The Role of Ambulatory Oxygen in Improving the Effectiveness of Pulmonary Rehabilitation for COPD patients

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Study Management Group

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Clinical Queries

Clinical queries should be directed to Chief Investigator who will direct the query to the appropriate person

Sponsor

Imperial College Healthcare NHS Trust is the main research Sponsor for this study. For further information regarding the sponsorship conditions, please contact the Head of Regulatory Compliance at:

Joint Research Compliance Office
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Funder

NIHR Imperial BRC/ Imperial Charity- Research Fellowship

This protocol describes the study and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator.

This study will adhere to the principles outlined in the NHS Research Governance Framework for Health and Social Care (2nd edition). It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

Table of Contents

GLOSSARY OF ABBREVIATIONS

COPD	Chronic Obstructive Pulmonary Disease
PR	Pulmonary Rehabilitation
LTOT	Long Term Oxygen Therapy
SpO_2	Oxygen Saturations
BTS	British Thoracic Society
CRQ	Chronic Respiratory Questionnaire
CAT	COPD Assessment Tool
HAD	Hospital Anxiety and Depression score
6MWT	6 Minute Walk Test
6MWD	6 Minute Walk distance

KEYWORDS
COPD, Ambulatory Oxygen, Pulmonary Rehabilitation

STUDY SUMMARY

TITLE The Role of Ambulatory Oxygen in Improving the Effectiveness of Pulmonary Rehabilitation for COPD patients

DESIGN Single Blinded Randomised Controlled Trial

AIMS Assess the effects of ambulatory oxygen on outcomes from Pulmonary Rehabilitation

OUTCOME MEASURES 6 Minute Walk Distance, Muscle strength, Dyspnoea, Quality of life questionnaires, anxiety and Depression score

POPULATION COPD patients only

ELIGIBILITY COPD patients between the age of 35-85, eligible for PR and who desaturate on exercise

DURATION 1 year

1. INTRODUCTION

1.1 BACKGROUND

Pulmonary rehabilitation (PR) is recognized as a core component of the management of patients with COPD (1) and has been clearly demonstrated to improve exercise capacity, reduce dyspnoea and improve quality of life. Although the benefits of PR in COPD are well established there remain a number of unanswered questions regarding how to maximise performance during PR, including the use of ambulatory oxygen. Studies investigating the effects of oxygen use during PR have had conflicting results with one study finding no benefit (2), while another study did report improved walking distance in patients administered oxygen (3). This latter study is used to justify the use of oxygen in PR programmes but the assessment was carried out while breathing the gas to which patients were randomised so it remains unknown if this was an acute effect of the oxygen or a true training effect. Limitations of these studies include inclusion of patients on LTOT, use of a standard oxygen flow rate rather than targeting to correct hypoxemia, limited outcome measures and short term follow-up. It is not known if short term improvements in exercise capacity translate into increased activity after patients complete PR. More sophisticated methods of measuring activity using pedometers are now available that can be used to assess whether oxygen during PR improves activity. Current practice appears to be moving towards administration of oxygen to COPD patients with exercise-induced desaturation during PR despite the lack of evidence that this has any benefits. In addition patients may be given ambulatory oxygen to use long term after completing PR, however it is not known whether patients continue to use oxygen as studies have shown that use of ambulatory oxygen in their home environments is generally poor (4). This has considerable cost implications due both to the direct costs of providing oxygen and the staff time required assessing patients. This lack of evidence is recognised in the British Thoracic Society (BTS) guidelines on PR(1). The guidelines state that ‘Supplemental oxygen during pulmonary rehabilitation should be offered to those who fulfil the assessment criteria for long term or ambulatory oxygen unless there are compelling clinical reasons to use alternative criteria.’ However the evidence level for this recommendation is Grade D which is the weakest level of evidence. Therefore it remains unknown whether oxygen improves outcomes in PR in COPD patients with exercise-induced desaturation.

1.2 RATIONALE FOR CURRENT STUDY

As described in the previous section the evidence base for the use of oxygen in PR is very limited. In the BTS guideline on PR it is stated that the one study that showed benefit for oxygen 'carried a significant risk of bias that influenced its findings. Therefore its results require replication before they can be widely applied', and that 'Supplemental oxygen may be of benefit in selected individuals, but there is currently little information to inform this choice.' Therefore further studies are needed to assess the effects of oxygen on outcomes from PR to justify its cost this. More sophisticated methods of measuring activity using pedometers are now available that were not available in previous studies of oxygen during PR. Therefore the rationale for the current study is to investigate the use of oxygen in COPD patient undergoing PR using a more robust study design and improved methods of assessing exercise capacity.

2. STUDY OBJECTIVES

The aims of this study are to

1. Assess the effects of oxygen on outcomes from PR.
2. Assess how many patients wish to continue to use ambulatory oxygen.
3. Assess the usage of ambulatory oxygen following completion of PR.

