

BMJ Open Medium-term cost-effectiveness of an automated non-invasive ventilation outpatient set-up versus a standard fixed level non-invasive ventilation inpatient set-up in obese patients with chronic respiratory failure: a protocol description

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ABSTRACT

Introduction: Obesity is an escalating issue, with an accompanying increase in referrals of patients with obesity-related respiratory failure. Currently, these patients are electively admitted to hospital for initiation of non-invasive ventilation (NIV), but it is unknown whether outpatient initiation is as effective as inpatient set-up. We hypothesise that outpatient set-up using an autotitrating NIV device will be more cost-effective than a nurse-led inpatient titration and set-up.

Methods and analysis: We will undertake a multinational, multicentre randomised controlled trial. Participants will be randomised to receive the usual inpatient set-up, which will include nurse-led initiation of NIV or outpatient set-up with an automated NIV device. They will be stratified according to the trial site, gender and previous use of NIV or continuous positive airway pressure. Assuming a 10% dropout rate, a total sample of 82 patients will be required. Cost-effectiveness will be evaluated using standard treatment costs and health service utilisation as well as health-related quality of life measures (severe respiratory insufficiency (SRI) and EuroQol-5 dimensions (EQ-5D)). A change in the SRI questionnaire will be based on the analysis of covariance adjusting for the baseline measurements between the two arms of patients.

Ethics and dissemination: This study has been approved by the Westminster National Research Ethics Committee (11/LO/0414) and is the trial registered on the UKCRN portfolio. The trial is planned to start in January 2015 with publication of the trial results in 2017.

Trial registration number: ISRCTN 51420481.

INTRODUCTION

In the UK, almost a quarter of all adults are obese and this has an annual cost to the National Health Service (NHS) of £4.2

Strengths and limitations of this study

- A multinational, multicentre randomised controlled trial.
- An important clinical trial which will change practice in a rapidly increasing group of patients.
- Cost effectiveness is the primary outcome measure and clinical effectiveness is the secondary outcome measure nested within the study.
- Health economics will be established across England, France and Switzerland.
- Only relevant to patients with stable chronic respiratory failure.

billion, which is predicted to double by 2050.¹ A significant proportion of these patients have respiratory comorbidities, including obstructive sleep apnoea (OSA)² and obesity hypoventilation syndrome.³ Indeed, 50% of patients with a body mass index (BMI) above 40 kg/m² have OSA⁴ and up to one-third of patients with morbid obesity have chronic respiratory failure⁵ with associated morbidity, mortality and healthcare utilisation costs.⁶ Specifically, obese patients with chronic respiratory failure have a fourfold mortality risk compared with eucapnic obese patients.⁵ With the increasing scale of the problem, prompt action is required to roll out a more simplified management strategy for obese patients with chronic respiratory failure.⁷

The authors have reported a doubling in the incidence of patients requiring non-invasive ventilation (NIV) to treat chronic respiratory failure as a consequence of obesity⁸ and, more recently, a survey from the authors has demonstrated that obesity is

currently the primary diagnosis for home mechanical ventilation (HMV) in the UK.⁹ The current treatment option with overnight NIV has demonstrated that HMV reduces the partial pressure of arterial carbon dioxide (PaCO₂), improves dyspnoea as well as enhancing health-related quality of life.^{10 11} In addition, trial data from the authors have shown that 3 months of nocturnal NIV results in increased physical activity with and weight loss of 4.4%,⁷ and therefore important outcome measures for trials studying obese individuals with chronic respiratory failure.

Currently, the length of inpatient stay for NIV set-up is between 4.5 and 6 days.¹² Although there are no data to support the clinical effectiveness and cost-effectiveness of NIV set-up on an outpatient basis, compared with inpatient overnight titration by specialist respiratory nurses, this is increasingly used as a strategy in smaller units with limited inpatient facilities. Financial constraints are driving a clinical practice that is lacking satisfactory evidence. Despite the outpatient approach potentially having financial benefits, these must be balanced against the loss in optimisation of NIV set-up, which could negatively impact on treatment effectiveness. Only one study has compared outpatient and inpatient NIV initiation with similar outcomes observed in both groups.¹³ However, this study was performed in a small group of patients with neuromuscular and chest wall disease, and the relevance to the obese group remains uncertain. Such obese patients with chronic respiratory failure will often require much higher inspiratory and expiratory delivered ventilator pressures, which necessitate inpatient titration to gain adequate control of the sleep-disordered breathing. This current trial will investigate the medium-term clinical effectiveness and cost-effectiveness of outpatient NIV set-up, using an automated titrating device, against standard inpatient nurse-led protocolised initiation with a standard fixed level device.

