Clinical Study Protocol

A Study to Compare Intergroup Effects of High-Intensity Interval Training (HIIT) with the Addition of High Flow Nasal Oxygen (HFNO) versus HIIT plus oxygen delivered through a nasal cannula (NC) in Patients with Fibrosing Interstitial Lung Disease (FILD).

Sponsor	The University of Edinburgh and Lothian Health Board ACCORD The Queen's Medical Research Institute 47 Little France Crescent Edinburgh EH16 4TJ
Protocol authors	**Jaime Jimenez, Roberto Rabinovich, Nikhil Hirani, Hillary Pinnock**
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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this Clinical Study Protocol.

Abbreviation or Special term	Explanation

CI	Chief Investigator
COPD	Chronic Obstructive Pulmonary Disease
CPET	Cardiopulmonary Exercise Test
CWRET	Constant Work Rate Exercise Test
DLCO	Diffusing capacity for Carbon Monoxide
ESWT	Endurance Shuttle Walking Test
FIO2	Fraction of Inspired Oxygen
FEV1/FVC	Forced Expiratory Volume in one second/ Forced Vital Capacity Ratio
FVC	Forced Vital Capacity
HADS	Hospital Anxiety Depression Scale
HIIT	High Intensity Interval Training
HFNO	High Flow Nasal oxygen
HRCT	High-Resolution Computed Tomography
ILD	Interstitial Lung Disease
IPF	Idiopathic Pulmonary Fibrosis
ISWT	Incremental shuttle walking test
MIET	Maximal Incremental Exercise Test
6MWT	6 Minute Walking Test
mMRC	Modified version of Medical Research Council Scale
NC	Nasal Cannula
NSIP	Non-specific Interstitial Pneumonia
PaCO2	Partial Pressure of Carbon Dioxide in the arterial blood
PEEP	Positive End-Expiratory Pressure
PI	Principal Investigator
PR	Pulmonary Rehabilitation
QMVCT	Quadriceps Maximal Voluntary Contraction Test
QoL	Quality of Life
RIE	Royal Infirmary of Edinburgh
SGRQ	Saint George Respiratory Questionnaire
TLC	Total Lung Capacity
Tlim	Exercise Endurance
VO2max	Maximal Oxygen Consumption

1. INTRODUCTION

1.1 BACKGROUND

Interstitial lung disease (ILD) is a diverse group of entities that cause damage to the lung parenchyma through varying degrees of inflammation and fibrosis. Fibrotic ILDs result in restrictive ventilatory physiology and impaired gas exchange, frequently leading

to exertional hypoxemia and functional limitation (1). These diseases have been classified into various groups: ILD of known cause such as occupational or environmental exposures including Pneumoconiosis and Hypersensitivity Pneumonitis, ILD associated to connective tissue diseases/vasculitis, idiopathic interstitial pneumonias including idiopathic pulmonary fibrosis (IPF) and nonspecific interstitial pneumonia (NSIP), granulomatous ILD such as sarcoidosis and other rare forms of ILD including lymphangioleiomyomatosis (2, 3, 4). Among all these diseases the most common is IPF whose number of deaths in the UK according to the data from the office of national statistics increased from 1.66 per 100,000 people in 1979 to 8.29 per 100,000 people in 2016 (5). The mechanisms of reduced exercise capacity in ILD are multi-factorial. Impaired gas exchange occurs as a result of destruction of the pulmonary capillary bed and thickening of the alveolar-capillary membrane, resulting in ventilation-perfusion mismatch and oxygen diffusion limitations. Circulatory limitation results from pulmonary capillary destruction and pulmonary vasoconstriction and leads to pulmonary hypertension and cardiac dysfunction in some patients. Ventilatory limitations to exercise may also occur, although these are not thought to be a major contributor in most patients (6, 7). Peripheral muscle dysfunction is also a key factor to exercise limitation. Patients who suffer from ILD tend to avoid activities that trigger dyspnoea and fatigue, consequently they reduce their levels of physical activity, which leads to physical deconditioning and increasing symptoms. Furthermore, treatment with corticosteroids and immunosuppressants, as well as systemic inflammation, may also negatively impact on peripheral muscle function in some patients with ILD (6, 7). Pulmonary rehabilitation is an evidence-based, multidisciplinary and comprehensive intervention for patients with chronic respiratory disease who are symptomatic and often have decreased daily life activities. PR programmes include exercise training - which is the cornerstone of PR and includes aerobic conditioning, strength and endurance training respiratory therapy, education, nutritional interventions, psychological and social support and behaviour modification techniques (8, 9, 10). PR can be performed in different places; such as hospital outpatient departments, community health centres and even at home, showing similar results. PR has demonstrated improvements in symptoms, exercise tolerance and quality of life in chronic respiratory diseases other than COPD, including ILD and pulmonary hypertension, despite differences in underlying pathophysiology among them. Nevertheless, there is much less evidence of these improvements and the mechanisms by which pulmonary rehabilitation might improve outcomes in ILD compared to COPD (6, 7). Despite this, guidelines for pulmonary rehabilitation recommend its use in patients with chronic respiratory disorders other than COPD. Emerging evidence suggests that pulmonary rehabilitation may result in meaningful short-term benefits in patients with ILD, mainly on exercise tolerance, muscle function, dyspnoea and quality of life. However, the magnitude of these benefits is smaller than those generally seen in COPD and its ongoing effects are not evident six months after training (7). This may reflect the challenges in providing pulmonary rehabilitation for conditions such as idiopathic pulmonary fibrosis (IPF) that can be rapidly progressive (11). Guidelines for clinical management ILD point out that more information is needed on the benefits of pulmonary rehabilitation for this group of patients (7, 12). The greater prevalence of exercise-induced hypoxia, pulmonary hypertension and arrhythmia compared with other chronic lung diseases in this patient population raises the possibility that response to exercise rehabilitation may also differ (6, 7). In turn, high flow nasal oxygen allows the delivery of a well humidified high flow of air with a mix of oxygen from 21 to 100% and also provides a low level of positive end-expiratory pressure (PEEP). This strategy can achieve higher values of oxygenation even in acutely ill patients with ILD (13, 14) and may

constitute a strategy to ameliorate hypoxemia triggered by exercise in these patients and therefore increase the tolerance to higher training loads.

1.2 RATIONALE FOR CONDUCTING THIS STUDY

Patients with fibrotic ILD have greater oxygen desaturation during 6MWT compared to patients with COPD when adjusting for demographic features and pulmonary physiology. These findings suggest the need for disease-specific studies to evaluate the potential utility of ambulatory oxygen in fibrotic ILD (1). In general, these diseases manifest as dyspnoea on exertion. Progression of disease results in marked exercise limitation, predominantly due to impairment of gas exchange and secondarily due to pulmonary hypertension and other mechanisms including muscle deconditioning. These patients require high levels of supplemental oxygen (> 6 L/ min) to sustain daily activities (15), which could not be satisfied using traditional oxygen delivery methods comfortably. High-Flow Nasal Oxygen might potentially be an alternative to conventional oxygen therapy in patients requiring both high flows and high oxygen concentrations to correct hypoxemia and control dyspnoea, however the evidence is still limited (13, 16,). HFNO can deliver very high flows (up to 60 L/min) and utilizes an air oxygen blend allowing from 21 to 100% FIO2 delivery (13, 14). Furthermore, this system facilitates the delivery of humidified oxygen and improve gas exchange by delivering a small amount of Positive End Expiratory Pressure (PEEP). In turn, HFNO contributes to reduce PaCO2 by reducing the death space (i.e. washout of CO2 from the upper airway) (13, 14). It has been demonstrated that patients with Idiopathic pulmonary fibrosis (IPF) have reduced exercise tolerance, which can be assessed among other tests with a CPET, constant work rate exercise test (CWRET), six minute walking test (6MWT), incremental/endurance shuttle walking test (ISWT/ESWT) among other tests. A lower exercise capacity is related to a worse mortality rate. Exercise training has shown to improve exercise tolerance, functional capacity, dyspnoea and quality of life in patients with IPF. Exercise-induced hypoxaemia is sometimes seen in patients with IPF even without resting hypoxaemia, and has been shown to increase mortality risk. Although the IPF guidelines recommend that IPF patients with resting hypoxaemia receive supplemental long-term oxygen therapy, the clinical benefit of exertional supplemental oxygen is unclear in patients with exertional hypoxaemia without resting hypoxaemia. Possible physiological benefits of oxygen supplementation on exercise in IPF may include alterations of muscle metabolism, improvements in oxygen transport at the periphery and improvements in muscle oxidative capacity (17).

Furthermore, it is important to explore and optimize the relationship between outcomes (i.e. improvement on exercise tolerance and quality of life) and the characteristics of the exercise training programme. It is also important to further explore strategies that, by minimising the oxygen desaturation, can allow patients to exercise at higher loads (7).

Strategies to increase the load of training include:

• High Intensity Interval Training (HIIT): This strategy, opposite to constant work rate exercise, divides the training load into bouts of high-intensity exercise divided by resting periods. This reduces desaturation, lowers ventilatory (circa 20%) and heart rate response and, therefore enables longer tolerance to exercise (circa 60%) (12).

