University Hospitals Coventry and Warwickshire NHS Trust

ISWT vs CPET

A comparative assessment of the relationship between the measurements made in an incremental shuttle walk test and an incremental cycle ergometry test in patients with idiopathic pulmonary fibrosis

PROTOCOL

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Confidentiality statement

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SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Research Governance Framework, the ICH Good Clinical Practice guidelines and the Sponsor's SOPs.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the Study Sponsor:

Signature: Date:

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Name (please print):

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Position:

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Chief Investigator:

Signature: Date:

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Name: (please print):

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Position:

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KEY TRIAL CONTACTS

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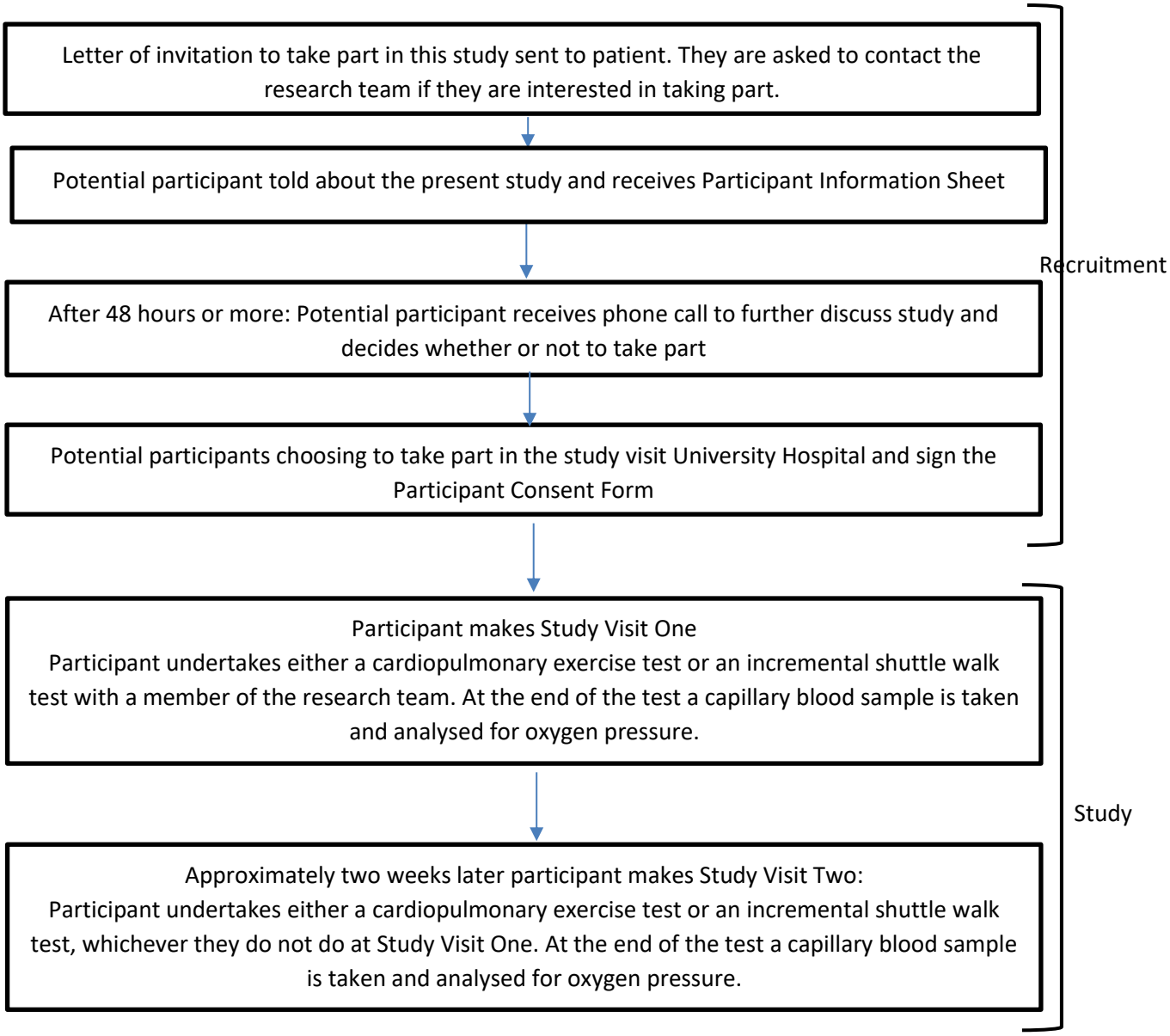
STUDY SUMMARY