PRIMARY RESEARCH OBJECTIVE

To evaluate the medium-term cost-effectiveness of outpatient NIV set-up with an automated device compared with inpatient nurse-led protocolised fixed level NIV set-up in obese patients with chronic respiratory failure at 3 months.

SECONDARY RESEARCH OBJECTIVES

To evaluate the health-related quality of life improvements between outpatient NIV set-up and inpatient set-up at 3 months.

To evaluate the gas exchange improvements between outpatient NIV set-up and inpatient set-up at 3 months.

METHODS AND ANALYSIS

Study design

A 1:1 randomised controlled trial design with stratification (gender, previous continuous positive airway

pressure or NIV use and recruiting centre) will be employed in order to test the hypothesis that outpatient NIV set-up in obese patients with chronic respiratory failure is more cost-effective in the medium term than inpatient nurse-led protocolised fixed level set-up at 3 months.

Patient entry

Obese patients with chronic respiratory failure will be recruited from participating specialist HMV centres. Patients will be screened; if they meet the inclusion criteria, they will be given a patient information sheet and offered participation in the study. In addition, patients who are identified as eligible and who have an upcoming appointment at the recruitment site for the management of their chronic respiratory failure will receive an invitation letter and patient information sheet prior to their visit and be seen by the research team at this time. The inclusion and exclusion criteria are shown in [boxes 1 and 2](#).

Treatment and follow-up phase

All eligible patients will be assessed at baseline, 6 weeks and 3 months. All patients enrolled in the trial (both inpatients and outpatients) will receive weekly telephone follow-up for the first 6 weeks, then every 2 weeks until 3 months. All measurements are described in [table 1](#).

Withdrawal and stopping criteria

Patients who demonstrate significant clinical respiratory deterioration, defined as an increase in daytime PaCO₂ ≥ 1 kPa and a decrease in partial pressure of oxygen ≥ 1 kPa, during the 3-month trial period will be withdrawn from the trial.

Recruitment and retention

If a participant withdraws from the trial, the data collected prior to the withdrawal date will be used with the patient's consent. All reasons for voluntary withdrawal from the study will be documented according to CONSORT rules.¹⁹

Box 1 Inclusion criteria

- ▶ Obese patients with chronic respiratory failure
- ▶ Age >18 years
- ▶ Chronic hypercapnia (daytime arterial partial pressure of carbon dioxide (PaCO₂) >6.5 kPa)
- ▶ Evidence of sleep-disordered breathing on overnight oximetry study (4% oxygen desaturation index >10 events/h and/or >30% of the total analysis time with an oxygen saturation <90%)
- ▶ Patients with a recent acute episode requiring non-invasive ventilation (NIV) will need a minimum of 2 weeks stability prior to enrolment into the trial (no NIV requirement for 2 weeks and pH ≥ 7.3)
- ▶ Body mass index ≥ 35 kg/m²
- ▶ Forced expiratory volume in 1 s/forced vital capacity >70%

Box 2 Exclusion criteria

- ▶ Persistent hypercapnic respiratory acidosis defined as pH <7.30
- ▶ Severe hypoxic and/or hypercapnic respiratory failure defined as an arterial partial pressure of oxygen <7.0 kPa and/or an arterial partial pressure of carbon dioxide >9 kPa
- ▶ Failure to tolerate non-invasive ventilation during initiation or if required to treat acute decompensation
- ▶ Prior acute hypercapnic respiratory failure requiring intubation
- ▶ Hypercapnic respiratory failure secondary to an identifiable cause other than obesity
- ▶ Acute coronary syndrome or unstable angina
- ▶ Cognitive impairment that would prevent informed consent into the trial and/or inability to comply with the protocol
- ▶ Psychiatric disease necessitating antipsychotic medication, ongoing treatment for drug or alcohol addiction, persons of no fixed abode postdischarge
- ▶ Patients undergoing renal replacement therapy
- ▶ Patients with coexistent cancer and a prognosis likely to be less than 12 months
- ▶ Critical peripheral vascular disease awaiting revascularisation procedure (or claudication distance <100 m)
- ▶ Stroke with hemiparesis
- ▶ Age <18 years
- ▶ Pregnant

