</td>
<td>Dr Rob Angus, Dr Nick Duffy</td>
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<tr>
<td><strong>Subsequent Trial Centres</strong></td>
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<tr>
<td>Birmingham Heartlands Hospital</td>
<td>Dr Dev Banerjee, Dr Rahul Mukherjee</td>
</tr>
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<td>Swansea University Hospital</td>
<td>Prof K Lewis</td>
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<tr>
<td>Newport Hospital</td>
<td>Dr Sara Fairbairn</td>
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<tr>
<td>Health Psychologist, Kings College London</td>
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Trial Summary

Although HMV has been shown to improve physiological parameters as well as have clinical benefits in terms of dyspnoea and exercise capacity in severe COPD, the published randomised controlled trials have been less positive. The trial has been designed to robustly answer an important clinical question and is powered using UK data.

The trial involves 12 sites across the UK and is powered to recruit 116 patients (58 in each arm) with persistent hypercapnia following an episode of acute hypercapnic respiratory failure. During the acute hypercapnic episode the patient would have been eligible for non-invasive ventilation with a pH < 7.35 and a partial pressure of carbon dioxide (PₐCO₂) > 6.0kPa. They will be randomised, for a 12 months, to either

1. HMV and home oxygen therapy (Treatment Group)
2. Home oxygen therapy alone (Control Group)

This study would allow the investigators to answer a number of questions pertaining to clinical efficacy of HMV in COPD as well as the mechanism of action of HMV in COPD.

- Does HMV effect admission-free survival?
- Does HMV reduce exacerbation frequency?
- Does HMV impact on disease progression?
- Does HMV improve health-related quality of life?
- Does HMV improve exercise capacity?
- Is there a dose-response between hours of ventilator compliance and daytime PₐO₂ and PₐCO₂?
- Do patients increase hours of ventilator use during acute exacerbations?
- Is ventilator compliance with HMV and home oxygen acceptable?
- Does HMV reduce healthcare utilisation?

Follow-up assessments will be performed at 6 weeks, 3, 6 and 12 months. These data collected will include admission-free survival (primary outcome), hours of compliance with HMV, HRQL, gas exchange, lung function, body composition, exercise capacity, exacerbation frequency primary care consultations and compliance with home oxygen, time to withdrawal of home oxygen/night-time oxygen therapy based on daytime PₐO₂ and overnight SaO₂ (secondary outcome measures). The relation of any changes to factors predicting severity of COPD will be studied. The cost effectiveness and cost-utility analysis of HMV will be studied.

A schematic diagram of the trial is shown in the appendix A (study flow diagram).

Trial Interventions

There will be a control arm (home oxygen therapy) and a treatment arm (HMV). There is a potential risk that the treatment HMV arm will improve outcome as a placebo effect e.g. effect of the device itself (mask and non-invasive ventilator) will influence outcome through lifestyle and other changes. This concern is commonly stated in the design of device trials, although it may be overstated particularly in trials with a long follow-up and the meta-analysis comparing sham-continuous positive airway pressure (CPAP) therapy with best supportive care as trial comparator for the management of obstructive sleep apnoea (OSA) does not suggest a machine specific placebo effect. Furthermore, problems with differential placebo effects may also be decreased in this trial since home oxygen is a substantial intervention requiring to be administered for at least 15 hours daily (including overnight). As home oxygen is the standard treatment for hypoxic (and hypercapnic) respiratory failure in COPD, the investigators propose a two-arm comparison of home oxygen against HMV.

Enrollment of Patients

To enhance recruitment, we will identify patients during an acute hypercapnic exacerbation of COPD meeting the criteria for non-invasive ventilatory support. At least 2 weeks following normalisation of pH (pH>7.30), patients with persistent hypercapnic respiratory failure (PₐCO₂ > 7kPa) would be consented and recruited into the study. For safety, at the time of randomisation patients will be required to be free of ventilator use during the daytime and be requiring ≤6 hours nocturnal ventilatory support. All patients will have an overnight assessment on oxygen therapy and be excluded if acidosis develops (pH<7.30 ≥2 hours following waking). The patients would be randomised following informed consent at an assessment performed not more than 4 weeks following resolution of the exacerbation requiring NIV and or within 8 weeks of admission for the index exacerbation. Every effort will be made to answer all questions in full and where patients and/or their relatives decline enrolment into the study, the team will act positively and ensure that the care given will not be in any way compromised.