Full study title	A comparative assessment of the relationship between the measurements made in an incremental shuttle walk test and an incremental cycle ergometry test in patients with idiopathic pulmonary fibrosis	
Short study title	ISWT vs CPET	
Study aim	1. To test the relationship between VO_2 peak in a CPET and the distance walked in an ISWT 2. To test the hypothesis that PO_2 is the same at the end of an ISWT and a CPET.	
Study design	Single centre	
Study participants	Patients over the age of 16 with a confirmed diagnosis of IPF	
Study arms	Not applicable	
Sample size	43	
Planned study period	4 months	
Planned recruitment start date	1st December 2017	
Planned recruitment end date	1st March 2018	
Planned study end date	31st March 2018	
	Objectives	**Outcome Measures**
Primary	To test the relationship between distance walked in an ISWT and VO_2 peak measured in a CPET.	VO_2 peak

Key Words: Idiopathic pulmonary fibrosis, cardiopulmonary exercise test, incremental shuttle walk test, VO_2 peak

STUDY FLOW CHART

Figure 1: Flow of participants through the study



SCHEDULE OF OBSERVATIONS

Table 1: Schedule of measures:

Schedule of events

Procedure	First meeting	Phone conversation	Second meeting	Visit one	Visit two
Eligibility Check	X				
Decision to take part in study or not to take part in study		X			
Informed consent			X		
Participant questionnaire			X		
Incremental shuttle walk test				X^A	X^B
Cardiopulmonary exercise test				X^B	X^A
Capillary blood gas				X	X

X – applies to all patients, whether in group A or group B.

X^A – patient randomly assigned to group A. These patients complete the ISWT at visit one and CPET at visit two.

X^B – patient randomly assigned to group B. These patients undertake CPET at visit one and ISWT at visit two.

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LIST OF ABBREVIATIONS

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CI	Chief Investigator
GCP	Good Clinical Practice
HRA	Health Research Authority
ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use.
NICE	National Institute for Health and Care Excellence
SOP	Standard Operating Procedure

STUDY PROTOCOL

A comparative assessment of the relationship between the measurements made in an incremental shuttle walk test and an incremental cycle ergometry test in patients with idiopathic pulmonary fibrosis

1. INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a chronic and fatal lung disease. As IPF progresses, patients become increasingly breathless with reduced exercise capacity and quality of life. Average life expectancy is three years from diagnosis but IPF progresses at different rates in different people. In 2012 the British Lung Foundation estimated that 32,500 in the UK had IPF.

An accurate prognosis can help determine the most appropriate treatment option and allow patients and their families to make suitable plans. Currently, measurements made during resting lung function tests are used to predict prognosis. However, evidence suggests that measurements made during a cardiopulmonary exercise test (CPET), particularly peak oxygen consumption (VO_2 peak) are more sensitive predictors of survival. CPET is the gold standard for assessing IPF but has not been adopted in clinical practice.

The incremental shuttle walk test (ISWT) is quicker, cheaper and more widely available than CPET. This study builds on previous research from our department which showed a relationship between the distance walked in an ISWT and VO_2 peak during a CPET. We will identify any relationship between ISWT distance and VO_2 peak in a new cohort of patients and compare this with the relationship of the previous study. Patients will undertake both ISWT and CPET and the results will be compared. This study paves the way for a simple, standardised test to more accurately predict prognosis in IPF.

1.1 Background

IPF is a chronic, progressive lung disease of unknown cause characterised by uncontrolled fibrosis of the lung interstitium. IPF causes progressive lung function decline, exercise limitation, reduced quality of life and ultimately death (NICE, 2013b; Miki et al., 2003). Life expectancy is approximately three to four years from the time of diagnosis though there is much variation between individuals (King et al., 2001; Navaratnam et al., 2011; Gribbin et al., 2006). Over 5000 people are diagnosed with IPF each year in the UK with an estimated 5% increase in incidence year-on-year since 1968 (Navaratnam et al., 2011).

ISWT vs CPET

Patients with IPF may be referred for lung transplantation. Alternatively, disease management options focus on slowing progression and maintaining quality of life. These include symptom relief, management of comorbidities, withdrawal of ineffective or harmful therapies and palliative care (NICE, 2013b). Two pharmacological therapies, Pirfenidone and Nintedanib, are licensed for the treatment of IPF for the purpose of slowing disease progression (NICE, 2013a; NICE, 2016).

