Clinical Study Protocol

Effect of HFNO on Exercise Tolerance in Patients with Interstitial Lung Diseases during a Constant Work Rate Cycle Test Compared with the Effect Obtained using Oxygen through Nasal Cannula.

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 Irani, Hillary Pinnock**
Funder	**Chilean National Scholarship Program for Graduate Studies**
Funding Reference Number	**72200060**
Chief Investigator	**Dr Roberto Rabinovich**
Sponsor number	AC**21047**
REC Number	**299088**
Project registration	**In progress**
Version Number and Date	**Version 1.0. 28 April 2021**

TABLE OF CONTENTS **PAGE**

LIST OF APPENDICES

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
COPD	Chronic Obstructive Pulmonary Disease
CPET	Cardiopulmonary Exercise Test
CWRET	Constant Work Rate Exercise Test
FIO2	Fraction of Oxygen Inspirited
FEV1/FVC	Forced Expiratory Volume in one second/ Forced Vital Capacity Ratio
HFNO	High Flow Nasal oxygen
HRCT	High-Resolution Computed Tomography
ILD	Interstitial Lung Disease
IPF	Idiopathic Pulmonary Fibrosis
MIET	Maximal Incremental Exercise Test
6MWT	6 Minute Walking Test
NSIP	Non-specific Interstitial Pneumonia
PaCO2	Partial Pressure of Carbon Dioxide in the arterial blood
PEEP	Positive End-Expiratory Pressure
PR	Pulmonary Rehabilitation
Tlim	Exercise Endurance

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). We believe that HFNO might improve the exercise capacity in patients who suffer from ILD during a CWRET. This increment in the load tolerated during exercise may justify its use during exercise training and, thus, contribute to improve the effects of pulmonary rehabilitation programmes in these patients..

1.3 RESEARCH QUESTION

Does HFNO increase exercise tolerance in patients with ILD in a lab setting assessed as exercise endurance (Tlim) during a CWRET?.

2 STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVE

To evaluate the effect of HFNO on exercise tolerance (Tlim) measured with a constant work rate cycle test at 75% of the maximal work load obtained from a maximal CPET (CPET) conducted beforehand in comparison to oxygen delivered through a nasal cannula. The high-intensity CWRET is considerably more responsive than incremental exercise tests or the 6-minwalking 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 work load (obtained beforehand from a maximal CPET).

3.2 SECONDARY OUTCOMES

The secondary outcome variables will be SpO2, heart rate, Borg scale (dyspnoea and leg fatigue).

4 METHODS

4.1 STUDY DESIGN

Prospective randomised controlled cross over study of 20 patients with ILD. Patients will be randomised to perform two constant work rate cycle tests at 75% of the maximal work load achieved in a maximal CPET. Patients will attend 2 days. On the first day anthropometric and lung function data will be obtained and CPET with incremental load in a cycle-ergometer will be performed. On the Second day patients will perform two constant work rate cycle tests at 75% of the maximal work load obtained from a Maximal Incremental Exercise Test (CPET) separated by 60 minutes. Patients will receive randomly oxygen delivered via nasal cannula or HFNO. Therefore, participants will receive both. On the second day, on the first cycle test they will have either HFNO or Standard care and then on the second cycle test they will receive the opposite to the first cycle test. The study will take place in The Royal Infirmary of Edinburgh.

4.2 NUMBER OF PARTICIPANTS

20 participants with ILD will be recruited in the Lothian region, 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 80 years old will be recruited and with ability to give informed consent.

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. - Involvement in the planning and/or conduct of the study.

4. - Participants should not be taking part in other interventional studies.

5. - Patient is unable to attend the assessment sessions or would like to withdraw from the study.

6. - 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 noncardiopulmonary 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 will be invited by a member of the direct care team to participate and will receive a patient's information sheet with an invitation to attend pre-assessment for this study. Patients will be given more than 24 hours to consider participation in the study, signing the informed consent. 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

Anthropometric data (gender, age, height and weight), lung function (spirometry and carbon monoxide transfer factor) will be taken the first day of the study, during the spirometry 4 puffs (up to 400 micrograms) of salbutamol inhaler will be administered and CT characterisation will be recorded from medical records. Furthermore, at baseline all participants will perform a maximal CPET in a cycle-ergometer to assess the maximal exercise capacity in maximal watts achieved. Oxygen will be supplied, when needed, via nasal cannula and titrated to maintain a SpO2 □ 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 HFNO or nasal cannula. Patients will be sequentially randomised. Randomisation code and sealing of envelopes will be done by the research nurse Andrew Deans and stored in a room at RIE accessible with a key.