Inclusion Criteria

Patients with COPD
Acute hypercapnic exacerbation of COPD, with normalised pH (pH≥7.30) for at least 2 weeks
Chronic hypoxia requiring LTOT (P_{\text{a}O_2} <7.3kPa or a P_{\text{a}O_2} >7.3 and <8.0kPa and one of the following:
primary polycythaemia; nocturnal hypoxaemia SaO2 <90% for >30% of the time; peripheral oedema; or PHT)
Chronic hypercapnia (P_{\text{a}CO_2} ≥7kPa)
≥20 pack year smoking history
FEV1/FVC <60%
FEV1 <50% predicted

Exclusion
Persistent hypercapnic respiratory failure with acidosis (defined as pH <7.30 after bronchodilators)
Failure to wean from NIV as defined by requirement of daytime use or >6 hours of nocturnal use to maintain arterial pH≥7.30
Development of worsening hypercapnic respiratory failure with acidosis during initiation of home oxygen therapy (the subjects will be retained in the study and followed up and will be included in the adverse event monitoring)
Assessment more than 4 weeks from resolution of index exacerbation
Failure to tolerate NIV during the acute illness preceding trial identification
Post extubation or decannulation following AHRF requiring intubation
Primary diagnosis of restrictive lung disease causing hypercapnia i.e. obesity hypoventilation and chest wall disease, however these patients will be included if the FEV1/FVC ratio is ≤60% and the FEV1 <50% if the predominant defect is considered to be obstructive by the center clinician.
Clinical diagnosis of Obstructive Sleep Apnoea Syndrome felt to be contributing to patient morbidity
BMI >35kg/m²
Unstable coronary artery syndrome
Cognitive impairment that would prevent informed consent into the trial
Psychiatric disease necessitating anti-psychotic medication, ongoing treatment for drug or alcohol addiction, persons of no fixed abode post-discharge
Patients undergoing renal replacement therapy
Age <18 years
Pregnant
Inability to comply with the protocol

Allocating Patients and Protecting Against Bias
Participants will be allocated following inclusion and baseline assessment. Patients will be randomised to home oxygen or home oxygen and HMV from a computer model using a minimisation procedure to maintain balance within centres. The Oxford Respiratory Clinical Trials Unit will confirm eligibility over the telephone for recruitment into the trial. Randomisation details will also be held by the statistician. The allocated group will be confirmed by fax or e-mail.

Stratification variables

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<thead>
<tr>
<th>Variable</th>
<th>Stratification Level</th>
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<tr>
<td>Age</td>
<td>&lt;65 years, ≥ 65 years</td>
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<tr>
<td>BMI</td>
<td>≤20 kg/m² or &gt;20 kg/m²</td>
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<tr>
<td>Prior home oxygen</td>
<td>yes or no</td>
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<tr>
<td>COPD related admissions in previous 12 months</td>
<td>&lt;3 or ≥3</td>
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<tr>
<td>Participating centre</td>
<td>Treatment allocation</td>
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 ≥80% of the night. After randomisation, HMV and HOT and HOT alone patients will be admitted to hospital for 1-2 days, during which time the initial sleep study will be performed and HMV initiated in the treatment group, whilst the home oxygen alone group will receive education about the benefits of home oxygen. Previous studies on HMV in COPD have stressed the importance of commencing HMV as an in-patient to improve tolerance and compliance. All the assessments will be performed with standardised protocols and the exercise tests will be performed with standard instructions and where possible by technicians who will be kept unaware of the study group to which the patient has been allocated. Patients will also be asked not to disclose to which group they have been allocated during the assessments. Arterial blood gas measurements and lung function spirometric measurements will also be performed by the lung function technicians, who will be also be unaware of the study group allocation. All data will be recorded on standardised forms in each of the trial centres. A formal exercise programme will not be administered within 3 months of randomisation as recent evidence suggests that patients with chronic hypercapnia have severe disability and show a poor response to exercise training, in contrast to COPD patients with less disability. However, all patients will be given a standardised educational programme and information about the study. Analysis of the trial data will be on an intention to treat basis. Treatment with pulmonary rehabilitation will not be withheld in months 9-12 according to each centres standard practice.

HMV Set Up
The test treatment will be HMV using a pressure support (PS) ventilator for a period of at least 6 hours overnight in addition to the control treatment of daily home oxygen for at least 15 hours. The test treatment will be applied for a minimum period of 12 months. HMV will be administered through a nasal or full face mask depending on preference. Pressures will be titrated according to a standardised protocol during initiation to the maximal level that is tolerated by the patient. It is expected that this will result in a fall in transcutaneous carbon dioxide (max $T_{cCO_2}$) of 0.5-1.0 kPa. $T_{cCO_2}$ monitoring and oximetry overnight will be performed at baseline. The aim will be to keep overnight $S_{aO_2}$ between 88-92% by initially maximising ventilation, by IPAP to maximal tolerated, and then increasing the entrained oxygen flow rate. It is expected that the IPAP level will be ≥25 cmH2O. The back-up rate will be set between 12-14 breaths per minute depending on patient preference. EPAP will be set at 3-6 cmH2O.