IPF progresses at different rates in different individuals (Travis et al., 2013). This has led to calls for a validated scoring system to predict a patient's likely prognosis using clinical tests (Swigris et al., 2005; Ley et al., 2011). Similar scoring systems are already recommended for patients with chronic obstructive pulmonary disease (NICE, 2010). An accurate prognosis informs selection of the most suitable treatment and allows patients, their families and their care providers to make appropriate plans (Raghu et al., 2011; Swigris et al., 2005). Prognostic models are also useful in therapeutic trials for making baseline comparisons between individuals assigned to different treatment groups and including prognostic variables in analyses (Swigris et al., 2005).

Current NICE guidelines (2013b) for IPF management recommend using resting measurements of spirometry and gas transfer to assess disease severity and likely prognosis. However, patients with IPF demonstrate significant exercise limitation due to impaired gas exchange and ventilation (Miki et al., 2003). Measurements made during exercise have been shown to be more sensitive to the changes in oxygen transfer associated with IPF than those made at rest (Ley et al. 2011). CPET is recognised as a gold standard test for IPF assessment but has not been routinely adopted in practice (Bonini and Fiorenzano, 2017).

A study of IPF by Kawut et al. (2005) showed that VO_2 peak in a maximal CPET was inversely proportional to a patient's risk of death. Similarly, Fell et al. (2009) found that a VO_2 peak of < 8.3 ml/kg/min in a CPET was associated with an increased risk of death in patients with IPF. Oxygen consumption during an incremental treadmill test and an ISWT increases similarly (Singh et al., 1994) and, because an ISWT is cheaper, quicker and easier to perform, the usefulness of measurements made during an ISWT should be evaluated in more detail.

Moloney et al. (2003) demonstrated a significant correlation between total distance walked in a corridor ISWT by patients with IPF and the VO_2 max measured during a shuttle walk test on a treadmill. In a previous study in our department the distance walked in an ISWT by patients diagnosed with IPF

correlated with the individual's VO_2 peak during an incremental cycle ergometry test (ICET) (Fielding et al., 2015). Linear regression was used to derive a formula which predicted VO_2 peak using ISWT distance. The present study looks to test this formula in a new cohort of patients with IPF.

Arterial oxygen pressure (PaO_2) at the end of a maximal CPET has also been shown to be a significant predictor of survival in patients with IPF (King et al., 2001). This study also investigates the relationship between blood oxygen pressure (PO_2) at the end of a CPET and the end of an ISWT.

1.2 Proposed study

Patients at University Hospital, Coventry and St Cross Hospital, Rugby will be invited to take part in a letter. Those who express an interest in taking part will be given more information about the study including a written document and then at least 48 hours to decide whether or not to take part in the study. Should they decide to take part, each participant will be asked to make two visits to University Hospital Respiratory Physiology and Sleep Department.

At one visit participants will be asked to undertake an ISWT; walking 10 m between cones at an increasing speed dictated by a standardised audiotape. The ISWT will be performed according to the standardised protocol set out by Singh et al. (1992) and our department protocol. At the other visit participants will undertake an ICET. The ICET will be performed on a static exercise bike following the department protocol. The order in which these two tests are done will be randomly assigned to each participant.

After both the ISWT and the ICET, an earlobe capillary blood sample will be taken by a trained member of staff and the sample analysed for blood oxygen pressure. Each participant will also fill in a questionnaire about their experience of the test.

The relationship between ISWT distance and VO_2 peak will be analysed and the oxygen pressure of capillary blood gas after each test will be compared.

1.3 Study population

This is a prospective study of patients with a diagnosis of IPF confirmed by a multi-disciplinary team. We aim to recruit a minimum of 43 patients to this study, all of whom will already be under the care of a Respiratory Consultant at University Hospitals Coventry and Warwickshire NHS Trust.

1 RATIONALE

2.1 Aims and hypothesis

- To test the relationship between VO_2 peak and the distance walked in an ISWT
- To test the hypothesis that PO_2 is the same at the end of an ISWT and a CPET.

2.2 Justification

This project tests a formula proposed by Fielding et al. (2015) to predict VO_2 peak during an ICET using distance walked in an ISWT. It will compare predicted VO_2 peak value with the actual value in a new cohort of patients with IPF. In addition, this study will test the relationship between PO_2 at the end of an ICET and at the end of an ISWT.

NICE recognises the importance of providing patients and their families with information when IPF is diagnosed and as the disease progresses (NICE, 2013b). Patients can be better informed about expectations of future symptoms and management, their treatment options and their life expectancy if more accurate prognostic tests are available.

This study paves the way for a relatively cheap and widely available incremental exercise test to be used to gather helpful information about a patient's prognosis. In the future, such a test could be recommended for making prognostic predictions in IPF.