Data management*Sample size statement*

Previous data⁷ in obese patients with chronic respiratory failure showed that the mean increase from the baseline of the health-related quality of life at 3 months, as assessed by the severe respiratory insufficiency (SRI) questionnaire, was 20% (55±16 to 66±19) in the autotitrating NIV group and 12% (51±14 to 57±15) in the fixed level pressure support (PS) group. In an analysis of covariance (ANCOVA) study, a sample size of 37 from the intervention group and 37 from the control group achieves 90% power with a 5% significance level to detect differences among the means at 3 month follow-up using an F test. The correlation in SRI between baseline and follow-up was assumed to be 0.72, and the size of the variation in the means was represented by their SD estimated from the pilot study. Assuming a 10% dropout rate, a total sample of 82 patients (17 patients will be expected to be recruited from the six sites—London (2 sites, UK), Leeds (UK), Grenoble (France), Rouen (France) and Geneva (Switzerland)). Based on previous recruitment data from the pilot study,⁷ with an enrolment rate of 1 patient in alternate months recruited from each site (14 patients per site), the enrolment will be completed in 28 months. The proposed completion of the trial would be 3 years including data analysis and manuscript publication.

A priori non-inferiority clinical effectiveness safety power calculation

To ensure that effective treatment is delivered in both arms of the trial, on the basis of the recent pilot study,⁷ we will also embed a non-inferiority substudy. The

hypothesis for the non-inferiority study is that the intervention arm is neither superior nor inferior to the standard treatment arm in terms of daytime decrease in PaCO₂. In an ANCOVA analysis using simulation data from the previous pilot study, assuming an SD of 0.7, a sample of 74 (37 in each group) achieves 86% power to detect non-inferiority of the autotitrating NIV group at 3 months, with a PaCO₂ margin of 0.5 kPa, using a one-sided test with a significance level of 0.025.

Statistical analysis

A full statistical description will be analysed. For each of the variables analysed, univariate descriptive statistics provide an overall picture of the data. Continuous variables will be presented as the median and IQR, unless otherwise stated. For categorical variables, frequency counts and percentages will be presented as summary statistics for the subgroups of interest. Univariate analyses will be performed to compare study groups using appropriate statistical tests according to the type and the distribution of the data: χ^2 or Fisher's exact test for categorical data and independent t test or Mann-Whitney for continuous variables. Change in SRI will be based on ANCOVA adjusting for the baseline measurements between the two arms of patients. Cost utility analysis will be evaluated using standard treatment costs and health service utilisation (hospital admissions, bed days, nurse interaction time, doctor interaction time, telephone consultations, outpatient consultations, visit frequency to general practitioner) and using both health-related quality of life EuroQol-5 dimensions (EQ-5D) and SRI. A secondary analysis based on ANCOVA models will also be constructed to isolate the effect of the intervention on each arm after adjusting for any significantly different baseline characteristics between groups. Similar analysis will be used for other secondary outcomes (spirometry, gas exchange, exercise capacity, body composition, physical activity, breathlessness, somnolence, anxiety and depression). Differences will be considered at the 5% significance level.

