OXYPuF

Trial Protocol

Ambulatory OXYgen for Pulmonary Fibrosis

Version Number:	**1.0**
Version Date:	**04 April 2022**

This protocol has regard for the HRA guidance and is compliant with the SPIRIT guidelines (2013)

PROTOCOL DEVELOPMENT

Protocol Amendments				
The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version.				
Amendment number	**Date of amendment**	**Protocol version number**	**Type of amendment**	**Summary of amendment**

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The views expressed in this protocol are those of the author(s) and not necessarily those of the NHS, the National Institute for Health Research, Health Education England or the Department of Health and Social Care. The funder had no role with respect to trial design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication.

PROTOCOL SIGN OFF

Chief Investigator (CI) signature page	
I, the Chief Investigator, confirm that I have read and agree with the following protocol, and that I will conduct the trial in compliance with the version of this protocol approved by the REC and any other responsible organisations. I agree to ensure that the information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor. I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as stated in this and any subsequent approved protocol will be explained.	
Trial name:	OXYPuF
Protocol version number:	Version: 1.0
Protocol version date:	04 / April / 2022
CI name: Signature and date:	Professor Alice Turner _____ __ __ / __ __ / __ __ __ __

Sponsor statement
By signing the IRAS form for this trial, the University of Birmingham acting as sponsor, confirm approval of this protocol.
Compliance statement
This protocol describes the OXYPuF trial only. The protocol should not be used as a guide for the treatment of participants not taking part in the OXYPuF trial. The trial will be conducted in compliance with the approved protocol, the UK Policy Framework for Health and Social Care Research, Medicines for Human Use (Clinical Trials) Regulations 2004, Data Protection Act 2018 and the Principles of Good Clinical Practice (GCP) as set out in the UK Statutory Instrument (2004/1031), Human Tissue Act 2004 and subsequent amendments thereof. Every care has been taken in the drafting of this protocol, but future amendments may be necessary, which will receive the required approvals prior to implementation.

Principal Investigator (PI) signature page	
As Principal Investigator, I confirm that the following protocol has been agreed and accepted, and that I will conduct the trial in compliance with the approved protocol where this does not compromise participant safety. I agree to ensure that the information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.	
Trial name:	OXYPuF
Protocol version number:	Version: 1.0
Protocol version date: PI name:	04 / April / 2022
Name of Site: Signature and date:	_____ __ __/ __ __/ __ __ __ __

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ABBREVIATIONS

Abbreviation	Term
6MWT	6 Minute Walk Test
AE	Adverse Event
AHRF	Acidotic Hypercapnic Respiratory Failure
AOT	Ambulatory Oxygen Therapy
AR	Adverse Reaction
AUC	Area Under the Curve
BCTU	Birmingham Clinical Trials Unit
BTS	British Thoracic Society
CBC	Complete Blood Count
CI	Chief Investigator
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
DCF	Data Clarification Form
DLCO	Diffusing capacity of lung for carbon monoxide
DMC	Data Monitoring Committee
DSA	Data Sharing Agreement
DSUR	Development Safety Update Report
FBC	Full Blood Count
FEV1	Forced Expiratory Volume
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GP	General Practitioner
HRA	Health Research Authority
HRQoL	Health-related Quality of Life
ICF	Informed Consent Form
ILD	Idiopathic Lung Disease
IMP	Investigational Medicinal Product
IPAQ	International Physical Activity Questionnaire

IPF	Idiopathic Pulmonary Fibrosis
ISF	Investigator Site File
K-BILD	King's Brief Interstitial Lung Disease questionnaire
LTOT	Long Term Oxygen Therapy
MA	Marketing Authorisation
MCID	Minimum Clinically Important Difference
MDT	Multi-Disciplinary Team
MRC	Medical Research Council
NHS	National Health Service
NICE	National Institute for Clinical Excellence
NIHR	National Institute for Health Research
NIV	Non-Invasive Ventilation
NSIP	Non-Specific Interstitial Pneumonitis
FT	Foundation Trust
PI	Principal Investigator
PIS	Participant Information Sheet
PPI	Patient/Public Involvement
QA	Quality Assurance
QALY	Quality Adjusted Life Year
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RGT	Research Governance Team
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TDI	Transition Dyspnoea Index
TLCO	Transfer factor for Carbon Monoxide
TMF	Trial Master File
TMG	Trial Management Group

TSC	Trial Steering Committee
UAR	Unexpected Adverse Reaction
UE	Unexpected Event
UoB	University of Birmingham
UK	United Kingdom
VAS	Visual Analogue Score

DEFINITIONS

Term	Abbreviation	Description
Oxygen de-saturation on exercise	DSAT	Defined as dropping of oxygen levels as measured by a finger probe from normal to below 88%.
MRC Dyspnoea Score	MRC score	This is a validated measure of disease severity irrespective of patient's FEV1 in relation to breathlessness (dyspnoea). It is graded from 1 to 5 (5 being the most severe).
Gender-Age-Physiology score	GAP score	A score accounting concurrently for patient age, gender, FVC and D_{LCO}, where a higher score is associated with increased risk of mortality.

TRIAL SUMMARY

Title:

Ambulatory Oxygen Therapy for Pulmonary Fibrosis (OXYPuF)

Primary Objective:

To determine whether ambulatory oxygen therapy (AOT) is clinically and cost effective in patients with idiopathic pulmonary fibrosis (IPF).