HOT Set Up
As described above, $T_{cCO_2}$ monitoring and oximetry overnight will be performed during the set-up period. Overnight $S_{aO_2}$ will be maintained between 88-92% by increasing entrained oxygen flow rate. Special consideration will be given to the $T_{cCO_2}$ to ensure that the patients do not develop significant nocturnal hypercapnia (>2kPa rise in $T_{cCO_2}$). Early morning arterial blood gases measurements will be performed 2-4 hours after waking and if acidotic hypercapnic respiratory failure is demonstrated (pH <7.3), the patient will be excluded from the trial on safety grounds.

Proposed Duration of the Treatment Period
Patients will be enrolled over a period of 12 month period and followed up for 12 months. Longer term follow up will be conducted through the NHS information centre to monitor survival and all cause mortality.

Proposed Frequency and Duration of follow up
After baseline assessment, all patients will be asked to record daily symptoms on diary cards. Because patients randomised to receive HMV will require careful monitoring during the set up period to ensure ventilator acceptance and optimal adjustment of ventilator settings, all patients will receive a follow up telephone call 2 weeks after discharge. All patients will be reviewed at 6 weeks. Thereafter, patients will be seen at 3 months, 6 months and 12 months. At these visits, the patients will be assessed as per the measurements described in below.

Proposed Outcomes

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<tr>
<th>Proposed Outcomes</th>
<th>Primary Measures</th>
<th>Assessment</th>
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<tr>
<td></td>
<td>Admission free survival</td>
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<table>
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<tr>
<th>Proposed Outcomes</th>
<th>Secondary Measures</th>
<th>Assessment</th>
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<tr>
<td></td>
<td>Progress of Disease</td>
<td>Peripheral oedema Exacerbation frequency* Hours of daytime and nocturnal use of NIV during exacerbations Home oxygen use according to diary card Time to cessation of home oxygen based on BTS/NICE guidelines ($P_aO_2&lt;7.3kPa$ or a $P_aO_2$)</td>
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>7.3 and <8.0kPa and one of the following: secondary polycythaemia; nocturnal hypoxaemia SaO₂ <90% for >30% of the time; peripheral oedema; or PHT)

Adherence to treatment
Overall hours of compliance in HMV group
Daytime and nocturnal use of NIV
Comparison of hours of compliance according to internal clock on ventilator and diary cards

Health-related Quality of life, Breathlessness, Anxiety, Depression, Functional Independence/daily activities
SRI, SGRQ, Euroqol, MRC Dyspnoea score, Epworth sleepiness score

Lung function
FEV₁, FVC, TLC, RV, FRC, DLCO

Body composition measurements (bioelectrical impedance)
Height, Weight, BMI & FFMI

Arterial blood gas measurement/Full Blood Count (breathing room air)
PaCO₂ PaO₂ pH HCO₃⁻ Haematocrit

Exercise Capacity
ISWT (including Borg score at start and end of test)

Daytime activity & sleep disruption
Actigraphy / accelerometry

Hospital Admissions
Hospital re-admissions, ICU admissions, HDU admissions, length of hospital stay; episodes of decompensated AHRF

Survival
All-cause mortality

Healthcare utilisation
Exacerbation frequency, visit frequency to GP, number of courses of antibiotics, number of courses of steroids, cost of oxygen supplementation

Ventilator Settings & home oxygen use
Recording of IPAP and EPAP settings
Diary cards for home oxygen

Physiological Measurements
TLC, FRC, IC and HCVR**

*Exacerbation frequency to be measured by diary card using definition used in the London COPD Cohort; FEV₁ = forced expiratory volume in 1 second; FVC = forced vital capacity; BMI = body mass index; fat free mass index; PaCO₂ = arterial carbon dioxide tension; PaO₂ = arterial oxygen tension; HCO₃⁻ = bicarbonate level; ISWT = incremental shuttle walk test; IC = inspiratory capacity; SRI = severe respiratory insufficiency questionnaire; CDRQ = chronic respiratory questionnaire; ADL = activities of daily living; AHRF = acute hypercapnic respiratory failure; TLC = total lung capacity; FRC = functional residual capacity; HCVR = hypercapnic ventilatory response; **Only be performed in 3 centres (Royal Brompton Hospital, St Thomas’ Hospital and Kings College Hospital)