Cost-effectiveness analysis

Cost-effectiveness will be investigated by estimating the healthcare costs and quality of life gains of the two treatment options; the differences between each of these; and the incremental cost per unit of quality of life gained. Cost data will be obtained by collecting data on resource use for the two options and converting these to a common monetary base using either locally obtained unit cost data or nationally representative data from sources such as the Personal Social Services Research Unit (PSSRU) costs of care and English reference costs. Quality of life data will be obtained by collecting EQ-5D data, which will be converted to utility scores using standard EQ-5D value sets. These will in turn be converted into quality adjusted h year (QALY) estimates using survival data. This will enable the estimate of a cost per unit of clinical effectiveness gained and also a

Table 1 Outcome measures between baseline and 3 months

Outcome	Measurement
Primary	
Cost-effectiveness	Standard treatment costs and health service utilisation Δ Health-related quality of life (SRI ¹⁴ ¹⁵ questionnaire and EQ-5D)
Clinical effectiveness	Δ PaCO ₂ between baseline and 3 months
Secondary	
Patient-centred	
Symptoms	Medical Research Council dyspnoea score; ¹⁶ Epworth sleepiness score; ¹⁷ HAD score ¹⁸
Proxy healthcare-related quality of life	EQ-5D-5 L by partner and/or carer
Body composition	Weight Loss, BMI, fat mass, fat-free mass, fat-free mass index, neck circumference (cm), chest circumference (cm), waist circumference (cm), hip circumference (cm), waist-to-hip ratio
Non-invasive ventilation adherence	Hours per night use
Physician-centred	
Daytime gas exchange	PaO ₂ , PaCO ₂ , pH, HCO ₃ ⁻ , packed cell volume of haemoglobin
Spirometry	Forced expiratory volume in 1 s, forced vital capacity
Exercise capacity	6MWT
Limited overnight polygraphy	Outpatient SpO ₂ and HR; inpatient SpO ₂ , TcCO ₂ and HR
Sleep quality	14-day actigraphy*
Physical activity	14-day actigraphy*
Cardiovascular	Blood pressure and HR
Healthcare organisation-centred	
Health economics	Healthcare utilisation (total bed days, premium and standard nurse-interaction time, premium and standard doctor-interaction time, staff time for non-invasive ventilation set-up, frequency of setting changes, premium and standard nurse technical and nursing support postdischarge, outpatient appointments, outpatient reviews, telephone consultations, GP consultations, emergency care attendances costed as per standard treatment costs, equipment cost, hospital admissions)

*Measured using Philips Actiwatch spectrum.

6MWT, 6 min walk test; BMI, body mass index; EQ-5D, EuroQol-5 dimensions; GP, general practitioner; HAD, hospital anxiety and depression; HCO₃⁻, arterial bicarbonate level; HR, heart rate; PaCO₂, arterial partial pressure of carbon dioxide; PaO₂, arterial partial pressure of oxygen; SpO₂, oxygen saturation; SRI, severe respiratory insufficiency questionnaire; TcCO₂, transcutaneous carbon dioxide level.

cost per QALY gained. These data will be collected by each country, and cost-effectiveness calculated for each country.

In undertaking statistical analysis of cost and quality of life data, it will be necessary to take into account the fact that there is considerable uncertainty about the distributions of such data. As a result, it will be necessary to approach this with bootstrapping analysis. Moreover, the main method by which the cost-effectiveness analysis will be conducted is by constructing an economic appraisal model to account for the uncertainty inherent in the data and the cost-effectiveness estimates. This will include extensive sensitivity analysis. If appropriate, it will also take account of cost-effectiveness acceptability via estimation of net benefit and also explore uncertainty using the value of information approach.

Randomisation process

Consenting patients will be randomised in a 1:1 manner to either the inpatient or outpatient NIV set-up arm. The first assessment will occur following randomisation. Randomisation will be performed using an internet-based system for randomisation and data entry

(<http://www.medscinet.se/laktat>, MedSciNet AB, Stockholm, Sweden) via the Guy's and St Thomas' Biomedical Research Centre and King's College London.

Stratification

To ensure that balance groups are achieved in terms of body composition, NIV set-up across the six sites and previous exposure to ventilator support patients will be stratified at randomisation (table 2).