Secondary Objectives:

- Determine whether breathlessness, determined by sub-scales of the King's Brief Interstitial Lung Disease (K-BILD) is superior after AOT compared to standardised breathlessness advice at 6 months.
- Determine whether MRC dyspnoea score, is superior after AOT compared to standardised breathlessness advice at 6 months.
- Determine whether exercise capacity and physical activity, as measured by the six minute walk test (6MWT) or a sit to stand test (depending on local policy), and a self-reported activity questionnaire (International

Physical Activity Questionnaire; IPAQ) respectively, is superior after AOT compared to standardised breathlessness advice at 6 months

Trial Design

A multicentre randomised controlled, open-label, pragmatic clinical trial, with internal pilot phase, designed to test both the clinical and cost effectiveness of AOT in patients with IPF.

Participant Population and Sample Size

260 consenting adults diagnosed with IPF confirmed via a multidisciplinary team (MDT) meeting or an IPF specialist.

Setting

Approximately 20 hospital outpatient clinics or community oxygen services.

Eligibility Criteria:

Inclusion

- Aged 18 or over
- Clinically diagnosed IPF, confirmed by an ILD MDT linked to an NHS specialist commissioned IPF service
- Breathlessness with MRC dyspnoea score ≥2
- Willing and able to comply with completion of questionnaires out to 6 months post-randomisation
- Able to complete a 6MWT or 1 minute sit to stand test
- Able to use oxygen safely in the opinion of the local investigator

Exclusion Criteria

- Unable to provide informed consent
- Requires LTOT, defined by need for resting oxygen in the opinion of the local investigator
- Life expectancy <6 months
- On the active transplant list
- Previous acidotic hypercapnic respiratory failure (AHRF) requiring non-invasive ventilation (NIV)

Intervention Arm

Ambulatory Oxygen Therapy and standardised breathlessness advice.

Control Arm

Standardised breathlessness advice.

Outcome Measures:

Primary Outcome

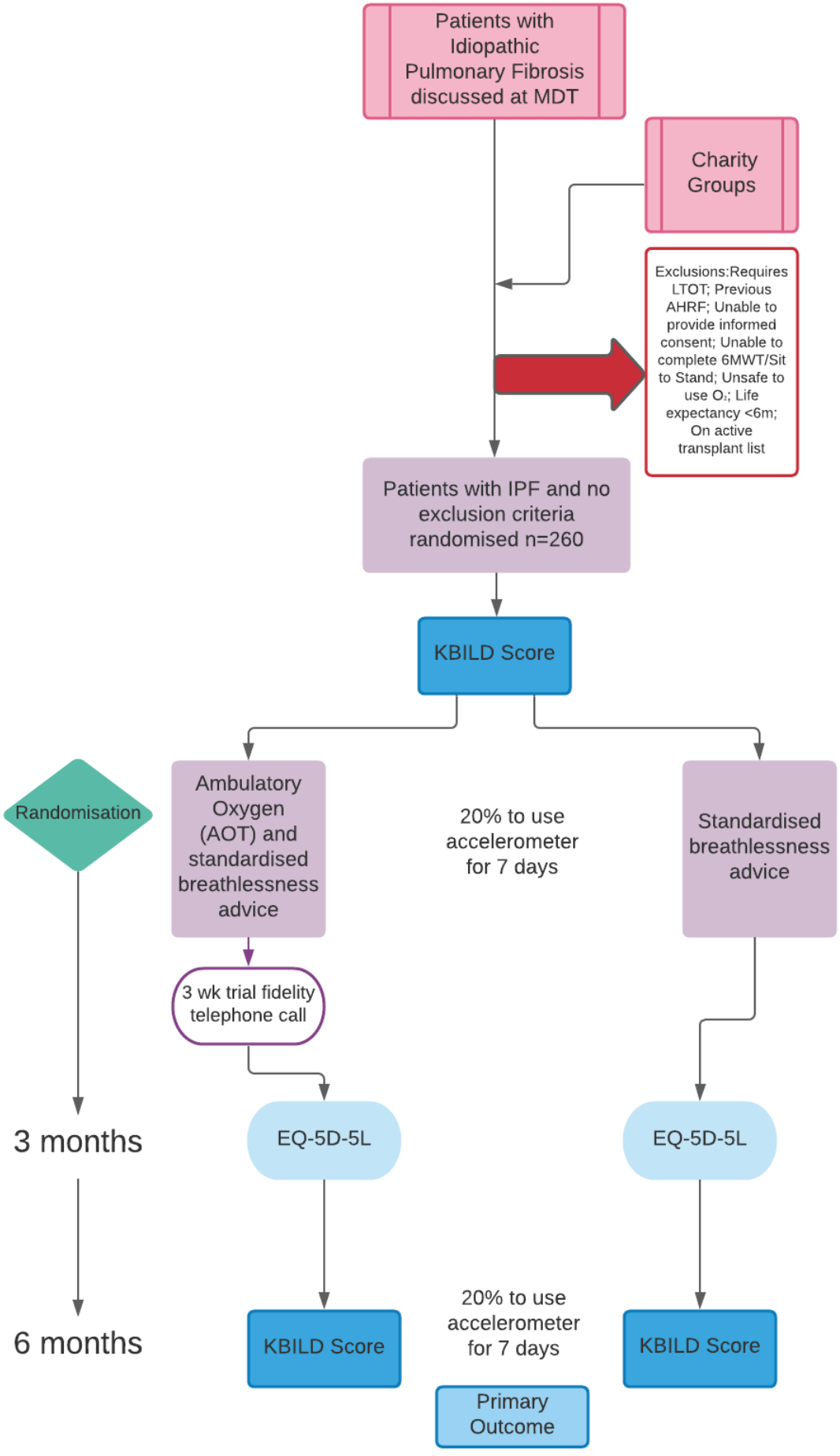
Total K-BILD score at 6 months.