4.9 BLINDING

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

4.10 INTERVENTION

The intervention consists of supplemental oxygen delivered via HFNO at 37°C. Patients that find too warm this temperature can receive HFNO at 34°C. HFNO has a humidifier that saturates the gas mixture at temperature of 31 to 37 C. 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 CWRET will be performed at the same work load (75% of the maximal watts achieved beforehand during a maximal CPET). (see CPET protocol, Appendix A)

Assessment	Screening	Day 1	Day 2
Assessment of Eligibility Criteria	X		
Written informed consent		X	
Demographic data, contact details	X		
Weight		X	
Height		X	
Spirometry		X	
DLCO		X	
CPET		X	
CWRET 1			X
CWRET 2			X

4.11 DURATION OF THE STUDY

Patients will attend 2 days. On the first day anthropometric and lung function data will be obtained and CPET with incremental load in a cycle-ergometer will be performed.
On the Second day patients will perform two constant work rate cycle tests at 75% of the maximal work load obtained from a Maximal Incremental Exercise Test (CPET) separated by 60 minutes. Patients will receive randomly oxygen delivered via nasal cannula or HFNO. During all these tests, heart rate, oxygen levels in the blood and blood pressure will be monitored.

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.

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. The data will be collected

in paper and held in The Royal of Infirmary of Edinburgh in a locked room. The study data will be entered in an anonymised database where patients will be with the study related unique identifier number held in a university computer at CIR. Personal data will be stored for 3 years.

5.2 DATA INFORMATION FLOW

Personal data will be collected during approximately 6 months and these will be used for 6 more months and will be deleted 3 years after finishing the study.

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 and NHS Lothian Data Protection Officers who will onward report to the relevant authority according to the appropriate timelines if required.

6. STATISTICS AND SAMPLE SIZE

Based on previous studies, a sample size of 16 patients with randomization was required to detect a mean difference in the endurance time of 2 min between VM and HFNC (8 patients in each group), with a power of 80% at a two-sided alpha level of 0.05 (21, 22). Considering an expected dropout rate of 10% in a previous exercise training study of FILD patients, a total of 20 patients were recruited(20, 21).

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. A generalized linear mixed-effects model will be applied for both primary and secondary endpoints; the model included device, sequence, and period as fixed effects, and subject within sequence as a random effect. The Bonferroni post-hoc test will be performed for multiple comparisons of groups. As a sub-analysis, we will compare nasal cannula and HFNC data with baseline CWRET. A CWRET good responder will be defined as a patient with > 100 s or 33% improvement of endurance time from baseline CWRET (18, 20). Subgroup analyses of endpoints in nasal cannula/HFNC good responders will be conducted. We will also investigate the relationship between nasal cannula/HFNC non-responders and

pulmonary hypertension (PH) assessed by either echocardiography (right ventricular systolic pressure > 35 mmHg) or right heart catheterization (mean pulmonary artery pressure ≥ 25mmHg) (20, 23, 24). All tests will be performed at a significance level of $p < 0.05$. Analysis was completed using IBM SPSS statistics ver. 21 (IBM Corp. Armonk, NY, USA).

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 Ectopics 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. We would not envisage an immediate benefit to the patient but 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 Physiotherapists Jo Pentland and Susan McNarry.

9. PROJECT MANAGEMENT AND QUALITY ASSURANCE

The project team, consisting of a grantholder 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)
- Flowhead (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 flowhead to the blue rubber end with the side containing the holes facing into the syringe

Connect the umbilicus to the top of the flowhead

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 flowhead 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.

Instruct the patient to undress to the waist and prepare the skin with the skin prep pads and sterets as necessary. Shave the appropriate areas if required. Connect the ECG electrodes and leads. Strap the box around the patient's waist. The patient can then put a loose fitting top back on.

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 earprobe 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 flowhead 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 Ectopics 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 ectopics 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

- Flowhead
- 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 flowhead 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)
- Flowhead (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 flowhead to the blue rubber end with the side containing the holes facing into the syringe

Connect the umbilicus to the top of the flowhead

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 flowhead 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.

Instruct the patient to undress to the waist and prepare the skin with the skin prep pads and sterets as necessary. Shave the appropriate areas if required. Connect the ECG electrodes and leads. Strap the box around the patient's waist. The patient can then put a loose fitting top back on.

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 earprobe 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).

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 flowhead 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 Ectopics 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 ectopics 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
- Flowhead
- 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 flowhead 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

Relative contraindications

• Elderly and frail patients with multiple comorbidities who are unlikely to prognostically benefit from the use of HFNO.

• Patients in whom HFNO is simply likely to prolong the dying phase of the patients illness

• Patients in whom there is no identifiable reversible cause (e.g. progression of pulmonary fibrosis)

For these patients a discussion with the Respiratory team in hours (or Medical Registrar out of hours) should be had BEFORE HFNO is initiated

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. Most patients will commence with at least 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.

• It is important to note that if the flow rate is adjusted then the oxygen percentage will also change and will therefore need adjusting at the oxygen flow meter.

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%.

14. REFERENCES

1.- Du Plessis J, Fernandes S, Jamal R, et al. Exertional hypoxemia is more severe in fibrotic interstitial lung disease than in COPD. Respirology 2018; 23: 392–398.

2. - Dowman L, Donald Ch, Hill C, et al. The benefits of exercise training in interstitial lung disease: protocol for a multicentre randomized controlled trial. BMC Pulmonary Medicine 2013; 13: 1–8.