TRIAL DESIGN Screening

Obese patients (BMI > 35 kg/m²) with chronic respiratory failure (PaCO₂ > 6.5 kPa) and evidence of sleep-disordered breathing on a single night self-ventilation oximetry study (4% oxygen desaturation index (ODI) > 10 events/h and/or > 30% of the total analysis time with an oxygen saturation (SpO₂) < 90%) will be recruited and randomised. All potential patients referred to each of the centres (BMI > 35 kg/m² and suspected chronic respiratory failure from the referral letter) will undergo a home overnight oximetry study prior to a clinic consultation. Obese patients with

Table 2 Variables used to stratify subjects for randomisation

Stratification criteria	Minimisation variable
Gender	Male/female
Home mechanical ventilation centre	London (LFU STH) UK London (RBH) UK Leeds UK Grenoble FRANCE Rouen—FRANCE Geneva SWITZERLAND
Use of acute NIV or acute or long-term CPAP in past 3 months	Yes/no

CPAP, continuous positive airway pressure; LFU STH, Lane Fox Unit, St Thomas's Hospital; NIV, non-invasive ventilation; RBH, Royal Brompton Hospital.

chronic respiratory failure (determined by arterial blood gas measurement at the clinic consultation) and sleep disorder will be recruited and randomised. The trial is outlined in online supplementary appendix 1.

Intervention arm (outpatient automated NIV set-up)

Patients randomised to the intervention arm will be initiated on NIV during an elective outpatient clinic review during which an arterial blood gas measurement will be obtained to confirm the presence of chronic respiratory failure. All outpatient NIV set-ups will follow a standard protocol for the automated device (A40 AVAPS-AE machine; Philips-Respironics, Murraysville, Pittsburgh, USA; online supplementary appendix 2) and patients will be discharged with the machine and a full face mask or nasal interface. Patients will then undergo a 1–2-night home oximetry study to ensure adequate control of overnight oxygenation. Those who are not adequately controlled, defined by a change in 4% ODI of less than 5 events/h and a change in total analysis time of SpO₂ less than 90% of less than 5%, will be asked to return for a further outpatient review within 72 h for re-titration of the device. Patients will be reviewed clinically as outpatients at 6 weeks, adherence to NIV will be evaluated and an arterial blood gas measurement will be undertaken. A full clinical review and optimisation of NIV and interface will be performed at this visit. Patients will be reviewed at 3 months as inpatients where overnight transcutaneous carbon dioxide (TcCO₂) level and SpO₂ studies will be performed. All other patient-centred, physician-centred and healthcare utilisation measurements will be assessed at baseline, 6 weeks and 3 months (online supplementary appendix 1).

Standard treatment arm (inpatient nurse-led protocolised NIV set-up)

Patients randomised to the standard treatment arm will be admitted for an inpatient initiation of NIV. The patient will follow a specialist nurse-led protocolised set-up of spontaneous/timed (S/T) mode PS

ventilation (A40 AVAPS-AE machine; Philips-Respironics, Murraysville, Pittsburgh, USA) using limited respiratory polygraphy, including overnight TcCO₂ and SpO₂ studies (online supplementary appendix 3). Following the inpatient set-up, patients will be reviewed as outpatients at 6 weeks, adherence with NIV will be evaluated and arterial blood gas measurements will be performed. Patients will then be reviewed at 3 months as inpatients where overnight respiratory polygraphy, TcCO₂ and SpO₂ studies will be repeated. All other patient-centred and physician-centred measurements and healthcare utilisation measurements will be assessed at baseline, 6 weeks and 3 months (online supplementary appendix 1).

ETHICS AND DISSEMINATION

Regulatory issues

Ethics

The study has been submitted for Site Specific Assessment (SSA) at each participating NHS Trust. The Study Coordination Centre will require a copy of the SSA approval letter before accepting participants into the study. The study will be conducted in accordance with the recommendations for physicians involved in research on human participants adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions. All protocol amendments will be disseminated to participating centres.

Consent

Consent to enter the study must be sought from each participant only after a full explanation has been given, an information leaflet offered and time allowed for consideration. Signed participant consent should be obtained. The right of the participant to refuse to participate without giving reasons must be respected. After the participant has entered the trial, the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant's best interest, but the reasons for doing so should be recorded. In these cases, the participants remain within the study for purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

Confidentiality

Participants' identification data will be required for the registration process. The Study Coordination Centre will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act. Data collection will be entered centrally via King's College London Clinical Trials Unit.