Secondary Outcomes at six months after randomisation unless otherwise stated

- Subscales within K-BILD (breathlessness, activity, chest symptoms)
- Exercise capacity using the 6MWT or 1 minute sit to stand

- MRC dyspnoea score
- Physical activity using the IPAQ
- Sleepiness using the Epworth Sleepiness Scale
- Hospitalisations (all cause and IPF specific)
- Cough using a 6 point Visual Analogue Scale (VAS)
- Targeted adverse events
- Mortality (6 months, and from medical record only at 12 months)
- Medication use: benzodiazepines, antifibrotics; ACEis and opiates for breathlessness
- Completion of pulmonary rehabilitation
- Acceptability of AOT
- Cost-effectiveness (using EQ-5D-5L, and scheduled and unscheduled health service use relating to IPF).

TRIAL SCHEMA



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1. BACKGROUND AND RATIONALE

1.1 Background

Idiopathic Pulmonary Fibrosis (IPF) is the most common of a disparate group of conditions that lead to pulmonary fibrosis. Studies suggest that the incidence (4.6/ 100 000) and prevalence is rising over time, even allowing for more accurate and earlier identification (1, 2). Prognosis is poor with inexorable decline towards respiratory failure. Duration from initial symptoms to presentation at specialist interstitial lung disease (ILD) clinics can be variable, adding to the difficulty in predicting prognosis in individual cases and to the frustration of sufferers, their families and their supporting clinical teams. Whilst overall, there is a linear decline in forced vital capacity (FVC), for some this is experienced as a steady deterioration, for others, there are periods of stability with episodes of accelerated decline, which does not always have a tangible, treatable trigger. There may be increasing dyspnoea and plummeting functional status over a short period; median survival is approximately 3 years from the time of diagnosis (3).

The GAP score, which uses FVC and transfer capacity of the lung for carbon monoxide (TLCO) in addition to age and gender, has been used in research settings to predict mortality, however, for an individual in the clinic this is a less useful predictor (4). Individual tolerance of falling FVC, gas transfer and exercise desaturation in terms of dyspnoea can also make an individual's experience and level of disability difficult to predict. A significant proportion of time from diagnosis is spent with debilitating symptoms and increasing dependency. Healthcare costs are considerable (5), comprising supportive measures for breathlessness, pulmonary rehabilitation and antifibrotic agents such as nintedanib and pirfenidone in selected patients (6). Treatment with antifibrotics in the UK is centrally commissioned and is of high cost. In order to be eligible, the FVC must be between 50 and 80%, a figure based on trial data. However some groups, such as those with emphysema or premorbid supranormal physiology, for example, will not be eligible for treatment until later in their disease journey. These antifibrotic treatments slow progression of FVC decline (7), reduce the risk of acute respiratory deteriorations (8), which are associated with high morbidity and mortality, and reduce the risk of mortality (8). There is however, only limited evidence to suggest that there may be an improvement in cough (9), and nothing to support that these drugs confer a reduction in dyspnoea. Consequently, concomitant treatment approaches are still required for these symptoms; oxygen could address the latter. Furthermore, antifibrotics are associated with clinically significant side effects, primarily gastrointestinal in nature, limiting their tolerability. The loss of appetite can increase weight loss, sarcopenia and morbidity.

Considerable uncertainty exists on the use of supportive treatments used in other respiratory diseases, such as oxygen. Supplemental oxygen is commonly prescribed in routine clinical practice, with the aim of improving dyspnoea, exercise capacity and health-related quality of life (HRQoL); its use may be considered to be the standard of care (10). Current recommendations for long-term oxygen therapy (LTOT) for resting hypoxaemia in IPF are largely extrapolated from trials conducted in Chronic Obstructive Pulmonary Disorder (COPD), where a survival benefit is well established (11), but there are factors in IPF which may impact efficacy. In particular, exercise desaturation is often a prominent problem in early disease, hastening deconditioning and limiting ability to engage with exercise, suggesting that use in this setting (rather than purely as LTOT) would need to differ. The most recent recommendations are from a Delphi consensus of 45 experts from 17 countries (12); use of supplemental oxygen for patients with fibrotic ILD is recommended where there is severe resting hypoxemia or exertional hypoxemia with attributable symptoms or exercise limitation.

Surprisingly, given the above consensus, there is very little conclusive evidence in IPF on whether oxygen is beneficial. LTOT use in marked hypoxia is not controversial, given that the mechanism of benefit (to prevent pulmonary hypertension/*cor pulmonale)* is likely the same as COPD, although a recent systematic review was unable to draw conclusions due to high levels of bias in relevant studies (n=2670 patients) (13). However, opinions of ambulatory oxygen therapy (AOT) are far less certain; one systematic review concluded no benefit (13) and noted that the studies included in the review were largely observational designs prone to bias. Some studies found a small benefit on objective exercise capacity (14-16) and a small, open-label, crossover, randomised controlled trial (RCT; n=84) is suggestive of AOT use improving HRQoL short term (17). The impact on long term HRQoL remains unknown, suggesting that a larger scale, longer term study in IPF is required. Furthermore, access to oxygen is dependent on local funding and criteria as well as practice of individual clinicians (18), resulting in great variability in access. Given that this intervention is expensive and burdensome (19), establishing benefit or lack thereof, could help target those

who would most benefit from AOT with the aim of reducing inequity in oxygen availability. If oxygen is not beneficial, focus should be on supportive measures i.e. counselling, pulmonary rehabilitation and early referral to palliative care (20).