Addendum
Consultations with general practitioners, extra out-patients visits and hospital admissions will be recorded on the case record forms. In addition to all cause hospital admissions COPD-related admission will be also analysed as a secondary endpoint. All diary cards will be sent to the trial co-ordinator at monthly intervals, so that reported and unreported exacerbations, information on hospital admissions and GP visits can be confirmed. The reason for the hospital admission will be noted. The NHS Information Centre will provide mortality data (e.g. cause of death, date of death) and track patients who move area. Quality of life scores questionnaires will be administered at baseline, 6 weeks, 3, 6, 12 months. Arterial blood gases will be measured with the patient self-ventilating on air and after 30 minutes of oxygen therapy at a flow rate to correct the SpO₂ to >90% with repeated measures until the PaO₂ is above 8kPa. Spirometry will be measured after use of the short-acting bronchodilators. TₐCO₂ monitoring and oximetry overnight will be performed at baseline only in each of the groups. Compliance with home oxygen and HMV will be assessed from diary card records and from meter readings on the equipment, both ventilators and oxygen concentrators. Any adverse effects relating to the treatment with HMV or home oxygen will be noted on case report forms. Specific questions relating to any possible side effects will be asked at all follow up assessments.

Health economics & Health Status
If the trial shows a clinical benefit, it will be important to know if the addition of HMV in patients with hypercapnic COPD represents an optimal use of medical resources. Any additional health benefits have to be judged against the costs of resources required to produce them. The trial will include an analysis of the incremental cost-effectiveness and cost-utility analysis of the two study treatments; HMV with home oxygen and home oxygen therapy alone. Data regarding health economic costs will be obtained on an on-going basis by the research team. The main end-point in the cost-effectiveness
analysis will be cost per admission avoided. Costs will include analysis of the equipment costs, maintenance and support costs for the HMV, analysis of medical, nursing and support staff and all hospital admissions. Cost-effectiveness and cost-utility acceptability curves will be analysed on the basis of a simulation exercise in order to represent the uncertainty surrounding these ratios. Health-related quality of life will be measured using a number of validated questionnaires and this will be overseen by John Weinman, Professor of Psychology as Applied to Medicine, Kings College London.

**Sample Size**

Current data from the Leeds COPD NIV Cohort (similar to the British Thoracic Society National COPD Audit) showed that 50% of patients receiving NIV for acute hypercapnic respiratory failure were re-admitted by 32 days with a mean time to re-admission of 70 days, assuming this has risen to 55% by 1 year, then based on 80% power, a two-sided type I error rate of 5% and assuming a reduction from 55% to 25% at one year, with a 22% loss to follow up, a total of 116 patients are required randomized on a 1:1 basis (based on logrank test).

**Planned Recruitment Rate**

The Lane Fox Respiratory Unit, 2007-2008, initiated 25 patients with COPD on HMV. There would be a similar number expected to be recruited from the other centres. If the refusal and non-suitability rate is approximately 50%, then each site would expect to recruit 1 patient per month. Initial projected recruitment time would be 12 months with a further 12 months for follow up. Due to slower than expected accrual rates the number of trial sites have been expanded and the recruitment target is now 1 patient per site every 2 months providing for trial completion by December 2013 (see appendix E).

**Analysis of the Data**

The primary outcome is to evaluate admission free survival with comparison between HMV and HOT and HOT alone. This data will be analysed by time to event analyses using the log rank test with Kaplan Meier plots; adjustment for potentially important baseline factors will be made using the Cox's proportional hazards model. Adjustment for baseline covariance will be made. Repeated measures analysis of variance, area under the curve and non-parametric analyses will be used to analyse the changes in arterial blood gases, exercise tolerance and quality of life scores. Changes in outcome measures will be taken as changes from baseline. Duration of hospital admissions will be analysed by the t test, or the appropriate non-parametric equivalent.

**Safety Measures**

As described earlier, we will exclude patients with persistent hypercapnic respiratory failure with acidosis (pH <7.3) at 2 weeks post index admission or are unable to wean from NIV. Patients who develop worsening hypercapnic respiratory failure with acidosis (pH <7.3) during HOT initiation, will be withdrawn from their randomised treatment, but retained in trial follow-up. Patients who have failed to tolerate NIV during acute illness and patients requiring intubation with tracheostomy formation due to failed NIV during the acute exacerbation will also be excluded. We will monitor patients at 6 weeks, 3 months, 6 months and 12 months. Patients randomised to HOT will not be precluded from use of NIV during acute exacerbations. It will be expected that patients will be discharged back on to HOT unless they breach the trial safety criteria.

**Potential recruitment sites**

Due to the need to ensure full recruitment to prevent under powering of the study, and the subsequent potential of missing a clinically important result, recruitment will be assessed at 3 monthly intervals by the trial steering committee. If it is felt that the recruitment is insufficient to complete the trial in an adequate timeframe then further sites will be approached to participate.