• Compared to conventional programmes, high-intensity programmes have shown superior and longer-lasting results in other chronic pulmonary diseases. The limitations of high-intensity exercise tolerance in ILD patients such as desaturations and ventilatory limitations can be ameliorated by the use of interval training.

Therefore, we believe that HIIT with the addition of HFNO might improve the exercise capacity in patients who suffer from ILD. This increment could justify its combined use and, thus, contribute to improve the effects of pulmonary rehabilitation programmes in these patients.

1.3 RESEARCH QUESTION

Will HIIT combined with HFNO lead to better outcomes (i.e. exercise capacity, QoL) in comparison to PR delivered without HFNO in ILD patients?

2 STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVE

To evaluate the effects of an 8-week HIIT plus HFNO on exercise capacity of patients with ILD, in comparison to standard PR measured with a constant work rate cycle test (CWRCT) at 75% of the maximal workload obtained from a maximal CPET conducted beforehand. The high-intensity CWRET is considerably more responsive than incremental exercise tests or the 6-min walking test to assess the effects of interventions (18, 19, 20).

3 OUTCOME MEASURES

3.1 PRIMARY OUTCOME

The primary outcome will be Exercise Capacity, which will be assessed as endurance time (Tlim) during a constant work rate cycle test at 75% of the maximal workload (obtained beforehand from a maximal CPET).

3.2 SECONDARY OUTCOMES

Physical activity levels in daily life using Actigraph GT3x activity monitor, quadriceps muscle strength through the quadriceps maximal voluntary contraction test (QMVCT), quality of life using IPF-specific version of the St George's Respiratory Questionnaire (SGRQ), anxiety and depression levels through the Hospital Anxiety and Depression Scale (HADS), dyspnoea trough the Modified version of the Medical Research Council scale (mMRC),. The number of patients using anti-fibrotic medication will also be assessed.

Additionally, we will explore impact in blood biomarkers associated with fibrosis selected from the ELFMEN study that have been shown to be associated with disease

progression (Inc. but not restricted to PAI-1, VEGF-A, PDGF-AA, PDGF-BB, Cystatin-C, Angiopotein-1, HE4/WFDC-2) (21).

We will also assess if the patients who are in treatment with antifibrotic medicines have better results than those who are not in treatment with antifibrotic medicines. This will be done in an exploratory way, where at the end of the study we will compare statistically if those patients who had a prescription of antifibrotics had better results compared to those who did not have a prescription of these medicines.

4 METHODS

4.1 STUDY DESIGN

This is a Randomized, Controlled, Multicentre Proof-of-Concept (PoC) Study of 30 patients with ILD, which will be randomized into 2 groups; the first group will be submitted to 8 weeks of a PR program based on HIIT plus HFNO and the second group will also be submitted to 8 weeks of a PR program based on HIIT, but with conventional oxygen delivery without HFNO. Which group will use HFNO or conventional oxygen will be randomly selected from a sealed envelope.

In general the study will consist of 8 weeks of intervention in the clinic plus 1 day of evaluations before and after the intervention. Spending 1 hour per day, three times a week every second day during the intervention and 2 hours during the other 2 days of evaluations approximately. The window between the baseline appointment and the first day of the intervention can be from 1 to 30 days, and the window between the last day of intervention and the post intervention appointment will be from 8 to 38 days. All the visits will take place in ward 204 (Respiratory Medicine) of the Royal Infirmary of Edinburgh (for participants from Edinburgh) and in the Royal Victoria Infirmary, Newcastle upon Tyne Hospital (for participants from Newcastle).

The following measurements will be conducted:

During the first day before of the intervention, a blood test will be taken (6 ml) to know the levels of blood biomarkers associated with fibrosis that have been shown to be associated with disease progression (Inc. but not restricted to PAI-1, VEGF-A, PDGF-AA, PDGF-BB, Cystatin-C, Angiopotein-1, HE4/WFDC-2). Additionally, a test called the quadriceps maximal voluntary contraction test (QMVCT) will be taken to measure the strength of the quadriceps muscle. The subjects are studied seated in a chair, with hip and knee flexion of 90 degrees. An inextensible strap is placed around the ankle, adjusted to ensure the knee remains at 90 degrees flexion. The ankle strap is connected to a strain gauge mounted on the back of the chair. A seatbelt is secured across the subject's hips to stabilise the pelvis. The patient has to do a knee extension and we can measure their strength.

Also, the shortness of breath will be assessed using the Modified version of the Medical Research Council scale (mMRC).

In addition, height and weight will be taken. Breathing tests will not be performed, because these procedures the participants have already done in the outpatient clinic.

In addition, a Cardiopulmonary Exercise Test (CPET) will be carried out.

Furthermore, a Constant work rate Cycle Test at 75% of peak work rate (obtained from a maximal exercise test conducted beforehand) will be carried out. The participants will be able to rest for about 20 minutes between each test and we will offer them refreshments.

Physical activity levels in daily life will also be measured using Actigraph GT3x activity monitor, which will be delivered during the baseline appointment to use in their house for only 1 week before and 1 week after of the intervention, this is a belt that the participants will have to use like any other. After of the intervention they should return it to us during their post intervention appointment.

Moreover, two questionnaires called St George's Respiratory Questionnaire (SGRQ) and the Hospital Anxiety and Depression Scale (HADS), will have to be answered to measure the quality of life and anxiety and depression levels respectively. These test will be answered at home.

During the first day after of the intervention, participants will be undergone exactly to the same tests as in the baseline appointment, except height.

Intervention, a group of participants will be submitted to 8 weeks of a PR program based on HIIT plus HFNO and the other group will also be submitted to 8 weeks of a PR program based on HIIT but with conventional oxygen delivery without HFNO. Both HIIT will be performed at the same workload, which will be progressive throughout the 8 weeks and will be modified during each session. Starting with high load intervals at 60% of the maximal watts achieved beforehand during a maximal CPET divided by lower load intervals at 40% maximum load during the first week, and finishing with high load intervals at 110% maximum load separated by load intervals at 80% maximum load in the last weeks. Basically the participants will have to pedal in a stationary bicycle for 30 minutes (aerobic training), during the other 20 minutes the patients will do exercises for their upper limbs using Thera bands and dumbbells (strength training). Muscles of upper limbs to work will be deltoids, pectorals and biceps (3 series of 10 repetitions each). Finally the participants will receive 10 minutes of respiratory physiotherapy including techniques to eliminate phlegm, breathing exercises and ludic activities to train the respiratory muscles such as inflating balloons.

Which group will use HFNO or conventional oxygen will be randomly selected from a sealed envelope. Randomized means that all participants will have the same chance of belonging to one group or another, they must choose a sealed envelope and inside it will be written to which group they will belong.

4.2 NUMBER OF PARTICIPANTS

15 participants with ILD will be recruited in the Lothian region, and another 15 participants in the Royal Victoria Infirmary, Newcastle upon Tyne Hospital (for

participants from Newcastle). The length of recruitment period will be approximately 6 months.

4.3 INCLUSION CRITERIA

1.- Fibrosing lung disease on HRCT obtained from medical records, defined as reticular abnormality with traction bronchiectasis with or without honeycombing, with disease extent of >10%, performed within 24 months of screening visit Clinical stability concerning pulmonary infections or acute exacerbations within the previous four weeks of inclusion in the study.

2.- Absence of recent Myocardial Infarction (within last 3 months), unstable angina, other significant cardiac problems, systolic blood pressure > 180 mmHg, diastolic blood pressure > 100 mmHg or tachycardia (higher than 100 bpm)

3. - Absence of significant orthopaedic, neurological, cognitive and/or psychiatric impairment restricting mobility.

4. - Not following any exercise programme in the last 3 months.

5. - Participants between 18 and 85 years old will be recruited and with ability to give informed consent.

6. - TLCO ≥ 25% and ≤ 80% predicted. FVC (or VC) ≥ 45%

7. -Patients that experience a drop in oxygen saturation with exercise below 90%

4.4 EXCLUSION CRITERIA

1. - Emphysema greater than extent of fibrosis on high resolution computed tomography (HRCT) of the thorax.

2. - FEV1/FVC ratio < 70%.

3. - Participants should not be taking part in other interventional studies currently. Our research is not a CTIMPs and co-enrolment will not be allowed under any circumstances.

4. - Absolute contraindications for cardiopulmonary exercise testing, which are:

a. - Unstable angina
b. - Uncontrolled arrhythmias causing symptoms or hemodynamic compromise.
c. - Syncope.
d. - Active endocarditis.
e. - Acute myocarditis or pericarditis.
f. - Symptomatic severe aortic stenosis.
g. - Uncontrolled heart failure.
h. - Acute pulmonary embolus or pulmonary infarction.
i. - Thrombosis of lower extremities.
j. - Suspected dissecting aneurysm.
k. - Uncontrolled asthma.

l. - Pulmonary edema.
m. - Room air desaturation at rest ≤ 85%
n. - Respiratory failure.
o. - Acute no cardiopulmonary disorder that may affect exercise performance or be aggravated by exercise (i.e. infection, renal failure, thyrotoxicosis)
p. - Mental impairment leading to inability to cooperate.