1.2. Trial rationale

In other conditions in which oxygen has evidence of patient benefit when used long term (typically ≥12 or ≥15 hours/day), such as COPD (11, 21), a systematic review has shown no consistent benefit of AOT (22). The prescription of AOT in COPD has historically been governed by an improvement in exercise capacity or Borg dyspnoea scores, wherein a 10% improvement in distance walked or reduction of ≥1 point in the Borg Score indicates it should be used in patients with desaturation of >4% on exertion (23). The systematic review showed there is not a benefit of this magnitude. Furthermore, compliance with AOT may be low, and COPD patients have reported multiple reasons why they did not use it as prescribed, namely they received no instruction on how to use it; were uncertain of the benefits; were afraid it would run out while they were using it; were embarrassed at being seen with it in public; and were unable to carry it because of cylinder weight (19). These factors are likely to be common to IPF patients, hence it is important to test AOT in a pragmatic RCT, to obtain information on effects in a real-life setting, and to assess in adherence and acceptability. Given that these attitudes may impact recruitment, we plan to conduct all acceptability work during the pilot phase of the proposed trial.

1.2.1. Justification for participant population

Selection of patients for treatment may be important, and again there may be transferable lessons from use of AOT in COPD. In a review, two studies (24, 25) used exertional dyspnoea as their main inclusion criterion. Few studies specified “acute responders” as an inclusion criterion (i.e. those with >10% improvement in walking distance); interestingly however, seven studies (24-30) included a single assessment acute oxygen test for all participants as part of their protocol. All but one (29) demonstrated a significant mean improvement in exercise capacity for participants with acute oxygen therapy compared to compressed air. It would therefore seem that acute improvement in walking distance observed in a single assessment study is lost over time, given that overall the studies showed no benefits. This has implications for clinical practice as prescriptions for AOT might not be appropriate to assess based on an on-oxygen exercise capacity e.g. 6 minute walk test (6MWT) result. Some studies of AOT in COPD (27, 29-32) were carried out as part of pulmonary rehabilitation. Although no benefit of long term AOT was demonstrated, exercise capacity (particularly 6MWT) in the pulmonary rehabilitation studies exceeded that of the domiciliary studies (24, 25), regardless of whether patients were randomised to AOT or placebo. Furthermore, the improvement in 6MWT distance gained by pulmonary rehabilitation far exceeded that gained by AOT (30), thus supporting guidance (23) that any assessment of AOT should be made following pulmonary rehabilitation. Whilst rehabilitation is beneficial in ILD (33), the effects tend to be sustained for a shorter period(34), and it is recognised that any improvement in exercise capacity can be negated by the weight of the AOT if carried by patients alone (35, 36). Tolerating this weight may be more likely in patients whose fitness is optimised by recent rehabilitation – consequently date of rehabilitation could be a confounder in studies of AOT and our protocol therefore accounts for this.

Participants in OXYPuF will have a clinical diagnosis of IPF and may have any disease severity, with or without anti-fibrotic treatment. Whilst MRC dyspnoea score ≥2 is more likely to occur in people who have more severe disease, the mechanism by which oxygen acts is likely to be independent of this, and of anti-fibrotics; this plus a desire for this trial population to reflect those likely to receive the intervention in real life has prompted us to keep the inclusion criteria broad. We will, however, balance the two intervention groups for key features such as disease severity and anti-fibrotic use.

We recognise that keeping the inclusion criteria as broad as possible, in order to ensure results are likely to be applicable to the whole IPF population in the United Kingdom, is desirable and for this reason have not included any other severity features (e.g. % predicted FVC) or prior treatment expectations, though we will balance this between intervention groups. In addition, patients with co-existent co-morbidities which might impact hypoxia and exercise tolerance (e.g. heart failure) will be eligible to participate, although this will be recorded and explored within the data to examine if sub-group effects are present. Such individuals would commonly be excluded from drug trials, but

constitute a large proportion of the IPF population in real life; for example, heart failure occurs in 21-30% of IPF patients (4, 40). Including such patients keeps our results generalisable.

We will therefore recruit 260 patients with IPF and an MRC dyspnoea score ≥2 from centres in the UK.

1.2.2. Justification for design

This trial is a multicentre open label pragmatic RCT, randomising at the level of the individual in a 1:1 ratio between AOT and standardised breathlessness advice or standardised breathlessness advice alone. AOT is delivered by cylinders or concentrator, via either face mask or nasal cannulae. As a result of this it would not be possible to conduct this study in a blinded fashion.

1.2.3. Justification for choice of intervention(s)

AOT is defined as oxygen used during physical activity, delivered by cylinders or concentrator, via either face mask or nasal cannulae, at a flow maintaining saturations >90% on oxygen, during the 6MWT. Current British Thoracic Society (BTS) oxygen guidance suggests that patients who desaturate on walking to <88% and are able to walk more or experience less dyspnoea with oxygen may benefit from AOT (37). Whilst the evidence on which this guidance was made is low grade and states that it should not be given routinely outside the context of LTOT, the end result has been extrapolation to any patient who desaturates, in part because the accompanying quality standards state that it may be ordered to improve mobility 'after appropriate formal assessment that includes an exercise test' (38). This standard does not specifically say that exercise duration or symptoms must decrease, so it is probable that expansion of AOT provision has occurred in any patient who has had exercise testing, in order to comply with this interpretation of the quality standard. Our trial team and collaborators agreed with this from their clinical practice. Consequently we have defined receipt of AOT as normal NHS care for those patients in the OXYPuF trial population who desaturate on exertion.