**Trial Committee**

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Independent members: Dr Steve Banham; Dr Martin Allen

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Expert: John Wort
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REFERENCES


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Meecham Jones DJ, Paul EA, Jones PW, Wedzicha JA. Nasal pressure support ventilation plus oxygen compared with oxygen therapy alone in hypercapnic COPD. Am J Respir Crit Care Med 1995; 152: 538-44.

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Appendix A - HMV in COPD Study flow chart

Treatment standardised

Screening PaCO₂ > 7 kPa 2 weeks post acute hypercapnic exacerbation of COPD

Admission - Initial assessments & diagnostic sleep study

Randomised

Titration sleep study

Assessments

HOT

HMV + HOT

Follow up at 6 weeks, 3 months, 6 months & 12 months

Primary Outcome
Admission free survival

Secondary Outcome
Compliance with NIV
HRQL
PaCO₂, PaO₂, pH, HCO₃⁻, Lung Function Tests
BMI, FFM, ISWT, HCVR
COPD-related hospital admissions
Compliance with LTOT
Withdrawal of LTOT (PaO₂ > 8 kPa)
Courses of antibiotics
Courses of steroids

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## Appendix B - HMV in COPD Study Plan

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<td>Pulmonary Physiology</td>
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</table>

### Testing required for protocol

- X

### Testing optional or site specific

- X

### Test not performed at visit
HMV in COPD study measures

- **Anthropometrics**
  - Weight, height, body mass index, fat free mass index

- **Clinical Assessment**
  - Diary card review noting the exacerbation frequency, medication changes, unscheduled care visits and symptom changes
  - Patient assessed for signs of peripheral oedema
  - Assess to ensure LTOT cannot be withdrawn

- **Arterial Blood Gases**
  - $P_aCO_2$, $P_aO_2$, $HCO_3^-$, pH, Hct

- **Spirometry / lung function**
  - FEV$_1$, FVC
  - Lung volumes, transfer factor

- **Respiratory Sleep Studies**
  - Oximetry and capnography
  - Embletta (optional)

- **Exercise Capacity**
  - Incremental shuttle walk test with Borg score at beginning and end

- **Health Related quality of life**
  - Severe respiratory insufficiency (SRI) questionnaire, Euroqol, St George’s Respiratory Questionnaire, MRC dyspnoea score

- **Compliance**
  - Patient reported compliance and ventilator data card

- **Actigraphy**
  - Accelerometry measurement of sleep disruption and daytime activity

- **Venous blood sampling**
  - FBC, Iron, Iron binding capacity, Ferritin, CRP, BNP
  - For storage to allow for future studies of genetic factors contributing to hypercapnic COPD and biomarkers for assessment of prognostic value

- **Pulmonary Physiology**
  - MIP, MEP, SNIP
  - FRC, TLC, IC, hypercapnic ventilatory response, respiratory muscle testing and PEEP
Appendix C - HMV in COPD initial assessment protocol

Screening
- Conducted 2 weeks post normalization of pH following an acute exacerbation
- If patient meets criteria obtain consent and arrange admission ASAP (minimum 2 night stay)

Baseline admission
- Recheck inclusion & exclusion criteria
- Perform baseline investigations
  - Anthropometrics
  - ABG
  - Lung function
  - Clinical assessment
  - HRQL
  - Exercise test
- Daytime HOT assessment
  - If PaO$_2$ <7.3 kPa or <8 kPa & one of the following secondary polycythaemia; nocturnal hypoxaemia SpO$_2$ <90% for >30% of the sleep time; peripheral oedema; or PHT
  - Oxygen administer at lowest flow rate able to improve PaO$_2$ >8 kPa
- If PaO$_2$ >7.3 kPa but <8 kPa and does not meet criteria for HOT then overnight oximetry & capnography performed on air to establish need for HOT on basis of nocturnal hypoventilation (SpO$_2$ <90% for >30% of the sleep time)
- If patient does not require HOT then discharge with standard care, otherwise continue with protocol
- Sleep study
  - Diagnostic oximetry & capnography performed with patient on prescribed oxygen treatment flow rate
  - ABG performed 2-4 hours after waking
  - Patient excluded if significant acidosis detected (pH <7.3)
- Randomisation
  - Contact Oxford Clinical Trials Unit for treatment allocation

Oxygen therapy arm
- Sleep study
  - Diagnostic oximetry & capnography performed with patient on prescribed oxygen treatment flow rate
  - ABG performed 2-4 hours after waking
  - Patient excluded if significant acidosis detected (pH <7.3)
- Ensure treatment standardized & baseline assessments performed
- Perform patient education to ensure adequate understanding of treatment and use of oxygen
- Book 6 week assessment