4.5 RECRUITMENT, CONSENT AND SCREENING

All Patients affected with interstitial lung diseases referred to the physiotherapy department to receive pulmonary rehabilitation in the Lothian region and Newcastle, also those from the ILD clinic will be invited by a member of the direct care team (Dr Roberto Rabinovich in Edinburgh and Dr Ian Forrest in Newcastle) to participate and will receive a patient's information sheet with an invitation to attend pre-assessment for this study. This appointment should occur at least 3 days after the patient has received the Patient Information Sheet. This is to ensure that the patient has adequate time to consider his or her decision to participate in the study. At pre-assessment, the study will be explained to them and written informed consent will be obtained from those agreeing to participate.

4.6 WITHDRAWAL OF STUDY PARTICIPANTS

Participants are free to withdraw from the study at any point or a participant can be withdrawn by the Investigator. If withdrawal occurs, the primary reason for withdrawal will be documented in the participant's case report form, if possible. The participant will have the option of withdrawal from:

(i) All aspects of the trial but continued use of data collected up to that point. To safeguard rights, the minimum personally-identifiable information possible will be collected.

(ii) The study will be stopped on patients that are presenting an acute exacerbation of their lung condition or unable to perform the exercise test. These patients will receive adequate treatment and the study will be delayed. Patients with disease progression that prevents them to continue their participation will be discontinue from their participation in the study.

4.7 BASELINE MEASUREMENTS

All the visits will take place in ward 204 (Respiratory Medicine) of the Royal Infirmary of Edinburgh (for participants from Scotland) and in the Royal Victoria Infirmary, Newcastle upon Tyne Hospital (for participants from Newcastle).

The visits during the first day before and after the intervention will take 2 hours each, and the following tests will be performed:

- Consent firstly will be re-confirmed at this visit.

- A blood test will be taken (6 ml) to know the levels of blood biomarkers associated with fibrosis that have been shown to be associated with disease progression (Inc. but not restricted to PAI-1, VEGF-A, PDGF-AA, PDGF-BB, Cystatin-C, Angiopotein-1, HE4/WFDC-2).

- A quadriceps maximal voluntary contraction test (QMVCT) will be taken to measure the strength of the quadriceps muscle.

- The shortness of breath will be assessed using the Modified version of the Medical Research Council scale (mMRC).

- Height.

- Weight.

- A Cardiopulmonary Exercise Test (CPET).

- A Constant work rate Cycle Test (CWRCT) at 75% of peak work rate (obtained from a maximal exercise test conducted beforehand) will be carried out.

- During this visit the PI will deliver to the participants the Actigraph GT3x activity monitor, which will have to be used at home for 1 week before and 1 week after of the intervention to measure the physical activity levels in daily life. The participants will have to return it during their post intervention appointment.

- Also during this visit two questionnaires called St George's Respiratory Questionnaire (SGRQ), which measure the quality of life will be delivered by the PI to be answered at home, the first one must be answered 1 day before of the intervention and returned during the first day of the intervention and the second one will have to be answered 1 day after of the intervention and returned during the post intervention appointment.

- Finally another 2 questionnaires called Hospital Anxiety and Depression Scale (HADS), which measure the anxiety and depression levels likewise will be delivered by the PI to be answered at home, the first one must be answered 1 day before of the intervention and returned during the first day of the intervention and the second one will have to be answered 1 day after of the intervention and returned during the post intervention appointment.

The participants will be able to rest for about 20 minutes between each test and we will offer them refreshments. Oxygen will be supplied, when needed, via nasal cannula and titrated to maintain a $SpO2 \geq 88\%$.

4.8 RANDOMISATION

Following confirmation of eligibility by the CI or PI and signature of the informed consent, patients will be randomised using sealed letters to HIIT plus HFNO or HIIT plus nasal cannula. Patients will be sequentially randomised. Randomisation code and sealing of envelopes will be done by the research nurses and stored in a room at RIE and Royal

Victoria Infirmary accessible with a key. This will be done before any baseline procedures.

4.9 BLINDING

In this open label study patients will not be blinded with respect to the modality of oxygen delivery but will not know the dose of oxygen they will be receiving or their SpO2 during the pulmonary rehabilitation program and the tests.

4.10 INTERVENTION

The intervention consists of HIIT plus HFNO versus HIIT plus oxygen delivered through a nasal cannula. The oxygen delivered via HFNO will be between 31 and 37°C according to patient preference. To minimize condensation, the heated humidified gas is delivered via heated tubings through a wide-bore nasal prong. Air flow will be 50 L/min and FiO2 will be titrated to maintain SpO2 above 88%. The comparator will be oxygen delivered via nasal cannula titrated to the same SpO2. Both HIIT will be performed at the same workload, which will be progressive throughout the 8 weeks and will be modified during each session in order to achieve a Borg score of 5, starting with high load intervals at 60% of the maximal watts achieved beforehand during a maximal CPET divided by lower load intervals at 40% maximum load during the first week, and finishing with high load intervals at 110% maximum load separated by load intervals at 80% maximum load in the last weeks (see Appendix A and C).

Basically the participants will have to pedal in a stationary bicycle for 30 minutes, during the other 20 minutes the patients will do exercises for their upper limbs using Thera bands and dumbbells. Muscles of upper limbs to work will be deltoids, pectorals and biceps (3 series of 10 repetitions each). Finally the participants will receive 10 minutes of respiratory physiotherapy including techniques to eliminate phlegm, breathing exercises and ludic activities to train the respiratory muscles such as inflating balloons.

Which group will use HFNO or conventional oxygen will be randomly selected from a sealed envelope. Randomized means that all participants will have the same chance of belonging to one group or another, they must choose a sealed envelope and inside it will be written to which group they will belong.

4.11 DURATION OF THE STUDY

In general, the study will consist of 8 weeks of intervention plus 1 day of evaluations before and after the intervention. The window between the baseline appointment and the first day of the intervention can be from 1 to 30 days, and the window between the last day of intervention and the post intervention appointment will be from 8 to 38 days.

Assessment	Screening	Baseline Appointment	To be done at home	Intervention (8 weeks)	Post-Intervention Appointment

		(1st day before Intervention)	(Pre &Post Intervention)		(1st day after Intervention)
Assessment of eligibility criteria	X				
Written informed consent	X				
Demographic data, contact details	X				
Randomisation	X				
Weight		X			X
Height		X			
Blood Test		X			X
Blood Pressure		X			X
QMVCT		X			X
mMRC		X			X
CPET		X			X
CWRCT		X			X
Physical activity levels in daily life			X		
SGRQ (Questionnaire)			X		
HADS (Questionnaire)			X		
Intervention 1st Group HIIT + HFNO				X	
Intervention 2nd Group HIIT + NC				X	

Observation: There will be continual ECG monitoring during all the tests.

4.12 DATA COLLECTION

The UK General Data Protection Regulation (GDPR) requires appropriate technical and organisational measures to be in place to implement the data protection principles effectively and safeguard individual rights. This is 'data protection by design and by default'.

In essence, this means we will integrate or 'bake in' data protection into our processing activities and business practices, from the design stage right through the lifecycle.

4.12.1 Data to be collected:

- Weight
- Height
- Blood Test (blood biomarkers associated with the progression of the fibrosis)
- Blood Pressure
- QMVCT (Strength of the Quadriceps muscle measured in Newtons)
- mMRC (score of dyspnoea from 1 to 5)
- CPET (Maximum workload measured in watts)
- CWRCT (tlim or exercise tolerance measured in minutes)
- Physical activity levels in daily life (measured in steps)
- SGRQ (Score of this questionnaire that measures the QoL)
- HADS (Score of this questionnaire that measures anxiety and depression levels)

4.12.2 Time points for collection: these data will be collected during the baseline and post intervention appointment by the CI (Dr Roberto Rabinovich) and the PI (Jaime Jimenez) in Edinburgh and by Fran Chambers (Physiotherapist) in Newcastle.

4.12.3 Details of standardised tools to be used:

- Modified version of the Medical Research Council scale (mMRC): see appendix D.

- Saint George Respiratory Questionnaire (SGRQ): see appendix E.

- Hospital Anxiety Depression Scale (HADS): see appendix F.

4.12.4 Methods to maximise completeness of data: PI will call participants who have not returned questionnaires.

4.12.5 How will data be recorded Data will be recorded using both eCRF and pCRF.

4.12.6 Source Data Documentation: Source data is defined as all information in original records and certified copies of original records or clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents.

Source documents are original documents, data and records where source data are recorded for the first time.

We will use the medical records from Trak to obtain information of the high resolution computed tomography (HRCT) of the thorax, echocardiograms, breathing tests including Spirometry, Lung volumes and DLCO.

4.12.7 Case Report Forms: The case report forms (paper and electronic) will be entered in an anonymised database where patients will be with the study related unique study identifier number (ILDHIIT001....n) held in a university computer at Centre for Inflammation Research (CIR).

5. DATA MANAGEMENT AND ANALYSIS

Data will be entered in an excel datasheet and imported to the statistical package SPSS version 23 for analysis. The anonymised database will be held in a university computer.

