PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	MEDIUM TERM COST EFFECTIVENESS OF AUTOMATED NON-INVASIVE VENTILATION OUTPATIENT SET UP VS. STANDARD FIXED LEVEL NON-INVASIVE VENTILATION INPATIENT SET UP IN OBESE PATIENTS WITH CHRONIC RESPIRATORY FAILURE: PROTOCOL DESCRIPTION
AUTHORS	Mandal, Swapna; Arbane, Gill; Murphy, Patrick; Elliott, Mark; Janssens, Jean-Paul; Pepin, Jean; Muir, Jean-Francois; Cuvelier, Antoine; Polkey, Mike; Parkin, David; Douiri, Abdel; Hart, Nicholas

VERSION 1 - REVIEW

REVIEWER	Prof. Dr. Wolfram Windisch Prof. Dr. Wolfram Windisch Head of the department of Pneumology Cologne Merheim Hospital Kliniken der Stadt Köln gGmbH Witten/Herdecke University Germany
REVIEW RETURNED	15-Dec-2014

GENERAL COMMENTS	This is a very nice study protocol from a top international research group including well known researchers in the field of home mechanical ventilation from different countries. The idea of the study is absolutely reasonable. Indeed, the choice of the best fitting ventilator settings in patients with obesity hypoventilation syndrome (OHS) is not easy, but on the other hand, inpatient establishment of OHS will more and more produce a significant economic burden. All in all, the authors should be applauded for the time and effort to create this very nice study. There are, however, very few remaining questions Specific comments 1. It is the pleasure for this reviewer to see the Severe Respiratory Insufficiency Questionnaire (SRI) included in the study design. This appears to be absolutely reasonable. The French version of the SRI, however, is not validated yet, in contrast to the English version, but there is a professional French translation available. Please refer to the correct references (still missing), and please indicate if there is a French validation study ongoing. Since the SRI is internationally widely accepted, the French version, even though not validated – but professionally translated, would be sufficient for the study. Nevertheless, the SRI is an important part of the study, and all available information should be provided. 2. OHS might rarely also present without sleep disordered breathing. Why are these patients excluded from the study? 3. Daytime hypercapnia is essential for the diagnosis of OHS. How

	many blood gases are taken to establish the diagnosis and what measurement is taken? 4. Exclusion criteria: Persistent hypercapnic respiratory acidosis defined as pH <7.30 reportedly serves as an exclusion criterion. What is “persistent”? Probably, any form of acidosis should prevent the patient from getting included into the study. 5. This reviewer would also recommend to more precisely define “Unstable coronary artery syndrome”. 6. The protocol for outpatient NIV establishment is crucial. Unfortunately, the Appendix 2 including this information is rather tiny and difficult to read, even when trying to enlarge the figure with the help of the computer. Therefore, the indicated information remains unclear. Please make sure that this figure is clear and easy to read.

REVIEWER	Jan H Storre, MD PD Dr. med. Jan H. Storre Leitender Oberarzt Lungenklinik - Abt. Pneumologie Kliniken der Stadt Köln gGmbH Germany Jan H Storre received research funding, travel funding and honorarium for lectures from different manufactures and home care providers dealing with mechanical ventilation.
REVIEW RETURNED	16-Dec-2014

GENERAL COMMENTS	Thank you very much for considering me as reviewer for Manuscript ID bmjopen-2014-007082, entitled "MEDIUM TERM COST EFFECTIVENESS OF AUTOMATED NON-INVASIVE VENTILATION OUTPATIENT SET UP VS. STANDARD FIXED LEVEL NON-INVASIVE VENTILATION INPATIENT SET UP IN OBESE PATIENTS WITH CHRONIC RESPIRATORY FAILURE: PROTOCOL DESCRIPTION." The focus of the well designed study is of great interest in the expanding field of home mechanical ventilation and targets one of the main indications such as focussed subjects suffering from hypoventilation due to obesity. The authors of the current project are all well known experts in the field of home mechanical ventilation and the target of a multi-national, multi-centre randomised controlled trial indicates the strength of the design. There are some minor concerns which should be addressed: 1) Table 2, INCLUSION CRITERIA: Is the daytime AGB performed in a defined period of time? I would suggest standardizing this important diagnostic procedure in a time window. 2) Table 2, INCLUSION CRITERIA: “Patients… will need a minimum of 2 weeks stability prior enrolment…” This short episode might influence the outcome since the target of the investigation is chronic care rather than acute care. In my opinion this period should be enhanced to 4 weeks to avoid the influence of acute on chronic ventilatory failure in the investigated subjects. 3) Table 1 is following Table 3, please rename Tables. 4) Table 1, page 12: Outcome measures between baseline and 3 months: In line to the first issue. Please clarify the period of time for the primary outcome “clinical effectiveness” by delta PaCO”. 5) Trial Design and Appendixes, page 16 and following: I appreciate the implementation of a noninvasive continuous monitoring of PCO2 as suggested. Comparing the text and Appendixes it is not clear to