The comparator is standardised advice for breathlessness which is the provision of advice on use of appropriate pharmacological agents (e.g. morphine, benzodiazepines) and non-pharmacological interventions (e.g. fan, breathing techniques). A true placebo of medical air would be both expensive, logistically difficult to blind (due to legal requirements for colouring of oxygen and air cylinders), and inappropriate in a pragmatic trial design, in which placebo effects on symptoms and activity that are separate from the biological effect of oxygen (i.e. correction of hypoxia) should occur in the group receiving AOT, and would occur in a real life context outside the trial. The advice about relief of breathlessness will be standardised and designed in conjunction with patients, and issued to both groups.

1.2.4. Justification of choice of primary outcome(s)

We have chosen to use both a specific validated breathlessness score (MRC), and relevant subscale of Kings' Brief Interstitial Lung Disease (K-BILD) questionnaire because breathlessness is an important outcome; whilst a subscale within a questionnaire validated in IPF obviously has value, the subscale itself is not a validated item, unlike the MRC. Cough and fatigue will also be specifically assessed, in accordance with the core dataset advised for IPF trials, by way of a visual analogue score (VAS) and relevant subscale in K-BILD. Activity levels were also required by the NIHR brief; we will objectively evaluate this in 20% of patients in both arms using the Actigraph device, validated for use both against calorimetry and in daily life in respiratory patients (45, 46). We felt this necessary as self-reported activity by the International Physical Activity Questionnaire (IPAQ) cannot be certain to relate to actual activity, and patients had concurred with this in pre-application patient and public involvement (PPI). We have chosen 20% (n=52) as this exceeds the median number required in 10 validation studies of the device in older adults (n=36), as reported in a systematic review of appropriate data collection and processing when using an Actigraph (47). We will adhere to guidance developed in this review when considering device placement and data analysis, including measures of activity intensity and duration, not just step count.

2. AIMS AND OBJECTIVES

2.1. Internal pilot objectives

The pilot phase of the trial will last 6 months and afford the opportunity to assess both recruitment rate and conduct a qualitative study to explore the acceptability of the trial intervention.

2.1.1. Recruitment rate objective

The aim is to open 50% of sites by 6 months from study approval by the relevant authorities, and target an overall recruitment rate of 2 patients per site, per month.

2.1.2. Qualitative aims and objectives

To explore social acceptability and practical responses to the intervention by conducting qualitative. interviews.

2.2. Main trial objectives

2.2.1. Clinical aims and objectives

To determine whether AOT is clinically and cost effective in patients with idiopathic pulmonary fibrosis (IPF). The clinical objectives are determined as follows:

- Whether HRQoL measured using the K-BILD questionnaire is superior after AOT compared to the standardised breathlessness advice alone at 6 months after using the trial allocation.
- Whether breathlessness, determined by the MRC dyspnoea score, is superior after AOT compared to the standardised breathlessness advice alone at 6 months after using the trial allocation.
- Whether exercise capacity and physical activity, as measured by the 6MWT OR the sit to stand test (according to local protocol), and a self-reported activity questionnaire (IPAQ) respectively is superior after AOT compared to to the standardised breathlessness advice alone at 6 months after using the trial allocation.

2.2.2. Economic aims and objectives

To assess the cost effectiveness of AOT compared to standardised breathlessness advice alone at 6 months after using the trial allocation using EQ-5D-5L and scheduled and unscheduled health service use relating to IPF.

2.2.3. Mechanistic aims and objectives

To assess objective physical activity by using accelerometers to compare this against self-reported physical activity (using the IPAQ) in the AOT arm compared to standardised breathlessness advice only at 6 months after using the trial allocation.

Collection of blood to be used as part of future research.

3. TRIAL DESIGN AND SETTING

3.1. Trial design

This study is a pragmatic, multicentre, open-label individually randomised controlled clinical trial, where patients will use AOT in a community setting, comparing AOT to standardised breathlessness advice only. There is an internal pilot phase, a detailed process evaluation and a cost-effectiveness study.

3.2. Trial setting

The study is set in secondary care, enrolling participants from approximately 20 hospital outpatient clinics or community oxygen services with the trial intervention used by patients in their own homes. For the treatment arm, oxygen cylinders will be delivered to the participant's home for use in their day-to-day life, hence whilst initial assessment is in secondary care, treatment is received in the community.

3.3.1 Qualitative sub-study

The qualitative sub-study will be conducted during the pilot phase of the trial. To explore social acceptability and practical responses to the intervention (48), we will conduct qualitative interviews with a range of clinical and non-clinical staff, including relevant policy makers and stakeholders (n=20) to understand attitudes to AOT and the overall goal of improving HRQoL symptoms and activity level. We are particularly interested in understanding willingness to randomise patients to no AOT, given that this is usual practice in many centres; areas which emerge could guide adjustments to information given to clinicians/sites to enhance recruitment if this is poor. We do not anticipate insurmountable issues with clinicians' equipoise, given the call for this kind of evidence to be generated in the last IPF National Institute for Clinical Excellence (NICE) guidance. However, if attitudes were negative and recruitment was below our amber progression targets, this would prompt discussion with the NIHR regarding continuation. In addition, we will interview approximately 20 of the invited patients in the OXYPuF trial, using photo-voice methods, with follow-up interviews or arts-based workshops 3-6 months later (N.B. which may not be within the pilot period), splitting the sample equally between AOT and standardised breathlessness advice arms, and ensuring diversity in the sample (age, gender, ethnicity etc. as far as possible).