Indemnity

Guys and St Thomas' Foundation Trust holds Public Liability ('negligent harm') and Clinical Trial ('non-negligent harm') insurance policies which apply to this trial.

Sponsor

Guys and St Thomas' Foundation Trust will act as the main sponsor for the UK sites. Delegated responsibilities will be assigned to the NHS trusts taking part in this study. The Swiss site will be sponsored by the Geneva Pulmonary League (Ligue Pulmonaire Genevoise). For the French sites, sponsorship will be processed in accordance with Comité de Protection des Personnes (CCP) in Grenoble (<http://www.cppsudest5.fr>).

Audits and inspections

The trial may be subject to inspection and audit by Guys and St Thomas' Foundation Trust under their remit as sponsor, the Study Coordination Centre and other regulatory bodies to ensure adherence to Good Clinical Practice guidelines.

Trial closure

The end of the trial will be on completion of 82 patients through the treatment and follow-up phases of the study.

Statistics and data analysis

Statistical support will be provided from the Kings College London Clinical Trials Unit. DP (Professor of Health Economics) and AD (Senior Lecturer in medical statistics) will be responsible for the statistical and health economic analyses. Data and all appropriate documentation will be stored for a minimum of 5 years after the completion of the study, including the follow-up period.

Trial Management Group

The Trial Management Group (TMG) will consist of the Trial Steering Committee (TSC) and Data Monitoring Committee (DMC). The TSC will include a Chairman (Professor John Gibson), a Trial Statistician (AD), a Health Economist (DP) as well as the Chief Investigator (Dr Nicholas Hart) and site principal investigators. The TSC will be responsible for overseeing the progress of the trial. The day-to-day management of the trial will be coordinated through the Guys and St Thomas' Foundation Trust and Kings College London Clinical Trials Unit. The DMC will include a Chairman (Professor Mary Morrell), an Independent Expert (Dr Steve Banham) and a Trial Statistician (Dr William Banya) and meet three times a year to review the progress of the trial and safety issues.

Publication policy

All publications and presentations relating to the study will be authorised by the TMG. The first publication of the trial results will include the TMG as named authors. Members of the DMC will be listed as contributors and will be cited by name. Data from the trial can be accessed by research members at the coordinating site only.

Timelines

The planned trial start date is January 2015 with an end date of May 2017 and a planned publication date of January 2018.

DISCUSSION

The outcome of this trial will provide the data to advise clinical practice on the use of outpatient autotitrating NIV in obese patients with chronic respiratory failure. If the treatment demonstrates parity in terms of clinical effectiveness, as predicted, and enhanced cost-effectiveness over standard inpatient set-up, this will change the current clinical approach to the management of these patients. Indeed, outpatient set-up will be expected to reduce healthcare utilisation costs providing cost savings to healthcare providers. Furthermore, the expectation is that, at the least, this approach will have an equal impact on improving health-related quality of life such that there will be an associated enhancement in cost-effectiveness. A change in the clinical pathway away from inpatient management of these stable obese patients with chronic respiratory failure will increase effectiveness in clinical management by optimising inpatient bed capacity in the local and regional respiratory centres. This will allow inpatient facilities to be better utilised for the care of more acute and complex patients with chronic respiratory failure. Finally, a positive primary outcome for this trial will allow not only the development of a simplified clinical approach, but also will provide the clinical data to support local outpatient set-up as well as avoiding unnecessary expansion of inpatient facilities and the purchase of expensive inpatient respiratory monitoring equipment increasing the potential cost savings.

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Contributors SM, GA, PM, MWE, JPJ, JLP, JFM, AC, MP, DP, AD and NH were involved in development of the trial protocol. SM, GA and NH were involved in writing the protocol for publication. DP and AD were involved in statistical calculations in powering the trial. SM, GA, PM, MWE, JPJ, JLP, JFM, AC, MP, DP, AD and NH were involved in the review and final approval of the protocol for publication.

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Competing interests NH is on the Pulmonary Executive Board for Philips.

Ethics approval This study has been approved by the Westminster National Research Ethics Committee (11/LO/0414).

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