	me if this is performed throughout the study in all patients or inpatient arm only. I would suggest performing this valuable diagnostic tool in both arms of run-in and follow-up visits. Following the course of nocturnal ventilation could be analyzed adequately which is a major goal of this trial addressing both interventions.

VERSION 1 – AUTHOR RESPONSE

Response to R#1's comments
General comments
This is a very nice study protocol from a top international research group including well known researchers in the field of home mechanical ventilation from different countries. The idea of the study is absolutely reasonable. Indeed, the choice of the best fitting ventilator settings in patients with obesity hypoventilation syndrome (OHS) is not easy, but on the other hand, inpatient establishment of OHS will more and more produce a significant economic burden. All in all, the authors should be applauded for the time and effort to create this very nice study. There are, however, very few remaining questions

We thank R#1 for their wholly supportive comments.

Specific comments
1. It is the pleasure for this reviewer to see the Severe Respiratory Insufficiency Questionnaire (SRI) included in the study design. This appears to be absolutely reasonable. The French version of the SRI, however, is not validated yet, in contrast to the English version, but there is a professional French translation available. Please refer to the correct references (still missing), and please indicate if there is a French validation study ongoing. Since the SRI is internationally widely accepted, the French version, even though not validated – but professionally translated, would be sufficient for the study. Nevertheless, the SRI is an important part of the study, and all available information should be provided.

We have added the reference to the manuscript as suggested. There are currently no validation studies available. However, the authors wish to highlight that the SRI was not validated in English for the study by Murphy et al [1] at the time of conception but it has now been validated. We will liaise with our French colleagues in order to validate the SRI in French.

2. OHS might rarely also present without sleep disordered breathing. Why are these patients excluded from the study?

The definition of OHS by the American Academy of Sleep Medicine is clear [2]. OHS is defined as daytime awake hypercapnia in the context of obesity with evidence of sleep disordered breathing. We will use this standard definition.

3. Daytime hypercapnia is essential for the diagnosis of OHS. How many blood gases are taken to establish the diagnosis and what measurement is taken?

Arterial blood gases will be taken at least 4 hours after waking and after at least one hour of rest during the day. We have added this to the protocol. Arterial blood gas measurements will include pH, PaCO2 (partial pressure of carbon dioxide in arterial blood) and PaO2 (partial pressure of oxygen in arterial blood), HCO3- (arterial bicarbonate) and base excess (BE).

4. Exclusion criteria: Persistent hypercapnic respiratory acidosis defined as pH <7.30 reportedly serves as an exclusion criterion. What is "persistent"? Probably, any form of acidosis should prevent

the patient from getting included into the study.

We agree with R#1's insightful comment. We have removed the word 'persistent'.

5. This reviewer would also recommend to more precisely define "Unstable coronary artery syndrome".

We have changed this to acute coronary syndrome and unstable angina [3].

6. The protocol for outpatient NIV establishment is crucial. Unfortunately, the
Appendix 2 including this information is rather tiny and difficult to read, even when trying to enlarge the figure with the help of the computer. Therefore, the indicated information remains unclear. Please make sure that this figure is clear and easy to read.

We have improved the quality of this image as suggested.