Physical activity level (PAL) data are handles in a standard manner: weekends are not being considered, only valid days (more than 8 h data) will be included in the analysis. At least valid data from two days need to be included as representative of valid PAL. Average of the days (minimum 2, max 5) will be the variable representing PAL. There will be different output of the monitor to include in the database (e.g. steps per day, energy consumption, etc.). Data from before the intervention and after the intervention will be generated in this manner and compared

5.1 PERSONAL DATA

The following personal data will be collected as part of the research: Name, CHI number, study related unique identifier number, gender, age, date of birth. The data will be collected in paper and held in The Royal of Infirmary of Edinburgh and in The Royal Victoria Infirmary within a fireproof lockable cabinet within a locked room. The study data will be entered in an anonymised database where patients will be with the study related unique study identifier number (ILDHIIT001....n) held in a university computer at Centre for Inflammation Research (CIR). Personal data will be stored for 3 years. Only the research team will have access to the personal data.

No personal information will be part of the database. Patients ID will be a number corresponding to when the patient was included (i.e. first patient 001, second 002……n). A separate file will include personal information and link this with the study ID. This separate database will be stored in an NHS computer.

5.2 DATA INFORMATION FLOW

Personal information collected will be stored in paper format and stored in the hospital under lock. Patients will be identified in the database by a study ID number (see section above) and, therefore, the database in excel format will be anonymised.

The personal data collected during approximately 6 months (stored in paper and on excel file) will be used for 6 more months and will be deleted 3 years after finishing the study. These are stored in paper (NHS facility locked room) and excel file on NHS computer.

5.3 TRANSFER OF DATA

Data collected or generated by the study (including personal data) will not be transferred to any external individuals or organisations outside of the Sponsoring organisation(s).

5.4 DATA CONTROLLER

A data controller is an organisation that determines the purposes for which, and the manner in which, any personal data are processed. The University of Edinburgh and NHS Lothian are joint data controllers along with any other entities involved in delivering the study that may be a data controller in accordance with applicable laws (e.g. the site).

5.5 DATA BREACHES

Any data breaches will be reported to the University of Edinburgh (dpo@ed.ac.uk) and NHS Lothian (Lothian.DPO@nhslothian.scot.nhs.uk) Data Protection Officers who will onward report to the relevant authority according to the appropriate timelines if required.

6. STATISTICS AND SAMPLE SIZE

We did no calculate the sample size, because this is a Randomized, Controlled, Multicentre Proof-of-Concept (PoC) study. However, we expect to recruit 30 ILD patients approximately.

Categorical variables will be summarized by frequency. Continuous variables will be expressed as mean ± standard deviation (SD) or mean (95% confidence interval [CI]).
For comparisons with the data for categorical variables or continuous variables between groups, a chi-squared test or Student's t-test will be used. The statistical analysis will be conduct with the program SPSS version 23. The level of significance for all comparisons will be set at $p<0.05$. We will collect any adverse event information and it will only be collected on an ae log.

7 STUDY RISKS AND BENEFITS

7.1 POTENTIAL RISKS AND MANAGEMENT

CPET with incremental and constant work load are part of the usual pulmonary rehabilitation programme tests. High flow nasal oxygen and exercise capacity assessment are commonly used in patients with interstitial lung diseases both, when stable and during exacerbations. Only stable patients will be part of this study. The tests will be monitored and stopped if any of the following occurs:

Progressive Chest Pain.

Oxygen desaturation to below 80%.

Hypotension, drop in systolic blood pressure or failure of BP to rise through exercise.

Severe Hypertension (>250/120 mmHg).

More than 2mm ST segment depression (horizontal or negative sloping).

3mm ST depression (positive sloping).

Progressive ST Segment elevation.

AV Block.

Frequent Ventricular Ectopic or Ventricular Arrhythmias.

Rapid Supra-ventricular Arrhythmias.

All aforementioned are test termination criteria and we have everything necessary to provide emergency care and stabilize the patient if this is needed.

7.2 POTENTIAL BENEFITS

The results of the assessments will be sent to their usual care provider if they wish. Any abnormalities found during the assessments, including of initial screening, will be reported to the general practitioner of the patient. The results of the study may help to identify a strategy to improve the delivery of pulmonary rehabilitation to patients with ILD with a potential to improve the effects of pulmonary rehabilitation in this population.

8. PROJETC TEAM AND TASK ALLOCATION

The overall project will be led by Dr Roberto Rabinovich with the support of Jaime Jiménez (PhD Student Respiratory Medicine), Dr Nikhil Hirani, Dr Hilary Pinnock and the Physiotherapist Jill Gill.

9. PROJECT MANAGEMENT AND QUALITY ASSURANCE

The project team, consisting of a grant holder and research staff, will meet twice monthly. There will be a weekly meeting between the lead researcher and his collaborators to discuss the progress of the study.

10 OVERSIGHT ARRANGEMENTS

10.1 INSPECTION OF RECORDS

Investigators and institutions involved in the study will permit trial related monitoring and audits on behalf of the sponsor, REC review, and regulatory inspection(s). In the event of audit or monitoring, the Investigator agrees to allow the representatives of the sponsor direct access to all study records and source documentation. In the event of

regulatory inspection, the Investigator agrees to allow inspectors direct access to all study records and source documentation.

10.2 STUDY MONITORING AND AUDIT

The ACCORD Sponsor Representative will assess the study to determine if an independent risk assessment is required. If required, the independent risk assessment will be carried out by the ACCORD Quality Assurance Group to determine if an audit should be performed before/during/after the study and, if so, at what frequency.

Risk assessment, if required, will determine if audit by the ACCORD QA group is required. Should audit be required, details will be captured in an audit plan. Audit of Investigator sites, study management activities and study collaborative units, facilities and 3rd parties may be performed.

11. GOOD CLINICAL PRACTICE

11.1 ETHICAL CONDUCT

The study will be conducted in accordance with the principles of the International Conference on Harmonisation Tripartite Guideline for Good Clinical Practice (ICH GCP).

Before the study can commence, all required approvals will be obtained and any conditions of approvals will be met.

11.2 INVESTIGATOR RESPONSIBILITIES

The Investigator is responsible for the overall conduct of the study at the site and compliance with the protocol and any protocol amendments. In accordance with the principles of ICH GCP, the following areas listed in this section are also the responsibility of the Investigator. Responsibilities may be delegated to an appropriate member of study site staff.

11.2.1 Informed Consent

The Investigator is responsible for ensuring informed consent is obtained before any protocol specific procedures are carried out. The decision of a participant to participate in clinical research is voluntary and should be based on a clear understanding of what is involved.

Participants must receive adequate oral and written information – appropriate Participant Information and Informed Consent Forms will be provided. The oral explanation to the participant will be performed by the Investigator or qualified delegated person, and must cover all the elements specified in the Participant Information Sheet and Consent Form.

The participant must be given every opportunity to clarify any points they do not understand and, if necessary, ask for more information. The participant must be given

sufficient time to consider the information provided. It should be emphasised that the participant may withdraw their consent to participate at any time without loss of benefits to which they otherwise would be entitled.

The participant will be informed and agree to their medical records being inspected by regulatory authorities and representatives of the sponsor(s).

The Investigator or delegated member of the trial team and the participant will sign and date the Informed Consent Form(s) to confirm that consent has been obtained. The participant will receive a copy of this document and a copy filed in the Investigator Site File (ISF) and participant's medical notes (if applicable).

11.2.2 Study Site Staff

The Investigator will be familiar with the protocol and the study requirements. It will be investigator's responsibility to ensure that all staff assisting with the study are adequately informed about the protocol and their trial related duties.

11.2.3 Data Recording

The Principal Investigator will be responsible for the quality of the data recorded in the CRF at each Investigator Site.

11.2.4 Investigator Documentation

The Principal Investigator will ensure that the required documentation is available in local Investigator Site files ISFs.

11.2.5 GCP Training

All the research personnel involved in the study have undertaken GCP training in order to understand the principles of GCP.

11.2.6 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain participant confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant. The Investigator and study site staff involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished information, which is confidential or identifiable, and has been disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee will be obtained for the disclosure of any said confidential information to other parties.

11.2.7 Data Protection

All Investigators and study site staff involved with this study comply with the requirements of the appropriate data protection legislation (including the General Data

Protection Regulation and Data Protection Act) with regard to the collection, storage, processing and disclosure of personal information. Computers used to collate the data will have limited access measures via user names and passwords. Published results will not contain any personal data and be of a form where individuals are not identified and re-identification is not likely to take place.

12. STUDY CONDUCT RESPONSIBILITIES

12.1 PROTOCOL AMENDMENTS

Any changes in research activity, except those necessary to remove an apparent, immediate hazard to the participant in the case of an urgent safety measure, will be reviewed and approved by the Chief Investigator.

Amendments will be submitted to a sponsor representative for review and authorisation before being submitted in writing to the appropriate REC, and local R&D for approval prior to participants being enrolled into an amended protocol.

12.2 MANAGEMENT OF PROTOCOL NON COMPLIANCE

Prospective protocol deviations, i.e. protocol waivers, will not be approved by the sponsors and therefore will not be implemented, except where necessary to eliminate an immediate hazard to study participants. If this necessitates a subsequent protocol amendment, this should be submitted to the REC, and local R&D for review and approval if appropriate.