NIV treatment arm
- Set up NIV during daytime for patient familiarization
  - Chose mask according to local protocol
  - Entrain O$_2$ at daytime flow rate
  - Start pressures - Ipap 18cmH$_2$O, Epap 4cmH$_2$O
  - Titrate pressures aim Ipap ≥25cmH$_2$O without inducing intolerance
  - Small rise in Epap (max 6cmH$_2$O to treat upper airway obstruction if present)
- Repeat sleep study after establishing treatment
  - Aim for treatment to reduce peak (or rise in) TcCO$_2$ overnight by >0.5kPa & SpO$_2$ 88-92%
  - Treatment titration according to local protocol to reach stated treatment aims, an example titration protocol is included for reference
- Ensure treatment standardized & baseline assessments performed
- Perform patient education to ensure adequate understanding of treatment and use of oxygen
- Book 6 week assessment
**Appendix D - Flow chart for initial assessment pre-randomisation**

1. **Patient receiving (or eligible for) NIV for acute hypercapnic exacerbation of COPD**

   - **Persistent Acidosis (pH<7.3)**
   - Daytime NIV use > 2 weeks after acute initiation
   - > 6 hours/night NIV use > 2 weeks after acute initiation

   - **Exclude**

2. **Meets preliminary criteria**

3. **Patient screening 2 weeks post normalisation of pH**

4. **Does not satisfy inclusion/exclusion criteria**

   - **Exclude**

5. **Meets inclusion/exclusion criteria**

6. **Admission ABG**

   - **PaO₂ 7.3 - 8 kPa**
   - **PaO₂ < 7.3 kPa**

7. **Diagnostic sleep study on air**

   - SpO₂ < 90% for > 30% TST

   - **Excluded**

8. **Daytime oxygen assessment**

   - **SpO₂ < 90% for > 30% TST**

9. **Sleep study on oxygen**

10. **Daytime ABG - 2-4 hours post waking**

   - **pH < 7.3**

11. **Randomisation**

   - **pH < 7.3**

*Note - All patients screened should be consented and data retained for data analysis whether the patient is excluded or randomised in order to comply with...*
HOT HMV

(A phase 3, open label, randomised, controlled clinical trial comparing home oxygen therapy and home mechanical ventilation to home oxygen therapy in hypercapnic chronic obstructive pulmonary disease patients post-acute hypercapnic exacerbation)

Registration: NCT00990132 (ClinicalTrials.gov)
ISRCTN: 28058693
UKCRN: 8059

PRIMARY SAFETY STATISTICAL ANALYSIS PLAN
Version 1.0

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1. **BACKGROUND AND DESIGN**

The main characteristics of this trial have been summarised using HOT HMV Protocol Version 13.0 (1 August 2011). Please refer to this protocol for full details.

1.1 Trial summary

By 2020, chronic obstructive pulmonary disease (COPD) is expected to be the 3rd leading cause of death in the world. COPD exacerbations are now the most common cause of medical hospital admission in the UK (15.9% of hospital admissions) accounting for 707,488 bed days at a cost the NHS of £253 million a year. Despite the improvements in survival by using non-invasive ventilation (NIV) to treat patients with exacerbations of COPD complicated by acute hypercapnic respiratory failure (AHRF), these patients are at high risk of re-admission and further life-threatening events. In the United Kingdom, 5.9% of admissions to intensive care are the result of respiratory failure due to COPD and this account for around 13,000 admissions per year with an in-hospital mortality of 49.4%. Furthermore, in a recent study of 110 patients who had AHFR requiring NIV, at one year after discharge 63% had another life-threatening event, and 49% had died. This is similar to the applicants’ unpublished data from the South London area showing a 50% mortality rate at 339 days, but with a re-admission rate of only 35%. Finally, severe acute exacerbations of COPD are now recognised as an independent negative prognostic factor with mortality increasing with the frequency of severe exacerbations. There is an urgent need to develop strategies to reduce the number and severity of exacerbations of COPD.

HOT HMV is a phase III open label, prospective randomised, controlled clinical trial that will compare home oxygen therapy (HOT) with home mechanical ventilation (HMV) and home oxygen therapy in patients with hypercapnic chronic obstructive pulmonary disease post-acute hypercapnic exacerbation. The primary outcome measure is admission-free survival, defined as time to hospital admission or death.