3.- Duchemann B, Annesi-Maesano I, Jacobe de Naurois C, et al. Prevalence and incidence of interstitial lung diseases in a multi-ethnic county of Greater Paris. Eur Respir J 2017; 50: 1602419 [https://doi.org/10.1183/13993003.02419-2016].

4. - American Thoracic Society, European Respiratory Society. International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. Am J Respir Crit Care Med 2002; 165: 277–304.

5.- Montesi S, Fisher J, Martinez F, et al. Update in Interstitial Lung Disease. Am J Respir Crit Care Med 2020; 202 (4): 500-507

6.- Dowman L, Hill CJ, May A, Holland AE. Pulmonary rehabilitation for interstitial lung disease. Cochrane Database of Systematic Reviews 2021, Issue 1. Art. No.: CD006322. DOI: 10.1002/14651858.CD006322.pub4

7.- Martijn A. Spruit, Sally J. Singh, Chris Garvey, et al. An Official American Thoracic Society/European Respiratory Society Statement: Key Concepts and Advances in Pulmonary Rehabilitation. Am J Respir Crit Care Med 2013; 188 (8): pp e13–e64.

8. - Huppmann P, Sczepanski B, Boensch M, et al. Effects of inpatient pulmonary rehabilitation in patients with interstitial lung disease. Eur Respir J 2013; 42: 444–453

9.- Nici L, Donner C, Wouters E, et al. American Thoracic Society/European Respiratory Society statement on pulmonary rehabilitation. Am J Respir Crit Care Med 2006; 173: 1390–1413.

10. - Rochester C, Vogiatzis I, Holland A, et al. An Official American Thoracic Society/European Respiratory Society Policy Statement: Enhancing Implementation, Use, and Delivery of Pulmonary Rehabilitation. Am J Respir Crit Care Med 2015; 192 (11): 1373–1386.

11.- Spruit MA, Janssen DJ, Franssen FM, Wouters EF. Rehabilitation and palliative care in lung fibrosis. Respirology 2009;14:781–787.

12.- Sabapathy S, Kingsley R, Schneider D, et al. Continuous and intermittent exercise responses in individuals with chronic obstructive pulmonary disease. Thorax 2004; 59:1026–1031

13.- Faverio P, De Giacomi F, Luca Sardella L, et al. Management of acute respiratory failure in interstitial lung diseases: overview and clinical insights. BMC Pulm Med 2018; 18:70

14- . - Spoletini G, Alotaibi M, Blasi F, et al. Heated humidified high-flow nasal oxygen in adults: mechanisms of action and clinical implications. Chest 2015; 148: 253–61.

15.- Cournoyera J, Ramosa C, Sturgilla B, et al. Effects of 100 % oxygen during exercise in patients with interstitial lung disease. Respiratory Physiology & Neurobiology 2020; 274: 103367

16.- Miller D, Bime C, Partharsarathy S, et al. High-Flow Oxygen Therapy Concepts: Time to Standardize Nomenclature and Avoid Confusion. Journal of Intensive Care Medicine 2020; 35(5): 519-523.

17.- Arizono S, Furukawa T, Taniguchi H, et al. Supplemental oxygen improves exercise capacity in IPF patients with exertional desaturation. Respirology 2020; 25: 1152–1159

18.- Gomes-Neto M, Magalhães C, Ezequiel D, et al. Impact of Pulmonary Rehabilitation on Exercise Tolerance and Quality of Life in Patients With Idiopathic Pulmonary Fibrosis a Systematic Review and Meta-analysis. Journal of Cardiopulmonary Rehabilitation and Prevention 2018; 38: 273-278.

19.- Xueqin Y, Xuanlin L, Liaoyao W, et al. Pulmonary Rehabilitation for Exercise Tolerance and Quality of Life in IPF Patients: A Systematic Review and Meta-Analysis. BioMed Research International 2019; 2019: 1-9. https://doi.org/10.1155/2019/8498603

20.- Suzuki A, Ando M, Kimura T, et al. The impact of high-flow nasal cannula oxygen therapy on exercise capacity in fibrotic interstitial lung disease: a proof-of concept randomized controlled crossover trial. BMC Pulmonary Medicine 2020; 20:51

21. - Cheng L, Tan B, Yin Y, et al. Short- and long-term effects of pulmonary rehabilitation for idiopathic pulmonary fibrosis: a systematic review and meta-analysis. Clinical Rehabilitation 2018; 32 (10) 1299–1307.

22.- Strookappea B, Saketkoob L, Elffericha M, et al. Physical activity and training in sarcoidosis: review and experience-based recommendations. Expert Review of Respiratory Medicine 2016; 10 (10): 1057–1068.

23. - Higgins JPT G. Cochrane handbook for systematic reviews of interventions version 5.1. 0 [updated March 2011]. The Cochrane collaboration 2011: 20011.

24. - Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Journal of clinical epidemiology 2009: 62(10): e1-e34.