Response to R#2's comments

Thank you very much for considering me as reviewer for Manuscript ID bmjopen-2014-007082, entitled "MEDIUM TERM COST EFFECTIVENESS OF AUTOMATED NON-INVASIVE VENTILATION OUTPATIENT SET UP VS. STANDARD FIXED LEVEL NON-INVASIVE VENTILATION INPATIENT SET UP IN OBESE PATIENTS WITH CHRONIC RESPIRATORY FAILURE: PROTOCOL DESCRIPTION."
The focus of the well designed study is of great interest in the expanding field of home mechanical ventilation and targets one of the main indications such as focussed subjects suffering from hypoventilation due to obesity. The authors of the current project are all well known experts in the field of home mechanical ventilation and the target of a multi-national, multi-centre randomised controlled trial indicates the strength of the design. There are some minor concerns which should be addressed:

We thank R#2 for their wholly supportive comments.

1) Table 2, INCLUSION CRITERIA: Is the daytime AGB performed in a defined period of time? I would suggest standardizing this important diagnostic procedure in a time window.

Arterial blood gases will be taken at least 4 hours after waking and after at least one hour of rest during the day. We have added this to the protocol.

2) Table 2, INCLUSION CRITERIA: "Patients… will need a minimum of 2 weeks stability prior enrolment…"

This short episode might influence the outcome since the target of the investigation is chronic care rather than acute care. In my opinion this period should be enhanced to 4 weeks to avoid the influence of acute on chronic ventilatory failure in the investigated subjects.

In our experience from other clinical trials, we have found 2 weeks to be satisfactory for the resolution of acute on chronic respiratory failure. Indeed, the randomisation strategy employing previous mask use was not only to identify patients who had previously received continuous positive airway pressure (CPAP) treatment, but more importantly to identify those patients who had received acute non-invasive ventilation. This recruitment plan will ensure that we have balanced groups.

3) Table 1 is following Table 3, please rename Tables.

We have made the changes as suggested.

4) Table 1, page 12: Outcome measures between baseline and 3 months: In line to the first issue. Please clarify the period of time for the primary outcome “clinical effectiveness” by delta PaCO”.

We have amended the protocol accordingly and clarified the time line as suggested.

5) Trial Design and Appendixes, page 16 and following: I appreciate the implementation of a noninvasive continuous monitoring of PCO2 as suggested. Comparing the text and Appendixes it is not clear to me if this is performed throughout the study in all patients or inpatient arm only. I would suggest performing this valuable diagnostic tool in both arms of run-in and follow-up visits. Following the course of nocturnal ventilation could be analyzed adequately which is a major goal of this trial addressing both interventions.

We will employ transcutaneous CO2 monitoring, however, in the intervention group this will be done as an outpatient basis during clinic attendance and will therefore be in the awake state. The outpatient group will receive nocturnal oximetry to evaluate their nocturnal ventilation. This is standard practice in many home ventilation units across Europe.

Best wishes,

Dr Nicholas Hart on behalf of the OPIP investigators
Clinical & Academic Director Lane Fox Respiratory Unit
St Thomas’ Hospital Guy’s & St Thomas’ Foundation Trust

1. Murphy PB, Davidson C, Hind MD, et al. Volume targeted versus pressure support non-invasive ventilation in patients with super obesity and chronic respiratory failure: a randomised controlled trial. Thorax 2012;67(8):727-34 doi: 10.1136/thoraxjnl-2011-201081[published Online First: Epub Date]|.
2. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The Report of an American Academy of Sleep Medicine Task Force. Sleep 1999;22(5):667-89
3. . Unstable Angina and NSTEMI: The Early Management of Unstable Angina and Non-ST-Segment-Elevation Myocardial Infarction. London, 2010.

VERSION 2 – REVIEW

REVIEWER	Prof. Dr. Wolfram Windisch Department of Pneumology Cologne Merheim Hospital Kliniken der Stadt Köln gGmbH Witten/Herdecke University Faculty of Health/School of Medicine Germany
REVIEW RETURNED	06-Jan-2015

GENERAL COMMENTS	The authors have absolutely improved their work! Thank you very much for giving me the opportunity to read this nice study protocol!

REVIEWER	Jan H Storre, MD PD Dr. med. Jan H. Storre Leitender Oberarzt Lungenklinik - Abt. Pneumologie Kliniken der Stadt Köln gGmbH Germany Jan H Storre received research funding, travel funding and honorarium for lectures from different manufactures and home care providers dealing with mechanical ventilation.
REVIEW RETURNED	06-Jan-2015

GENERAL COMMENTS	All of my concerns were addressed satisfactorily.