1.2 Patient eligibility criteria

**Inclusion Criteria**

1) Patients with COPD
2) Acute hypercapnic exacerbation of COPD, with normalised pH (pH≥7.30) for at least 2 weeks
3) Chronic hypoxia requiring LTOT (P_aO_2 <7.3kPa or a P_aO_2 >7.3 and <8.0kPa and one of the following: secondary polycythaemia; nocturnal hypoxaemia SaO2 <90% for >30% of the time; peripheral oedema; or PHT)
4) Chronic hypercapnia (P_aCO_2≥7kPa)
5) ≥20 pack year smoking history
6) FEV_1/FVC <60%
7) FEV_1 <50% predicted
1) Exclusion criteria

2) Persistent hypercapnic respiratory failure with acidosis (defined as pH < 7.30 after bronchodilators)

3) Failure to wean from NIV as defined by requirement of daytime use or >6 hours of nocturnal use to maintain arterial pH ≥ 7.30

4) Development of worsening hypercapnic respiratory failure with acidosis during initiation of home oxygen therapy (the subjects will be retained in the study and followed up and will be included in the adverse event monitoring)

5) Assessment more than 4 weeks from resolution of index exacerbation

6) Failure to tolerate NIV during the acute illness preceding trial identification

7) Post extubation or decannulation following AHRF requiring intubation

8) Primary diagnosis of restrictive lung disease causing hypercapnia i.e. obesity hypoventilation and chest wall disease, however these patients will be included if the FEV₁/FVC ratio is < 60% and the FEV₁ < 50% if the predominant defect is considered to be obstructive by the center clinician.

9) Clinical diagnosis of Obstructive Sleep Apnoea Syndrome felt to be contributing to patient morbidity

10) BMI > 35 kg/m²

11) Unstable coronary artery syndrome

12) Cognitive impairment that would prevent informed consent into the trial

13) Psychiatric disease necessitating anti-psychotic medication, ongoing treatment for drug or alcohol addiction, persons of no fixed abode post-discharge

14) Patients undergoing renal replacement therapy

15) Age < 18 years

16) Pregnant

17) Inability to comply with the protocol

1.3 Trial intervention

1.3.1 Intervention

Patients will receive home oxygen therapy (HOT) or home oxygen therapy plus home mechanic ventilation (HMV). The HOT intervention involves breathing higher than atmospheric concentrations of oxygen from a cylinder or machine at home for at least 15 hours on a daily basis. The HOT HMV intervention involves using a pressure support ventilator for a period of at least 4 hours overnight in addition to the daily home oxygen therapy for at least 15 hours. HMV will be administered through a nasal or full face mask, depending on the patient preference.

1.3.2 Randomisation

Eligible patients will be randomised in the ratio 1:1 by using a web-based randomisation system held at the Oxford Respiratory Clinical Trials Unit. Randomisation will be done...
using minimisation by the following criteria:

- Age (<65 years vs. ≥65 years)
- Body mass index (BMI; ≤20kg/m² vs. >20 kg.m²)
- Prior home oxygen use (yes vs. no)
- COPD related admissions in previous 12 months (<3 vs. ≥3)
- Centre of recruitment

Patients will be randomised to receive one of the following treatment arms:

- Home oxygen therapy (HOT; control)
- Home oxygen therapy plus home mechanical ventilation (HMV)

2. OUTCOME MEASURES

The primary outcome measure for this trial is admission free survival, up to 12 months. Secondary outcomes include all-cause mortality, efficacy measures and serious adverse events. The research arm will be compared against the control arm. All analyses will be performed using Stata version 13.0 or later unless otherwise stated.

2.1 Primary outcome measure

**Admission free survival, up to 12 months**

Admission free survival is defined as the time from randomisation to hospital admission or death.

2.2 Secondary outcome measures

**Efficacy measures**

- All-cause mortality up to 12 months
- Proportion of patients with respiratory related admissions
- Acute exacerbation of COPD frequency summarised as:
  - Proportion of patients with exacerbation(s) resulting in hospitalisation
  - Proportion of patients with exacerbation resulting in physician directed treatment
  - Proportion of patients with exacerbation resulting in self-management
  - Sub-clinical exacerbation resulting in no treatment change
- Change in arterial partial pressure of carbon dioxide (PaCO₂) at week 6 and at 3, 6 and 12 months
- Change in arterial partial pressure of carbon dioxide (PaO₂) at week 6 and at 3, 6 and 12 months
• Change in severe respiratory insufficiency questionnaire (SRI) at week 6 and at 3, 6 and 12 months
• Change in St George’s respiratory questionnaire (SGRQ) at week 6 and at 3, 6 and 12 months
• Change in 4% ODI at day 0, on allocated treatment and at 6 and 12 months
• Change in mean SpO2 at day 0, 6 and 12 months
• Change in total sleep time <90% at day 0, 6 and 12 months
• Change in mean TcCO2 at day 0, 6 and 12 months
• Change in max TcCO2 at day 0, 6 and 12 months

Serious adverse events (SAEs)

• Proportion of patients with a serious adverse event

3. SAMPLE SIZE

Current data from the Leeds COPD NIV Cohort (similar to the British Thoracic Society National COPD Audit) showed that 50% of patients receiving NIV for acute hypercapnic respiratory failure were re-admitted by 32 days with a mean time re-admission of 70 days. Assuming this is higher by 1 year, say 55%, then based on 80% power, a two-sided type I error rate of 5% and assuming a reduction from 55% to 25% at one year, with a 22% loss to follow up, a total of 116 patients are required (based on log rank test). There would be 83% power if the loss to follow up was 15% and 86% power if the loss to follow up was 5%.