Protocol deviations will be recorded in a protocol deviation log and logs will be submitted to the sponsors every 3 months. Each protocol violation will be reported to the sponsor within 3 days of becoming aware of the violation. All protocol deviation logs and violation forms will be emailed to QA@accord.scot

Deviations and violations are non-compliance events discovered after the event has occurred. Deviation logs will be maintained for each site in multi-centre studies. An alternative frequency of deviation log submission to the sponsors may be agreed in writing with the sponsors.

12.3 SERIOUS BREACH REQUIREMENTS

A serious breach is a breach which is likely to effect to a significant degree:

(a) The safety or physical or mental integrity of the participants of the trial; or

(b) The scientific value of the trial.

If a potential serious breach is identified by the Chief investigator, Principal Investigator or delegates, the co-sponsors (seriousbreach@accord.scot) will be notified within 24 hours. It is the responsibility of the co-sponsors to assess the impact of the breach on the

scientific value of the trial, to determine whether the incident constitutes a serious breach and report to research ethics committees as necessary.

12.4 STUDY RECORD RETENTION

All study documentation will be kept for a minimum of 3 years from the protocol defined end of study point. When the minimum retention period has elapsed, study documentation will not be destroyed without permission from the sponsor.

12.5 END OF STUDY

The end of study is defined as the last participant's last visit. The Investigators or the co-sponsor(s) have the right at any time to terminate the study for clinical or administrative reasons. The end of the study will be reported to the REC, and R+D Office(s) and co-sponsors within 90 days, or 15 days if the study is terminated prematurely. The Investigators will inform participants of the premature study closure and ensure that the appropriate follow up is arranged for all participants involved. End of study notification will be reported to the co-sponsors via email to resgov@accord.scot. A summary report of the study will be provided to the REC within 1 year of the end of the study.

12.6 INSURANCE AND INDEMNITY

The co-sponsors are responsible for ensuring proper provision has been made for insurance or indemnity to cover their liability and the liability of the Chief Investigator and staff.

The following arrangements are in place to fulfil the co-sponsors' responsibilities:

• The Protocol has been designed by the Chief Investigator and researchers employed by the University and collaborators. The University has insurance in place (which includes no-fault compensation) for negligent harm caused by poor protocol design by the Chief Investigator and researchers employed by the University.

• Sites participating in the study will be liable for clinical negligence and other negligent harm to individuals taking part in the study and covered by the duty of care owed to them by the sites concerned. The co-sponsors require individual sites participating in the study to arrange for their own insurance or indemnity in respect of these liabilities.

• Sites which are part of the United Kingdom's National Health Service will have the benefit of NHS Indemnity.

• Sites out with the United Kingdom will be responsible for arranging their own indemnity or insurance for their participation in the study, as well as for compliance with local law applicable to their participation in the study.

13 REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

13.1 AUTHORSHIP POLICY

Ownership of the data arising from this study resides with the study team.

Appendix A

Cardiopulmonary Exercise Test specifications and SOP

Two operators will be present during the test. If the patient has cardiac issues or other clinical conditions which may be of concern then a doctor will be present.

Before booking the appointment, ensure supervising doctor is available if appropriate.

Equipment Setup

Before patient testing, prepare the following;

- Mouthpiece for spirometry
- Serial sheet for spirometry
- CPET data sheet (located in the top drawer under the fridge)
- Mask (prepare a range of sizes)

- Flow head (located in plastic box on shelf on right of door)
- White ring adapter (located as above)
- ECG box (located as above)
- ECG electrodes (located in cupboard above the left of the sink)
- Skin prep pads (located as above)
- Ensure there is paper in the printer and the flap below is pulled out to catch it
- Ensure fan in room
- Print the patient referral (go to workbench on Trak, highlight patient + select print at the top of the page)
- Check if the patient has been before – if they have the patient should be tested at the same wattage

To Start System

Open gas cylinder and ensure adequate gas and pressure

Turn on system by pressing button on bottom right of the right hand monitor

Double click on “Breeze” icon on left hand screen to open program

Enter Login Name and Password and press “OK”

Ensure vacuum pump is on. If not, press “Vac” at the top of the screen (if the timer is stuck at 30:00, the vacuum pump is probably off)

Turn on the bike using the switch at the back below the seat

Calibration

Press “Calibrate” at the top of the screen

Take the 3L syringe from below the left hand side of the desk and attach the flow head to the blue rubber end with the side containing the holes facing into the syringe

Connect the umbilicus to the top of the flow head

Press “zero flow”

Press “start”

Withdraw and inject as directed until “calibration successful” is displayed

Replace the umbilicus to the port with the patterned side up

Remove the flow head and replace the syringe

Press the “O2 and CO2 analysers” tab

Click “calibrate” and wait until “calibration successful” is displayed

Click “OK” at the bottom left of the screen

Patient Details

For Existing Patients-

Click on yellow folder (Open Patient) to search for the patient.

Select Find.

Click on the drop down menu for search options, i.e. Name, ID etc.

Enter the search option selected to search for the patient.

If the patient is found it is highlighted.

Select Open and then add visit

Enter patient demographics and history as necessary.

Ensure that “GX Predicted Set Selection” has the option “Glaser” selected

For New Patients-

Search first as above, if not found, close that window.

Click on White folder (new Patient)

Enter all patient details.

Then select Add Visit.

Enter more details as necessary (Height, Weight, Requesting Physician/Unit, Site and Physiologist are Mandatory)

Ensure that “GX Predicted Set Selection” has the option “Glaser” selected

The Patient History tab should be used to enter more details, e.g. medication and clinical details, smoking history etc.

To close any patient demographic window, click on the yellow open folder to close.

Preparing the Patient

Check patient details and measure height and weight (NB Maximum weight for bike is 160kg).

Check with patient for any contraindications to testing.

Contraindications for Testing

- Recent/Acute M.I
- Unstable Angina
- Chest Pain
- ST depression > 2mm on resting ECG in most leads
- Uncontrolled hypertension at rest (>180/100 mmHg)
- Uncontrolled arrhythmias
- Severe Aortic Stenosis
- SpO2 < 80% at rest

Perform SVC and FVC manoeuvres as per SOP in section 3 folder. A white ring adapter is required to connect the flow head to the mouthpiece. If the spirometry was performed on box, predicted values must be refreshed – Click edit, then "rerun predicted values".

Fill in the CPET data sheet, including the predicted HRmax (220-age) and predicted Vemax (40 x FEV1).

Explain the test to the patient, e.g. "You are going to be doing a bicycle exercise test but we are going to monitor several things whilst you exercise. You will have electrodes on your chest to monitor your heart, a blood pressure cuff on your arm for your blood pressure, a small clip on your ear lobe to monitor your oxygen saturation and a face mask which will measure your breathing pattern and oxygen consumption. We will get you on the bicycle first, just breathing for 1 minute before we start you exercising and then there will be a warm up period of 3 minutes easy pedalling before we start increasing the workload as though you were going up a hill. We want you to really push yourself and do as much as possible."

Prepare earlobe with a vasodilator cream for pulse oximeter probe.

Stickers (called electrodes) and a band will be put onto the chest of the patients by themselves to monitor their heart rate and rhythm, therefore, their privacy will be ensured. Some men may need to have a small area of their chest shaved in order for the electrodes to stick to the skin. Seat patient on bike.

Check height of bike and adjust as necessary using the up and down arrows on the bike unit until the patient's extended leg has a slight bend at the knee. The handlebars can also be adjusted by loosening the black handles on handlebar unit. (If the screen displays a menu, select PC Mode)

Attach ear probe for oximetry and run the cable over the hook on the back wall to ensure it stays out the way.

Fit the blood pressure cuff by feeling for the brachial pulse and fitting the orange tab over it, 2-3cm above the cubital fossa. Secure the cable through the Velcro on the handlebars.

Fit mask over the patient's face. To ensure no leaks, instruct the patient to breathe in maximally then cover the hole in the mask with the palm of your hand as they exhale. Repeat with patient inhaling against the palm of your hand.

Establish appropriate workload for patient (CF patients are all tested at 25W).

Wasserman Equations for Predicted Work Rate Increment

- Unloaded VO2 = (150 + (6 x weight in kg))
- VO2 Peak = (height in cm – age) x 14 for females, x 20 for males
- Predicted Work Rate Increment = VO2 Peak - Unloaded VO2

Patient Testing

Click the "GX" tab at the bottom of the screen

Under "Script Name", select "JAI"

Select the desired work rate increment by choosing the appropriate ramp under "default protocol"

Ensure that "Borg Scale" is selected to "6-20"

Click on "summary" to gain a value for VO2 Max and write this on the CPET data sheet

Select the "test" tab at the bottom of the screen

Turn on SpO2 monitor

Ensure the umbilical is connected to the black port located below the screen to the left and click "Gas AutoCal".