The hypothesis is that use of oxygen in selected patients improves exercise capacity during PR. The measurable aims will be exercise capacity and on-going usage of oxygen in this patient group.

Primary Objective

Assess the effects of ambulatory oxygen on outcomes from Pulmonary Rehabilitation

Secondary Objectives

1. Assess the proportion of patients that wish to continue to use ambulatory oxygen.
2. Assess the usage of ambulatory oxygen following completion of Pulmonary Rehabilitation
3. Assess whether initiation of ambulatory oxygen before or after PR has any influence on adherence to usage at 8 and 12 weeks.

3. STUDY DESIGN

The study will be a randomised, single-blinded study comparing oxygen with air in COPD patients undergoing PR. The study subjects will be patients with a confirmed diagnosis of COPD who have been accepted for PR and who are not hypoxemic at rest, but have exercise-induced desaturation (defined as a fall in SaO_2 of ≥4% to at least <90%, or any fall to a SaO_2 <90%) and demonstrate positive improvement with use of ambulatory oxygen as per the British Thoracic Society 2015 Home Oxygen Guidelines. It is standard practice for patients to have this assessment prior to commencing PR and as part of the assessment the flow rate required to increase the SaO_2 to >90% during exercise will be determined. Patients will be recruited from PR programs at Imperial College Healthcare NHS Trust Hospital Sites. 20 patients are required in each group to detect a 30% effect size on the 6 minute walk test (6MWT) with 80% power at the 5% significance level and 29 patients in each group to detect a 25% effect with 80% power (5). Therefore a minimum of 20 patients per group will be included.

Baseline assessments prior to commencing PR will include symptom and quality of life assessments including Borg scale for assessment of breathlessness, Chronic Respiratory Questionnaire (CRQ), COPD Assessment Tool (CAT) and the Hospital Anxiety and Depression score (HAD); a 6MWT to measure exercise capacity and Handheld dynamometer to measure muscle strength. In addition we will measure activity at home during and after PR using pedometers as this has never been investigated previously. A yamax Digi-walker SW-200 pedometer will be used to count the number of steps taken per day. Patients will be instructed to wear the device on left side of the body all the time, except when sleeping or showering. Pedometer placement was standardised by placing it on the belt or waistband, in the midline of the thigh, consistent with the manufacturers recommendation and with other studies conducted previously (6, 7). Patients will be record daily step counts on daily diary cards until their final follow up. The subjects will be randomised to receive either oxygen at the flow rate determined at the initial assessment to a maximum flow rate of 6 litres per minute, or room air. The subjects will then undergo a standard program of PR over 6 – 8 weeks and then undergo reassessment. The measures of exercise capacity at the follow up assessment will be carried out off oxygen and will be carried out by an observer blinded as to whether they received oxygen or not during PR. All patients will be provided with ambulatory oxygen for domiciliary after completing PR. All patients will have repeat assessments at 8 and 12 weeks after completion of PR. At these visits data will also be collected on activity, number of exacerbations and hospitalisations and on-going usage of ambulatory oxygen.

3.1 STUDY OUTCOME MEASURES

Primary Outcome measure

Exercise capacity measured with the 6 Minute Walk Test (6MWT)

Secondary outcome measure

1) Quality of Life Questionnaire
2) Measure of Anxiety and Depression
3) Muscle strength
4) Borg dyspnoea score

4. PARTICIPANT ENTRY

4.1 PRE-REGISTRATION EVALUATIONS

6 Minute Walk Test as part of ambulatory oxygen assessment

4.2 INCLUSION CRITERIA

1) A confirmed diagnosis of Chronic Obstructive Pulmonary Disease (COPD)
2) Fulfil the clinical criteria for Pulmonary Rehabilitation (PR)
3) Demonstrate exercise-induced desaturation (defined as a fall in SaO_2 ≥4% to at least <90%, or any fall to a SaO_2 <90%) and demonstrate positive improvement with use of ambulatory oxygen as per the British Thoracic Society 2015 Oxygen Guidelines

4.3 EXCLUSION CRITERIA

1) Use of long term oxygen therapy
2) Unable to provide informed consent
3) Significant respiratory disease other than COPD
4) Any patient needing more than 6 litres per minute oxygen to correct desaturation
5) Severe desaturation: SaO_2 < 80% during 6 Minute Walk Test
6) Any absolute contraindication to Pulmonary Rehabilitation

4.4 WITHDRAWAL CRITERIA

Standard clinical practice criteria for PR will be used, as per BTS PR guidelines.

5. ADVERSE EVENTS

5.1 DEFINITIONS

Adverse Event (AE): any untoward medical occurrence in a patient or clinical study subject.