4. OUTCOME ANALYSIS

Analysis principles

All outcomes will be analysed for superiority. All superiority analyses will be two-sided and considered statistically significant at the 5% level. All analyses will be adjusted for the minimisation variables (age, BMI, prior home oxygen use, COPD related admissions in previous 12 months) with the exception of centre, due to potential over stratification, unless otherwise stated.

4.1.1 Primary outcome

Admission free survival

Admission free survival will be analysed by intention-to-treat (ITT), and will include all randomised patients on whom an outcome is available.

4.1.2 Secondary outcomes

All secondary outcomes will be analysed using ITT, and will include all randomised patients on whom an outcome is available.
4.2 Primary outcome

4.2.1 Admission free survival

Admission free survival, defined as time from randomisation to hospital admission or death, will be analysed using a Cox regression model, censoring for loss to follow up to estimate the hazard ratio. The analysis will be adjusted for the minimisation variables. In conjunction to this, the unadjusted hazard ratio will also be presented.

Time will be taken from the day of randomisation to hospital admission or death, whichever event occurs first. If admission to hospital does not occur and death does, time will be taken from day of randomisation to death. If neither event occurs, then time will be taken from day of randomisation to the last known follow up visit. If withdrawal occurs prior to death, time will be taken from the day of randomisation to day of withdrawal.

A repetition of the primary analysis will be done adjusting for centre to check the consistency of results.

4.3 Secondary outcomes

4.3.1 Efficacy measures

All-cause mortality

All-cause mortality up to 12 months will be analysed using a Cox model. Due to potential over stratification, the analysis will not adjust for centre, but will adjust for other minimisation variables. In addition to this, the unadjusted hazard ratio will also be presented.

Exacerbation frequency

The number of patients that experience one or more exacerbations resulting in hospitalisation will be presented descriptively, but no formal analysis will be performed.

The number of patients that experience an exacerbation resulting in physician directed treatment, self-management or no treatment change will be analysed as above.

Change in arterial partial pressure of carbon dioxide (PaCO2)

Change in PaCO2 will be taken from baseline (day of randomisation) up to week 6. A difference from baseline to week 6 will be calculated and the result of this difference will be analysed using a mixed effects linear regression model with a random effect for centre and adjusted for baseline PaCO2 level and minimisation variables, except for centre. In addition to this the difference of PaCO2 will be presented only adjusting for baseline PaCO2 level (i.e. not the minimisation variables). Change in PaCO2 will be taken from baseline up to 3, 6 and 12 months and will be analysed in the same way.

Change in arterial partial pressure of oxygen (PaO2) severe respiratory insufficiency questionnaire and in St George’s respiratory questionnaire will be analysed as above.
Change in 4% ODI

Change in 4% ODI will be taken from baseline (pre-treatment) up to day 0 on allocated treatment. A difference from baseline to day 0 will be calculated and the result of this difference will be analysed using a mixed effects linear regression model with a random effect for centre and adjusted for baseline 4% ODI and minimisation variables, except for centre. In addition to this the difference of 4% ODI will be presented only adjusting for baseline 4% ODI (i.e. not the minimisation variables). Change in 4% ODI will be taken from baseline up to 6 and 12 months and will be analysed in the same way.

Change in mean SpO2, total sleep time <90%, mean TcCO2 and max TcCO2 will be analysed as above.

Serious adverse events (SAEs)
The number of patients experiencing at least one SAE and the mean number of SAEs per patient will be presented descriptively, but no formal analyses will be performed. In addition to this, a full listing of SAEs will presented.

Sensitivity analyses
There are no planned sensitivity analyses

Subgroup analyses
A per-protocol analysis will be done for the primary outcome of time to hospital admission or death. The per-protocol analysis will include all randomised patients who did not switch treatment during the trial. An additional analysis will also be done looking at patients randomised to HOT HMV who complied with the treatment, defined as patients with an average daily use of HMV greater than 4 hours per night.

4.5 Compliance
The median number of average daily use (hours/night) reported from the ventilator card period will be presented descriptively, but no formal analyses will be performed.
## 5. SIGNATURES OF APPROVAL

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Version: 1.0

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<tr>
<td>Nick Hart</td>
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<td>Angela Crook</td>
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