Then plug the umbilical into the flow head and strap it over the patients head onto the headpiece

Click on the ECG icon on the right hand computer screen

Turn on the ECG box by pressing the button on the front of box

Observe the ECG

Press **Start**

Keep patient still on the bike

Take a resting BP measurement by pressing the red droplet with a circle inside

Record resting BP along with SpO2 and HR on the CPET data sheet

Click on ECG event icon

Change Mason-Likar to “interpret all”

Monitor resting ECG for any abnormalities

Press **Exercise**

Instruct the patient to begin pedalling at 70 rpm

Take a baseline BP measurement by pressing the red droplet with a circle inside

Record baseline BP along with SpO2 and HR on the CPET data sheet

After three minutes, tell the patient that the workload will begin to increase

The system will automatically take BP measurements approximately every 3 minutes – these must be recorded along with SpO2 and HR on the CPET data sheet

Encourage the patient throughout to perform maximally

Observe all parameters throughout, especially the ECG for ST depression or arrhythmias, but also to pick up any erroneous measurements arising from technical factors e.g. low VO2 from a leak etc.

Terminate the test if the patient fulfils any of the termination criteria;

Termination Criteria

- Maximal test – patient could not do any more
- Progressive Chest Pain
- Oxygen desaturation to below 80%
- Hypotension, drop in systolic blood pressure or failure of BP to rise through exercise.
- Severe Hypertension (>250/120 mmHg)
- More than 2mm ST segment depression (horizontal or negative sloping)
- 3mm ST depression (positive sloping)
- Progressive ST segment elevation

- AV Block
- Frequent Ventricular Ectopic or Ventricular Arrhythmias
- Rapid Supra-ventricular Arrhythmias

Press **Recovery**

Click recovery as soon the patient stops

Take a BP at beginning of recovery, and every three minutes until baseline HR and SpO2 values are reached again

Press **Stop**

Ask the patient what made them stop the test and record on the CPET data sheet

Give the patient a Borg Score scale for perceived exertion and record on CPET data sheet

Click on ECG icon to stop ECG

Turn off ECG by pressing the button on the box

Printing Results

ECG

Click “page review”

Deselect ectopic etc. unless you want to print an example of something specific

Press the running man icon at the top of the right hand screen

Press “preview”

At the top left of the left hand screen, deselect all tick boxes except “exam summary”, “rate/BP/workload trends” + “peak averages”

Click “refresh” at the bottom left of the screen

Click the “X” at the top right of the screen

Click “save” and then “exit”

Click the save icon on the right hand screen

AT

Click the AT tab at the bottom right of the screen

Move the AT line to the correct position

To view other graphs press F12

Click “save”

Print

Select Quick Print from menu bar at top of screen

Select “JAI Report”

Cleaning

Place ECG electrodes in the domestic waste bin

Wipe down;

- Bike
- BP cuff
- SpO2 sensor
- ECG box

Clean in the basin located under the sink with hot, soapy water;

- Mask
- Flow head
- Headgear

Hang the headgear from the hooks on the back wall

Prepare descogen by filling the appropriate lidded container with water and adding one scoop of descogen and place the mask and flow head in. Leave for 20 minutes then rinse and place on the side to dry

Closing down the System

Close the patient

Exit the program

Shut down the computer

Close the gas cylinders

Turn off the bike using the switch at the back

Reviewing Results

Open patient file to be reviewed.

Highlight date of tests to be reviewed and select Open visit.

Click on tab to review particular test results.

To see graphical display for test results, highlight the test time

Reviewing Reports

Open patient file to be reviewed.

Highlight date of tests to be reviewed and select Open visit.

Select Quick print from top menu bar.

Select Report switchboard.

Select appropriate report, e.g. JAI report

Select Preview to display the report

Appendix B

Constant Work Rate Exercise Test

Two operators will be present during the test. If the patient has cardiac issues or other clinical conditions which may be of concern then a doctor will be present. Before booking the appointment, ensure supervising doctor is available if appropriate.

Equipment Setup

Before patient testing, prepare the following;

- Mouthpiece for spirometry
- Serial sheet for spirometry
- CPET data sheet (located in the top drawer under the fridge)
- Mask (prepare a range of sizes)
- Flow head (located in plastic box on shelf on right of door)
- White ring adapter (located as above)
- ECG box (located as above)
- ECG electrodes (located in cupboard above the left of the sink)
- Skin prep pads (located as above)
- Ensure there is paper in the printer and the flap below is pulled out to catch it
- Ensure fan in room

- Print the patient referral (go to workbench on Trak, highlight patient + select print at the top of the page)

- Check if the patient has been before – if they have the patient should be tested at the same wattage

To Start System

Open gas cylinder and ensure adequate gas and pressure

Turn on system by pressing button on bottom right of the right hand monitor

Double click on “Breeze” icon on left hand screen to open program

Enter Login Name and Password and press “OK”

Ensure vacuum pump is on. If not, press “Vac” at the top of the screen (if the timer is stuck at 30:00, the vacuum pump is probably off)

Turn on the bike using the switch at the back below the seat

Calibration

Press “Calibrate” at the top of the screen

Take the 3L syringe from below the left hand side of the desk and attach the flow head to the blue rubber end with the side containing the holes facing into the syringe

Connect the umbilicus to the top of the flow head

Press “zero flow”

Press “start”

Withdraw and inject as directed until “calibration successful” is displayed

Replace the umbilicus to the port with the patterned side up

Remove the flow head and replace the syringe

Press the “O2 and CO2 analysers” tab

Click “calibrate” and wait until “calibration successful” is displayed

Click “OK” at the bottom left of the screen

Patient Details

For Existing Patients-

Click on yellow folder (Open Patient) to search for the patient.

Select Find.

Click on the drop down menu for search options, i.e. Name, ID etc.

Enter the search option selected to search for the patient.

If the patient is found it is highlighted.

Select Open and then add visit

Enter patient demographics and history as necessary.

Ensure that “GX Predicted Set Selection” has the option “Glaser” selected

For New Patients-

Search first as above, if not found, close that window.

Click on White folder (new Patient)

Enter all patient details.

Then select Add Visit.

Enter more details as necessary (Height, Weight, Requesting Physician/Unit, Site and Physiologist are Mandatory)

Ensure that “GX Predicted Set Selection” has the option “Glaser” selected

The Patient History tab should be used to enter more details, e.g. medication and clinical details, smoking history etc.

To close any patient demographic window, click on the yellow open folder to close.

Preparing the Patient

Check patient details and measure height and weight (NB Maximum weight for bike is 160kg).

Check with patient for any contraindications to testing.

Contraindications for Testing

- Recent/Acute M.I
- Unstable Angina
- Chest Pain
- ST depression > 2mm on resting ECG in most leads
- Uncontrolled hypertension at rest (>180/100 mmHg)
- Uncontrolled arrhythmias
- Severe Aortic Stenosis
- SpO2 < 80% at rest

Perform SVC and FVC manoeuvres as per SOP in section 3 folder. A white ring adapter is required to connect the flow head to the mouthpiece. If the spirometry was performed on box, predicted values must be refreshed – Click edit, then "rerun predicted values".

Fill in the CPET data sheet, including the predicted HRmax (220-age) and predicted Vemax (40 x FEV1).

Explain the test to the patient, e.g. "You are going to be doing a bicycle exercise test but we are going to monitor several things whilst you exercise. You will have electrodes on your chest to monitor your heart, a blood pressure cuff on your arm for your blood pressure, a small clip on your ear lobe to monitor your oxygen saturation and a face mask which will measure your breathing pattern and oxygen consumption. We will get you on the bicycle first, just breathing for 1 minute before we start you exercising and then there will be a warm up period of 3 minutes easy pedalling. **Then we remain a constant workload at 75% of the maximal work load obtained from the maximal CPET (CPET) conducted before. We want you to really push yourself and do as much as possible."**

Prepare earlobe with a vasodilator cream for pulse oximeter probe.

Stickers (called electrodes) and a band will be put onto the chest of the patients by themselves to monitor their heart rate and rhythm, therefore, their privacy will be ensured. Some men may need to have a small area of their chest shaved in order for the electrodes to stick to the skin. Seat patient on bike.

Check height of bike and adjust as necessary using the up and down arrows on the bike unit until the patient's extended leg has a slight bend at the knee. The handlebars can also be adjusted by loosening the black handles on handlebar unit. (If the screen displays a menu, select PC Mode)

Attach ear probe for oximetry and run the cable over the hook on the back wall to ensure it stays out the way.

Fit the blood pressure cuff by feeling for the brachial pulse and fitting the orange tab over it, 2-3cm above the cubital fossa. Secure the cable through the Velcro on the handlebars.

Fit mask over the patient's face. To ensure no leaks, instruct the patient to breathe in maximally then cover the hole in the mask with the palm of your hand as they exhale. Repeat with patient inhaling against the palm of your hand.

Establish appropriate workload for patient (at 75% of the maximal work load obtained from the maximal CPET conducted before).

<u>Patient Testing</u>

Click the "GX" tab at the bottom of the screen

Under "Script Name", select "JAI"

Select the desired work rate increment by choosing the appropriate ramp under "default protocol"

Ensure that "Borg Scale" is selected to "6-20"

Click on “summary” to gain a value for VO2 Max and write this on the CPET data sheet

Select the “test” tab at the bottom of the screen

Turn on SpO2 monitor

Ensure the umbilical is connected to the black port located below the screen to the left and click “Gas AutoCal”.