Serious Adverse Event (SAE): any untoward and unexpected medical occurrence or effect that:

- **Results in death**
- **Is life-threatening** – *refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe*

- **Requires hospitalisation, or prolongation of existing inpatients' hospitalisation**
- **Results in persistent or significant disability or incapacity**
- **Is a congenital anomaly or birth defect**

Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

5.3 REPORTING PROCEDURES

All adverse events should be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the Chief Investigator in the first instance.

5.3.1 Non serious AEs

All such events, whether expected or not, should be recorded.

5.3.2 Serious AEs

An SAE form should be completed and faxed to the Chief Investigator within 24 hours. However, relapse and death due to COPD Exacerbation and hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs.

All SAEs should be reported to the JRCO, Imperial College healthcare NHS trust where in the opinion of the Chief Investigator, the event was:

- 'related', ie resulted from the administration of any of the research procedures; and
- 'unexpected', ie an event that is not listed in the protocol as an expected occurrence

Reports of related and unexpected SAEs should be submitted within 15 days of the Chief Investigator becoming aware of the event, using the NRES SAE form for non-IMP studies. The Chief Investigator must also notify the Sponsor of all SAEs.

Local investigators should report any SAEs as required by their Local Research Ethics Committee, Sponsor and/or Research & Development Office.

Contact details for reporting SAEs
Fax:02033110203 Attention Joint Research compliance office
Please send SAE forms to: Vijay Padmanaban
Tel: 07919533414 (Mon to Fri 09.00 – 17.00)

6. ASSESSMENT AND FOLLOW-UP

The subjects will attend for 2 additional visits at 2 months and 3 months after completing PR for follow-up assessments that will involve completing questionnaires and measurements of exercise capacity (6 Minute Walk Test).

Definition of end of study

All patients recruited to the study will have completed the study when they attend for the 3 month follow up assessments.

7. STATISTICS AND DATA ANALYSIS

20 patients are required in each group to detect a 30% effect size on the 6MWT with 80% power at the 5% significance level and 29 patients in each group to detect a 25% effect with 80% power. Therefore a minimum of 20 patients per group will be included. The following statistical methods will be used for data analysis – T test, ANOVA and test for correlation between variables

Data and all appropriate documentation will be stored for a minimum of 10 years after the completion of the study, including the follow-up period.

8. REGULATORY ISSUES

8.1 ETHICS APPROVAL

The Chief Investigator has obtained approval from the Local Research Ethics Committee. The study must be submitted for Site Specific Assessment (SSA) at each participating NHS Trust. The Chief Investigator will require a copy of the Trust R&D 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 subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

8.2 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 study 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 the 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.

8.3 CONFIDENTIALITY

The Chief Investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act.

8.4 INDEMNITY

Imperial College Healthcare NHS Trust holds standard NHS Hospital Indemnity and insurance cover with NHS Litigation Authority for NHS Trusts in England, which apply to this study

8.5 SPONSOR

Imperial College Healthcare NHS Trust will act as the main Sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

8.6 FUNDING

NIHR Imperial BRC is funding this study. Total of 50000£ for a year, has been awarded to the chief investigator as part of the Research fellowship

8.7 AUDITS

The study may be subject to inspection and audit by Imperial College healthcare NHS trust under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the NHS Research Governance Framework for Health and Social Care (2nd edition).

9. STUDY MANAGEMENT

The day-to-day management of the study will be co-ordinated by the chief investigator

10. PUBLICATION POLICY

The results of the study will be presented at relevant conferences and published in peer review journals.

11. REFERENCES

1) C Bolton et al. BTS Guideline on Pulmonary Rehabilitation in Adults September 2013 Volume 68 Supplement 2 Thorax 2013

2) Garrod R et al. Supplemental oxygen during pulmonary rehabilitation in patients with COPD with exercise hypoxaemia. Thorax. 2000 Jul;55(7):539-43

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4) Lacasse Y et al. Randomised trial of ambulatory oxygen in oxygen-dependent COPD. Eur Respir J. 2005 Jun;25(6):1032-8.

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6)Crouter SE et al. Validity of 10 electronic pedometers for measuring steps, distance and energy cost. Medicine and science in sports and exercise. 2003;35(8):1455:60

7)Schneider PL et al. Pedometers measures of free living physical activity: comparision of 13 models. Medicine and science in sports and exercise 2004;36(2):331-5

Appendix 1. Summary of investigations, treatment and assessments

	Baseline	PR	At completion of PR	8 weeks after PR	12 weeks after PR
6MWT	X		X	X	X
Borg scale	X		X	X	X
Chronic Respiratory Questionnaire (CRQ),	X		X	X	X
COPD Assessment Tool (CAT)	X		X	X	X
Hospital Anxiety and Depression score (HAD)	X		X	X	X
Pedometer	X		X	X	X
Muscle strength	X		X	X	X
Informed consent	X				