Further recruitment for the qualitative study may be undertaken via patient groups. The topic guide will be developed drawing on existing literature and theories, in particular experience of breathlessness, social stigma of visible oxygen use and the perception that oxygen is always beneficial, in conjunction with our PPI group and co-applicants. Interviews will be audio recorded and transcribed verbatim, prior to qualitative analysis using the Framework method, as described in our previous work (49), which is a systematic approach well suited to interdisciplinary health research and to working with clinical and lay collaborators. A systematic review of arts based approaches in healthcare (50) has found 23 studies in which arts were used for knowledge generation/production mainly using visual (n=21) approaches. These can integrate well with qualitative data to explore patient experience (51), hence we will use visual arts such as painting and photography to add to our data, in particular how experience changes during the trial for an individual, and between groups. Some members of our PPI group will additionally be actively involved as co-researchers in the analysis stage of the research, through a series of data workshops facilitated by a qualitative methodologist, to help ensure that the patient voice remains central to this part of the work.

3.3.2 Objective physical activity study

This sub-study will be conducted at a limited number of centres, by invitation, and will collect physical activity data via an accelerometer. The aim is to enrol 20% of the cohort (n=52), split equally between the AOT and standardised breathlessness advice only arms. The first 26 participants recruited at the invited centres, in each arm, will be asked if they will wear an accelerometer for 7 days at 2 time points; at baseline and then again towards the end of the 6 month trial follow up period. If any of the first 26 participants in either arm do not wish to take part, the process of approaching participants will continue until 26 in each arm is achieved.

If the participant agrees to take part, the accelerometer will be sent via post (from the trials office) to the participant's home with instructions on how to use the accelerometer. They will be advised to wear the accelerometer at all times (except when in water) for 7 days. It is important to note that participating patients should be told that the accelerometer must be worn for 7 days post randomisation **prior to using the allocated trial intervention** and to then return it to the trials office by recorded delivery post after the 7-day period is completed.

Towards the end of the 6 month trial follow up period, prior to the 7 day period before the final study visit, an accelerometer will be sent via post to the participant. The accelerometer can be either returned via post to the trials office or handed to the research team at their final study visit (6 month follow up). The research team at site can then return the accelerometer via post to the trials office.

3.4. Assessment of risk

All clinical trials can be considered to involve an element of risk and in accordance with the Birmingham Clinical Trials Unit (BCTU) standard operating procedures this trial has been risk assessed to clarify any risks relating uniquely to this trial beyond that associated with usual care. A Risk Assessment has been conducted and concluded that this trial corresponds to the following categorisation:

Type A = No higher than the risk of standard medical care

4. ELIGIBILITY

4.1. Inclusion criteria

- Aged 18 or over
- Clinically diagnosed IPF, confirmed by an ILD multi-disciplinary team (MDT) linked to an NHS specialist commissioned IPF service
- Breathlessness with MRC dyspnoea score ≥2
- Willing and able to comply with completion of questionnaires out to 6 months post-randomisation
- Able to complete a 6MWT or 1 minute sit to stand test
- Able to use oxygen safely in the opinion of the local investigator

4.2. Exclusion criteria

- Unable to provide informed consent
- Requires LTOT, defined by need for resting oxygen in the opinion of the local investigator
- Life expectancy <6 months
- On the active transplant list
- Previous acidotic hypercapnic respiratory failure (AHRF) requiring non-invasive ventilation (NIV)

4.3. Co-enrolment

Enrolment to observational studies is permitted. In the case of interventional studies, where mutual agreement can be made between Chief Investigators that co-enrolment will not be harmful to the scientific integrity of either study this will also be allowed. We consider this an unlikely scenario, however what is more likely is that participating sites will use similar mechanisms to pre-screen or approach patients for multiple studies at once.

5. CONSENT

It is the responsibility of the Principal Investigator (PI) to obtain written informed consent for each participant prior to performing any trial related procedures. This task can be delegated by the PI to other members of the local research team, if local practice allows and this responsibility has been documented in the site signature and delegation log.

A Participant Information Sheet (PIS) will be provided to facilitate this process. The PI or delegate will ensure that they adequately explain the aim of the trial, the trial intervention, and the anticipated benefits and potential hazards of taking part in the trial to the participant. They will also explain that participation is voluntary and that the participant is free to decide to take part and may withdraw from the trial at any time. The participant will be given sufficient time to read the PIS and to discuss their participation with others outside of the site research team. The time period considered to be sufficient will be deemed locally at site by the research team. The participant will be given the opportunity to ask questions before signing and dating the latest version of the Informed Consent Form (ICF). If the participant then expresses an interest in participating in the trial, they will be asked to sign and date the

latest version of the ICF. The PI or delegate will then sign and date the ICF. A copy of the ICF will be given to the participant, a copy will be filed in the medical notes and the original placed in the Investigator Site File (ISF). Once the participant is entered into the trial, the participant's trial number will be entered on the ICF maintained in the ISF. In addition, the participant understands and acknowledges that, a copy of the signed ICF will be transferred to the trial team at BCTU for review.