Then plug the umbilical into the flow head and strap it over the patients head onto the headpiece

Click on the ECG icon on the right hand computer screen

Turn on the ECG box by pressing the button on the front of box

Observe the ECG

Press **Start**

Keep patient still on the bike

Take a resting BP measurement by pressing the red droplet with a circle inside

Record resting BP along with SpO2 and HR on the CPET data sheet

Click on ECG event icon

Change Mason-Likar to “interpret all”

Monitor resting ECG for any abnormalities

Press **Exercise**

Instruct the patient to begin pedalling at 70 rpm

Take a baseline BP measurement by pressing the red droplet with a circle inside

Record baseline BP along with SpO2 and HR on the CPET data sheet

After three minutes, tell the patient that the workload will remain constant at 75% of the maximal work load obtained from the maximal CPET conducted before.

The system will automatically take BP measurements approximately every 3 minutes – these must be recorded along with SpO2 and HR on the CPET data sheet

Encourage the patient throughout to perform maximally

Observe all parameters throughout, especially the ECG for ST depression or arrhythmias, but also to pick up any erroneous measurements arising from technical factors e.g. low VO2 from a leak etc.

Terminate the test if the patient fulfils any of the termination criteria;

Termination Criteria

- Maximal test – patient could not do any more
- Progressive Chest Pain
- Oxygen desaturation to below 80%
- Hypotension, drop in systolic blood pressure or failure of BP to rise through exercise.
- Severe Hypertension (>250/120 mmHg)
- More than 2mm ST segment depression (horizontal or negative sloping)
- 3mm ST depression (positive sloping)
- Progressive ST segment elevation
- AV Block
- Frequent Ventricular Ectopic or Ventricular Arrhythmias
- Rapid Supra-ventricular Arrhythmias

Press **Recovery**

Click recovery as soon the patient stops

Take a BP at beginning of recovery, and every three minutes until baseline HR and SpO2 values are reached again

Press **Stop**

Ask the patient what made them stop the test and record on the CPET data sheet

Give the patient a Borg Score scale for perceived exertion and record on CPET data sheet

Click on ECG icon to stop ECG

Turn off ECG by pressing the button on the box

Printing Results

ECG

Click “page review”

Deselect ectopic etc. unless you want to print an example of something specific

Press the running man icon at the top of the right hand screen

Press “preview”

At the top left of the left hand screen, deselect all tick boxes except “exam summary”, “rate/BP/workload trends” + “peak averages”

Click “refresh” at the bottom left of the screen

Click the “X” at the top right of the screen

Click “save” and then “exit”

Click the save icon on the right hand screen

AT

Click the AT tab at the bottom right of the screen

Move the AT line to the correct position

To view other graphs press F12

Click “save”

Print

Select Quick Print from menu bar at top of screen

Select “JAI Report”

Cleaning

Place ECG electrodes in the domestic waste bin

Wipe down;

- Bike
- BP cuff
- SpO2 sensor
- ECG box

Clean in the basin located under the sink with hot, soapy water;

- Mask
- Flow head
- Headgear

Hang the headgear from the hooks on the back wall

Prepare descogen by filling the appropriate lidded container with water and adding one scoop of descogen and place the mask and flow head in. Leave for 20 minutes then rinse and place on the side to dry

Closing down the System

Close the patient

Exit the program

Shut down the computer

Close the gas cylinders

Turn off the bike using the switch at the back

Reviewing Results

Open patient file to be reviewed.

Highlight date of tests to be reviewed and select Open visit.

Click on tab to review particular test results.

To see graphical display for test results, highlight the test time

Reviewing Reports

Open patient file to be reviewed.

Highlight date of tests to be reviewed and select Open visit.

Select Quick print from top menu bar.

Select Report switchboard.

Select appropriate report, e.g. JAI report

Select Preview to display the report

Appendix C

Administration of Oxygen trough HFNO and Nasal Cannula.

High Flow Nasal Oxygen is a System which delivers heated, humidified high flow oxygen therapy via nasal cannula or tracheostomy attachment. HFNO has become increasingly used for management of patients with type 1 respiratory failure. It delivers high inspiratory gas flow (up to 60 litres per minute), which is warmed and humidified. Oxygen can be titrated from 21-95%. If oxygen exceeds 95%, the oxygen reading will pulse red and the device will alarm.

Benefits include:

• Reversal of hypoxaemia

• Reduced work of breathing

• Improved secretion clearance

• Improved patient tolerance/ comfort

Absolute Contra-indications

• Patients with type 2 respiratory failure requiring Non-invasive ventilation (NIV)

• COVID or suspected COVID infections

• Nasal passage abnormalities or recent nasal surgery

• Cerebro-spinal fluid leaks

• Basal skull fractures

• Severe epistaxis

Equipment

• Fisher & Paykel AIRVO2 TM humidifier

• Opti-flow nasal cannula (small, medium or large) or Tracheostomy Direct Connection. A mask could be used if other options are not appropriate

• Heated breathing circuit and water chamber

• 1l bag of sterile water

• Bubble oxygen tubing

Setting patient up on the HFNO

• Explain procedure to patient/ carer and gain consent.

• Wash hands and wear appropriate Personal Protection Equipment (PPE) in line with infection control policy.

• Assemble equipment as per manufacturer's instructions. Label equipment with date for tubing change (according to manufacturer's instructions). All disposable components are single patient use. Select appropriate patient inter-face. Switch equipment on, connect oxygen supply if required and check it is ready for use (check disinfection status).

• Perform sounding alarm test by disconnecting tube from top of machine to check that alarm sounds.

Adjusting settings

• Press any button to enter the summary screen. Select temperature using the arrow right button. Press and hold down both the up and down arrows at the same time to unlock the screen. Use up and down arrows to select desired temperature. Ideally should be set at 37◦C as this will provide optimum humidification but this may not be comfortable so either 34 or 31◦C may be selected, if a mask is used then temperature should be set at 31◦C.

• Press the arrow right button to select flow rate screen. Unlock screen as above. Use up and down buttons to select required flow rate. All patients will receive 50 lpm flow to maintain a saturation of oxygen ≥ 88%.

• Press the arrow right screen to access oxygen percentage and use the attached flow meter to adjust the percentage of oxygen until required patient saturations are reached. The screen does not require unlocking to adjust the oxygen percentage.

Cleaning of equipment

• Once therapy has been discontinued discard all disposables in appropriate waste.

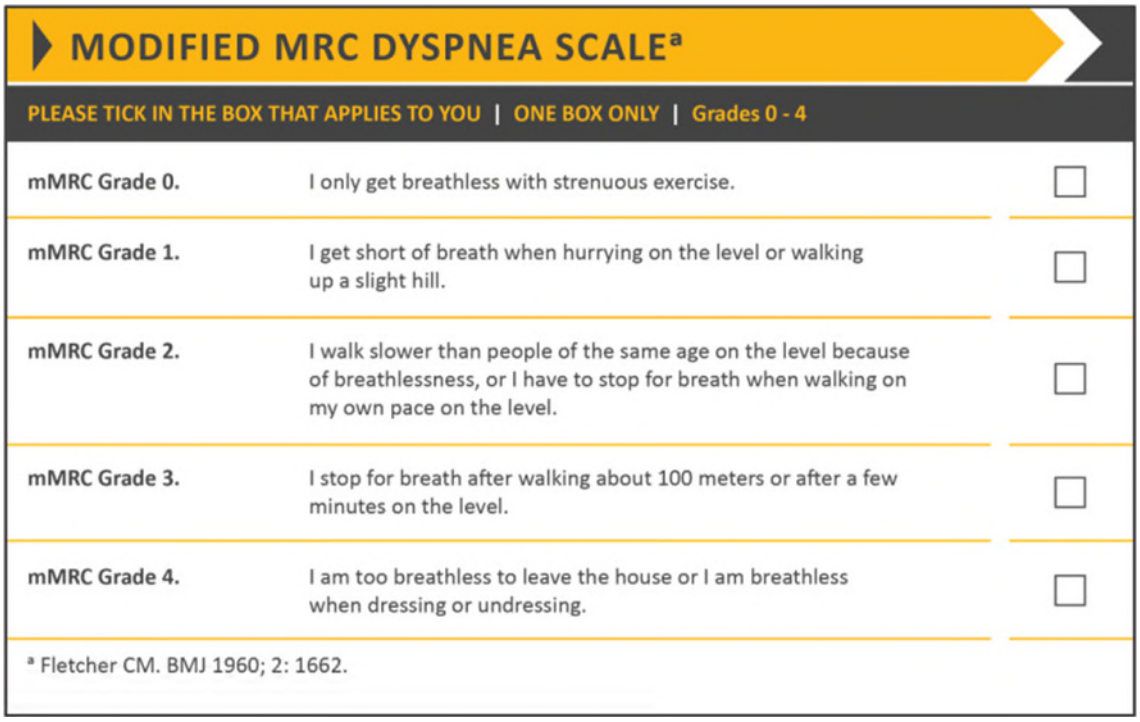
• Clean as per manufacturer's instructions including a disinfectant cycle.

Nasal Cannula

Oxygen through nasal cannula will be delivered to maintain an oxygen saturation ≥ 88%.