2.3 Assessment and management of risk

The ISWT and CPET require physical effort and exertion. In rare cases these tests can cause myocardial infarction, cardiac arrhythmia, orthopaedic injury or, in exceptional circumstances, death. A specialist physiologist will assess each participant's fitness to carry out these tests beforehand. If a participant reports any chest pain or severe discomfort then the test will be stopped.

3 OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

3.1 Primary objective

To assess the relationship between VO_2 peak and ISWT distance and to determine how similar it is to a linear relationship from other data collected in a previous study with the following relationship:

VO2 peak = 10.02 + (0.01575 x ISWT distance)

3.2 Primary endpoint/outcome

VO_2 peak

4 TRIAL DESIGN

This is a basic science study involving procedures with human participants

5 STUDY SETTING

This study will be conducted at University Hospital, Coventry. All visits will take place in the Respiratory Physiology and Sleep Department, located within the Outpatients area of the hospital.

6 ELIGIBILITY CRITERIA

We will recruit a minimum of 43 participants to this study. In each case, the following inclusion and exclusion criteria will apply.

6.1 Inclusion criteria

- A diagnosis of IPF confirmed by a multidisciplinary team
- Over 16 years of age

6.2 Exclusion criteria

- Patients absolutely contraindicated for ISWT or ICET. Contraindications are summarised in table one. Where a patient has a relative contraindication, the test will be discussed with their medical team and a decision made as to whether or not to proceed.
- Inability to undertake ISWT or CPET
- Inability to walk without a walking aid such as a stick or frame
- Inability to give informed consent for testing

Absolute contraindications	Relative contraindications
Acute myocardial infarction (3–5 days) Unstable angina Uncontrolled arrhythmias causing symptoms or haemodynamic compromise Syncope Active endocarditis Acute myocarditis or pericarditis Symptomatic severe aortic stenosis Uncontrolled heart failure Acute pulmonary embolus or pulmonary infarction Thrombosis of lower extremities Suspected dissecting aneurysm Uncontrolled asthma Pulmonary oedema Room air SpO2 at rest ≤ 85% Acute respiratory failure Acute non-cardiopulmonary disorder that may affect exercise performance or be aggravated by exercise (i.e. infection, renal failure, thyrotoxicosis) Mental impairment leading to inability to cooperate	Left main coronary stenosis or its equivalent Moderate stenotic valvular heart disease Severe untreated arterial hypertension at rest (200 mmHg systolic, 120 mmHg diastolic) Tachyarrhythmias or bradyarrhythmias High-degree atrioventricular block Hypertrophic cardiomyopathy Significant pulmonary hypertension Advanced or complicated pregnancy Electrolyte abnormalities Orthopaedic impairment that prevents walking

7 TRIAL PROCEDURES

7.1 Recruitment

7.1.1 Patient identification

Patients known to have IPF and included in departmental IPF database will be sent a letter inviting them to take part in this research project. The letter will include a description of the study and will ask anybody

who is interested in taking part to contact Lizzie Dobson by phone, email or letter. Potential participants who are interested in taking part will be given information about the study including a written document and then at least 48 hours to decide whether or not to take part.

7.1.2 Screening

Only patients with a confirmed diagnosis of IPF will be asked to take part in the study. All participants will then be asked to fill in a participant questionnaire which will ask participants if they are taking part in any other research trials at the moment, about any other medical conditions which could contraindicate their taking part and whether or not they require a walking aid.

7.2 Consent

This study will obtain consent from adult participants only. Only patients deemed fit to give informed consent will be included in the study. All patients will be given a verbal outline of the study, given an information sheet to read and time to ask any questions that they might have about the research and their involvement. Potential participants still interested in taking part will be given a minimum of two days to decide whether or not they would like to take part. After this time a member of the research team will call the patient. There will be time for questions to be answered. If they would like to take part then they will be invited into University Hospital to give their informed consent by signing the consent form.

7.3 Baseline data

Any comorbidities will be asked for on the participant information sheet. No other baseline data will be required before visit one.

7.4 Trial assessments

At one visit participants will be asked to undertake an ISWT; walking 10 m between cones at an increasing speed dictated by a standardised audiotape. The ISWT will be performed according to the standardised protocol set out by Singh et al. (1992) and our department protocol. At the other visit participants will undertake an Incremental Cycle Ergometry Test (ICET). The ICET will be performed on a static exercise bike following the department protocol. After each of these exercise tests a capillary blood sample will be taken from the participant’s earlobe by a trained member of staff following department protocol. The blood sample will be analysed and oxygen pressure will be recorded. Both visits will be in the Respiratory Physiology and Sleep Department at University Hospital, Coventry.