Details of the informed consent discussions will be recorded in the participant's medical notes. This will include date of discussion, the name of the trial, summary of discussion, version number of the PIS given to participant, version number of ICF signed and date consent received. Where consent is obtained on the same day that the trial related assessments are due to start, a note should be made in the medical notes as to what time the consent was obtained and what time the procedures started.

At each visit the participant's willingness to continue in the trial will be ascertained and documented in the medical notes. Throughout the trial, the participant will have the opportunity to ask questions about the trial. Any new information that may be relevant to the participant's continued participation will be provided. Where new information becomes available which may affect the participants' decision to continue, participants will be given time to consider and if happy to continue they will be re-consented. Re-consent will be documented in the medical notes. The participant's right to withdraw from the trial will remain.

Electronic copies of the PIS and ICF will be available from the Trial Office and will be printed or photocopied onto the headed paper of the local institution.

If at any point during the trial the PI or suitably qualified delegate deems that the participant has lost capacity to provide willingness to continue in the trial, then the participant should be withdrawn from the trial using the change of status CRF.

There is an additional statement on the ICF for the participant to acknowledge that they understand that the Trial Office might in the future, for other related research, collect participant data available in NHS routine clinical datasets, including primary care data (e.g., Clinical Practice Research Datalink, The Health Improvement Network, QResearch) and secondary care data (Hospital Episode Statistics) through NHS Digital and other central UK NHS bodies. The participant will acknowledge that they understand that the Trial Office might send their name, address, date of birth and NHS number to the relevant national registry, and then for the national registry to link this to their data and send the information back to the Trial Office. The acknowledgement by the participant will also allow access to other new central UK NHS databases that will appear in the future. This will allow us (subject to receipt of additional funding via another grant application) to assess longer-term impact and health service usage data without needing further contact with the trial participants.

6. SCREENING, RANDOMISATION and BLINDING

6.1. Identification

Potential participants will be identified in respiratory and medical departments in participating NHS trust sites during regular scheduled outpatient visits. MDT lists will also be used to identify potential participants as well community based oxygen services. The charity 'Action Pulmonary Fibrosis' have also agreed to send an introductory letter to any charity members who may be interested in taking part in research. This letter will provide information about the trial and include an invitation to contact the appropriate research department for further information if they are interested in participating.

6.2. Screening

The research team will screen the patient for eligibility and record information on the **OXYPuF Participant Screening Log** accordingly. The following assessments form part of the screening process in order to confirm the patient's eligibility for participation in the OXYPuF trial:

- Medical History
- Contraindicated medications

Eligibility must be confirmed by a suitably qualified medical practitioner who is on the **OXYPuF Trial Signature and Delegation Log.**

Details of all patients approached about the trial will be recorded on the **OXYPuF Participant Screening Log** which will be kept in the ISF and should be available to be sent to the Trials Office upon request.

6.3. Randomisation

After participant eligibility has been confirmed, informed consent has been received and the baseline **OXYPuF Patient Completed Booklet** has been completed, the participant can be randomised into the trial. **OXYPuF Randomisation Notepads** will be provided to investigators and may be used to collate the necessary information prior to randomisation. All questions and data items on the **OXYPuF Randomisation Notepad** must be answered before a Trial Number can be given. If data items are missing, randomisation will be suspended, and can be restarted once the information is available. Only when all eligibility criteria and baseline data items have been provided will a Trial Number and treatment group be allocated.

Participants will be randomised in a 1:1 ratio to either AOT and standardised breathlessness advice or standardised breathlessness advice alone.

Those patients who are randomised to the intervention will receive AOT and standardised breathlessness advice. One week following randomisation, this group of patients will also receive a telephone call from the trials office to check fidelity of the intervention.

Those patients who are randomised to standardised breathlessness advice will receive standardised breathlessness advice.

6.4. Randomisation process

Randomisation will be provided by a secure online randomisation system at the Birmingham Clinical Trials Unit (BCTU) (available at *<insert web address>*), thereby ensuring allocation concealment. Unique log-in usernames and passwords will be provided to those who wish to use the online system and who have been delegated the role of randomising participants into the study as detailed on the **OXYPuF Trial Signature and Delegation Log**. These unique log-in details must not be shared with other staff and in no circumstances should staff at sites access either the randomisation process or clinical investigation database using another person's login details. The online randomisation system will be available 24 hours a day, 7 days a week, apart from short periods of scheduled maintenance. In the event of the online system not being available a telephone toll-free randomisation service ((0044) 0800 953 0274) is available Monday to Friday, 09:00 to 17:00 UK time, except for bank holidays and University of Birmingham closed days. The availability of telephone randomisation may be reduced due to unforeseen circumstances such as epidemic/pandemic and/or natural disasters.

Following randomisation, a confirmatory e-mail will be sent to the randomiser, local PI, local Research Nurse, and trial manager.

The local research team should add the participant to the *OXYPuF* Participant Recruitment and Identification Log which links participants with their Registration/Trial Number. PIs must maintain this document securely and it must

not be submitted to the Trial Office. The *OXYPuF* Participant Recruitment and Identification Log should be held in strict confidence. Randomisation method

Participants will be randomised at the level of the individual in a 1:1 ratio to either AOT and standardised breathlessness advice or standardised breathlessness advice alone.