Appendix D

<u>Modified Medical Research Council Dyspnoea Scale (mMRC)</u>: this scale goes from 0 to 5



MODIFIED MRC DYSPNEA SCALE[a]

PLEASE TICK IN THE BOX THAT APPLIES TO YOU | ONE BOX ONLY | Grades 0 - 4

mMRC Grade 0.	I only get breathless with strenuous exercise.	☐
mMRC Grade 1.	I get short of breath when hurrying on the level or walking up a slight hill.	☐
mMRC Grade 2.	I walk slower than people of the same age on the level because of breathlessness, or I have to stop for breath when walking on my own pace on the level.	☐
mMRC Grade 3.	I stop for breath after walking about 100 meters or after a few minutes on the level.	☐
mMRC Grade 4.	I am too breathless to leave the house or I am breathless when dressing or undressing.	☐

[a] Fletcher CM. BMJ 1960; 2: 1662.

Appendix E

Saint George Respiratory Questionnaire (SGRQ)

IPF-Specific Version of the SGRQ

J Yorke, PW Jones, J Swigris

Symptoms Component

The original SGRQ contains 8 items in the Symptoms component. Items 6 and 8 were removed due to missing data. The remaining 6 items displayed disordered thresholds and required adjacent response categories to be collapsed. All of the 6 items displayed good-fit to Rasch model and were retained. The format for the SGRQ-I symptoms component is detailed below. Figure E1 displays the item map for this component.

SGRQ-I Symptoms Component

Item 1: I cough:
2 = Almost every day (new weight=80.6)
1 = Only with infections (new weight=40.2)
0 = Not at all (new weight=0)

Item 2: I bring up phlegm:
2 = Almost every day (new weight=76.8)
1 = Only with infections (new weight=41.4)
0 = Not at all (new weight=0)

Item 3: I have shortness of breath
2 = Almost every day (new weight=87.2)
1 = Only with infections (new weight=50.3)
0 = Not at all (new weight=0)

Item 4: I have attacks of wheezing
2 = Almost every day (new weight=86.2)
1 = Only with infections (new weight=51.0)
0 = Not at all (new weight=0)

Item 5: How many attacks of chest trouble have you had?
1 = more than one (new weight=66.2)
0 = none (new weight=0)

Item 6: How often do you have good days?

2 = every day	(new weight=93.3)
1 = a few days	(new weight=51.2)
0 = none	(new weight=0)

Activities Component

The original SGRQ contains 16 items in the Activity Component. All items were analysed using Rasch analysis.

Items 1, 5, 10, and 15 demonstrated the least fit to the Rasch model (x^2 $p<0.05$) and were removed. A further two items (8 and 9) demonstrated a high logit value (i.e. severity) and were removed to improve the targeting of the component (item 8 logit = 4.2, item 9 logit = 5.7) (Figure E2).

SGRQ-I Activities Component

Activities that make you short of breath

Item 1: Washing or dressing

1 = true (new weight=82.2)
0 = false (new weight=0)

Item 2: Walking in the house

1 = true (new weight=80.2)
0 = false (new weight=0)

Item 3: walking outside on ground level

1 = true (new weight=81.4)
0 = false (new weight=0)

Item 4: Walking up a flight of stairs

1 = true (new weight=76.1)
0 = false (new weight=0)

Item 5: Playing sports or active games

1 = true (new weight=72.1)
0 = false (new weight=0)

Activities that might be affected by your breathing problem

Item 6: Household chores take a long time

1 = true (new weight=70.6)
0 = false (new weight=0)

Item 7: Walking up one flight of stairs, I have to go slowly or stop

1 = true (new weight=71.6)
0 = false (new weight=0)

Item 8: If I hurry or walk fast, I have to slow down or stop

1 = true (new weight=72.3)
0 = false (new weight=0)

Item 8: Breathing problems makes it difficult to do things such as walking up hills

1 = true (new weight=74.5)
0 = false (new weight=0)

Item 12: Breathing problem makes it difficult to do things such as very heavy manual labour

1 = true (new weight=63.5)
0 = false (new weight=0)

Impacts Component

The original SGRQ contains 26 items in the Impacts Component, the SGRQ-I retains 18 of these. Items 17, 18, 19, and 20 had high levels of missing data and were removed. The remaining 23 items were analysed using Rasch analysis. Item 2 displayed disordered thresholds. This was corrected by rescoring the item; it now contains 2 response categories. Three items did not fit the Rasch model (x^2 $p < 0.0001$) and were removed (items 1, 13, and 14). Item 22 displayed adequate fit to the model but its logit score (i.e. severity) was high (4.6). This item was removed to improve the targeting of this component (Figure E3).

SGRQ-I Impacts Component

Item 1: If you ever held a job:

1 = My lung condition interferes or made me stop work (new weight=83.3)
0 = My lung problem does not affect my job (new weight=0)

About your cough and shortness of breath

Item 2: Coughing hurts

1 = true (new weight=81.1)
0 = false (new weight=0)

Item 3: Coughing makes me tired

1 = true (new weight=79.1)
0 = false (new weight=0)

Item 4: Short of breath when I talk

1 = true (new weight=84.5)
0 = false (new weight=0)

Item 5: Short of breath when I bend over

1 = true (new weight=76.8)
0 = false (new weight=0)

Item 6: Cough or breathing disturbs my sleep

1 = true (new weight=87.9)
0 = false (new weight=0)

Item 7: I become exhausted easily

1 = true (new weight=84.0)
0 = false (new weight=0)

Other effects that your lung problem may have on you

Item 8: Embarrassing in public

1 = true (new weight=74.1)
0 = false (new weight=0)

Item 9: A nuisance to my family

1 = true (new weight=79.1)
0 = false (new weight=0)

Item 10: Panic or afraid

1 = true (new weight=87.7)
0 = false (new weight=0)

Item 11: Not in control

1 = true (new weight=90.1)
0 = false (new weight=0)

Item 12: Exercise is not safe for me

1 = true (new weight=75.7)
0 = false (new weight=0)

Item 13: Everything seems too much effort

1 = true (new weight=84.5)
0 = false (new weight=0)

How your breathing usually affects your daily life

Item 14: I cannot play sports

1 = true (new weight=64.8)
0 = false (new weight=0)

Item 15: I cannot go out of the house to do grocery shopping

1 = true (new weight=81.0)
0 = false (new weight=0)

Item 16: I cannot do household chores

1 = true (new weight=79.1)
0 = false (new weight=0)

Item 17: I cannot move far from my bed or chair

1 = true (new weight=94.0)
0 = false (new weight=0)

Item 18: Which best describes how your breathing problem affects you

0 = does not stop me (new weight=0)
1 = stops one or two things (new weight=42.0)
2 =stops most things (new weight=84.2)
3 = stops me doing everything I would like to (new weight=96.7)

Appendix F:

Hospital Anxiety Depression Scale

Instructions: Doctors are aware that emotions play an important part in most illnesses. If your doctor knows about these feelings he or she will be able to help you more. This questionnaire is designed to help your doctor know how you feel. Read each item and circle the reply which comes closest to how you have been feeling in the past week. Don't take too long over your replies: your immediate reaction to each item will probably be more accurate than a long thought out response.

I feel tense or 'wound up':	**A**
Most of the time	3
A lot of the time	2
Time to time, occasionally	1
Not at all	0

I feel as if I am slowed down:	**D**
Nearly all of the time	3
Very often	2
Sometimes	1
Not at all	0

I still enjoy the things I used to enjoy:	**D**
Definitely as much	0
Not quite so much	1
Only a little	2
Not at all	3

I get a sort of frightened feeling like 'butterflies in the stomach':	**A**
Not at all	0
Occasionally	1
Quite often	2
Very often	3

I get a sort of frightened feeling like something awful is about to happen:	**A**
Very definitely and quite badly	3
Yes, but not too badly	2
A little, but it doesn't worry me	1
Not at all	0

I have lost interest in my appearance:	**D**
Definitely	3
I don't take as much care as I should	2
I may not take quite as much care	1
I take just as much care as ever	0

I can laugh and see the funny side of things:	**D**
As much as I always could	0
Not quite so much now	1

I feel restless as if I have to be on the move:	**A**
Very much indeed	3
Quite a lot	2

Definitely not so much now	2	Not very much	1
Not at all	3	Not at all	0

Worrying thoughts go through my mind:	**A**	**I look forward with enjoyment to things:**	**D**
A great deal of the time	3	A much as I ever did	0
A lot of the time	2	Rather less than I used to	1
From time to time but not too often	1	Definitely less than I used to	3
Only occasionally	0	Hardly at all	2

I feel cheerful:	**D**	**I get sudden feelings of panic:**	**A**
Not at all	3	Very often indeed	3
Not often	2	Quite often	2
Sometimes	1	Not very often	1
Most of the time	0	Not at all	0

I can sit at ease and feel relaxed:	**A**	**I can enjoy a good book or radio or TV programme:**	**D**
Definitely	0	Often	0
Usually	1	Sometimes	1
Not often	2	Not often	2
Not at all	3	Very seldom	3

Questions relating to anxiety are indicated by an 'A' while those relating to depression are shown by a 'D'. Scores of 0-7 in respective subscales are considered normal, with 8-10 borderline and 11 or over indicating clinical 'caseness'

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