7.5 Statistical analysis

The data collected in this study will be combined with data from the previous study in our department and distinguished by a study indicator. The similarity between the two datasets will be tested using a series of linear regression models. The value of PO_2, measured in capillary blood, after ISWT and after CPET will be compared using a paired t-test. All analyses will be performed in SPSS statistical software. We do not anticipate missing data. Should a participant withdraw from the study then none of the identifiable data that they generated will be used.

7.6 End of study definition

The end of the study will be defined when the last participant has completed the last study visit.

8 DATA HANDLING

8.1 Data collection tools and source document identification

Identifiable information will be saved in one database for this study. Each participant will be assigned a research number for this study which will be linked to their personal information only in this one database. All other project files and data collection sheets will be anonymised; the participant will only be identified by their research number.

All members of the Respiratory Physiology and Sleep team who have access to the office undertake annual information governance training and work within the guidelines of the Data Protection Act 1998.

8.2 Data handling and record keeping

Screening and recruitment logs of all participants approached to take part in the study and enrolled in the study will be kept for the study. Participants that agree to participate in the study will be assigned a unique identifier, which will be used to identify all documents associated with that participant for the duration of the study. All data generated in the study will be kept on site at UHCW. Participant consent will be recorded, in triplicate, on an informed consent form and stored securely at UHCW.

8.3 Access to Data

Access to study data will be restricted to members of the study team and patient identifiable data will be restricted to those members of staff that require it for the performance of their role. Direct access to data

will be granted to authorised representatives of the Sponsor, host institution and the regulatory authorities for the purposes of trial-related monitoring, audits and inspections.

8.4 Archiving

Following the resolution of queries and confirmation of study close-out by the CI, all essential documentation will transferred to a third party archiving service, which provides suitable fire and water-resistant facilities. Study files will be archived for a period of 25 years. Access to the study documentation will be restricted to named individuals within the study team with express permission from the CI.

9. TRIAL OVERSIGHT

9.1 Role and responsibilities of the Sponsor

UHCW has agreed to act as sponsor for this trial and will undertake the responsibilities of sponsor as defined by the Research Governance Framework and ICH Good Clinical Practice. An authorised representative of the Sponsor has approved the final version of this protocol with respect to the trial design, conduct, data analysis and interpretation and plans for publication and dissemination of results. As sponsor, UHCW provides indemnity for this trial and, as such, will be responsible for claims for any non-negligent harm suffered by anyone as a result of participating in this trial. The indemnity is renewed on an annual basis and will continue for the duration of this trial.

10. MONITORING, AUDIT & INSPECTION

The study may be monitored by the Research & Development Department at UHCW as representatives of the Sponsor, to ensure that the study is being conducted as per protocol, adhering to Research Governance and GCP. The approach to, and extent of, monitoring will be specified in a trial monitoring plan determined by the risk assessment undertaken prior to the start of the study.

11. ETHICAL AND REGULATORY CONSIDERATIONS

11.1 Ethical approval and research governance

The study will be conducted in compliance the principles of the ICH GCP guidelines and in accordance with all applicable regulatory guidance, including, but not limited to, the Research Governance Framework. Ethical approval for this study will be sought from the Research Ethics Committee combined with HRA approval. No study activities will commence until favourable ethical opinion and HRA approval has been obtained. Progress reports and a final report at the conclusion of the trial will be submitted to the approving REC within the timelines defined by the committee. Confirmation of capacity and capability will be obtained from the R&D department prior to commencement of the study at all participating sites.

11.2 Data protection and patient confidentiality

The study will comply with the Data Protection Act 1998 and regular checks and monitoring will be undertaken by the Trial Manger to ensure compliance. Participants will be assigned a unique identifier upon enrolment in to the study to allow link-anonymisation of patient-identifiable data. Access to patient identifiable data will be restricted to members of the study co-ordination team who require it for the performance of their role. Electronic data will be stored on password protected encrypted drives and hard copies of study documents will be stored in locked filing cabinets in secure entry-card protected sites..

12 DISSEMINATION POLICY

The results of this study will be written up as a report. This report will be given to all Respiratory Consultants and patients will be able to discuss the results with their consultant. The results will also be written up as a research project which will be handed in as part of a Clinical Science Masters programme at Manchester Metropolitan University. If accepted for presentation, the results will be presented to members of the Association of Respiratory Physiology and Technology at their annual conference.

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