A minimisation algorithm will be used within the online randomisation system to ensure balance in the treatment allocations over the following variables:

- Centre
- Desaturation to <88% on 6MWT or equivalent exercise test
- Current or recent (within 6 months) pulmonary rehabilitation
- Current antifibrotic use

randomised To avoid the possibility of the intervention allocation becoming predictable, a random element will be included in the algorithm. Full details of the randomisation specification will be stored in a confidential document at BCTU.

6.5. Blinding

The OXYPuF trial is an open label trial.

6.6. Informing the participant's GP and other parties

In order to be randomised into the OXYPuF trial, the participant must agree to their GP being contacted. The participant's GP should be notified that they are in OXYPuF trial, using the **OXYPuF GP Letter**.

7. TRIAL INTERVENTION

7.1. Name and description of investigational medicinal product

IMP	Name of IMP	Formulation
Medical Oxygen	Medical Oxygen, 100% inhalation gas	Oxygen Ph Eur 100%v/v (no other ingredients)

7.2. Trial intervention(s) and dosing schedule

The intervention is defined as oxygen used during physical activity, delivered by cylinders or concentrator, via either face mask or nasal cannulae, at a flow maintaining saturations >90%. Patients will be provided with instructions on how to use the oxygen cylinders/concentrators and informed that they will need to use the oxygen when they feel breathless. This can be different for each patient.

7.3. Drug interaction or contraindications

There are no relevant interactions. All patients contraindicated for oxygen are not eligible for the trial.

7.4. Accountability Procedures

For patients randomised to the oxygen arm, oxygen use will estimated in two ways..

7.5. Intervention modification or discontinuation

It is the nature of AOT that its use will be self-administered as required. There are no obvious clinical reasons for modifying the availability of oxygen to those allocated to the AOT arm.

7.6. Continuation of intervention after the trial

Since provision of AOT is a commonly used therapy, there would be no issue with a patient on the AOT arm continuing after the trial ends based on the opinion of the local investigator as to whether they have benefitted from it.

Similarly, patients on the breathlessness advice arm could be provided with AOT after the trial ends based on the opinion of the local investigator as to whether they have benefitted from it..

7.7. Intervention supply and storage

7.7.1. Intervention supplies

Local HOSAR (home O2 assessment and review services) will provide oxygen according to normal NHS practice to those patients randomised to the AOT group.

7.7.2. Packaging and labelling

Routine stock will be used and no additional labelling will be required in accordance with the Risk Adapted Approaches to the Management of Clinical Trials of Investigational Medicinal Product guidance regarding Type A trials for products with an MA, where the product is being used within the terms of its MA and the prescription for its use.

7.7.3. Drug storage

In the context of an IMP, oxygen cylinders can be stored at ambient temperature for longer than 6 months (the duration of the trial).

Oxygen concentrators are designed to operate at ambient temperatures. Cylinders which are partially full at the end of an individual's participation in the trial can be continued to be used if, in the opinion of the clinician, the participant would benefit from continuing AOT. Otherwise such cylinders will be returned to the supplier.

7.8. Accountability

The provision of oxygen cylinders to those patients randomised to the AOT arm will be via the normal routes (i.e. from the hospital oxygen service directly to the patient's homes). Re-provision is the responsibility of the patient and hospital oxygen service.

7.9. Adherence

Adherence will be monitored via collecting the number and type of oxygen cylinders a patient is using per week. This information will be self-reported by the patient and included on the baseline and follow up forms.

8. OUTCOME MEASURES

8.1. Internal pilot outcomes

8.1.1 Recruitment rate

The aim is to open 50% of sites by 6 months from study approval by the relevant authorities, and target an overall recruitment rate of 2 patients per site per month. If recruitment is sub-optimal, we will consider increasing the number of sites, enrolling other forms of pulmonary fibrosis (e.g. fibrotic non-specific interstitial pneumonitis (NSIP)), and enrolling a greater proportion of non-desaturating patients. We will not include connective tissue disease associated ILD as these patients may have other co-morbidities or functional deficits (e.g. mobility issues from joint disease), and this could influence outcomes. We will also examine reasons for non-inclusion of patients in the study; if high rates of identification occur, but patients decline screening, this implies the trial may not be possible

to complete, and such data would be interpreted alongside the acceptability analysis to determine if the study should continue.

8.1.2 Acceptability of intervention

To provide a description of the data, including different dimensions of acceptability and drawing out any differences (e.g. if some groups find it acceptable and others don't).

8.1.3 Progression Criteria for internal pilot to main trial

Progression criteria are based on recruitment and data received.

Recruitment rate. If sites, overall, recruit 2 patients per month, and each site has a target of ~17 patients; each site will complete recruitment in 11 months; this represents green as recruitment would be completed by 18 months, assuming a steady rate of sites opening. If overall recruitment was 0.5-1.9 patients/centre/month, we would amend recruitment methods as described above, and if there were <0.5 patients/centre/month this represents red (stop).

Critical data receipt. We do not anticipate issues with data collection, since the primary outcome is a questionnaire collected directly from patients. If ≥90% of critical data is received for patients this would be considered green, 80-89%=amber and ≤79%=red. Critical data refers to primary and safety data.

The progression criteria are summarised in the table 1 below:

Table 1 Progression Criteria

	Green (go)	Amber	Red (stop)
Recruitment rate average patients per site per month	≥1.9	0.5 to <1.9	<0.5
Acceptability	High	Low	Low
Non-adherence	≤20%	21-29%	≥30%
Critical data receipt	≥90%	80-89%	≤79%

8.2. Main trial outcomes

8.2.1. Primary outcome(s)

Health related quality of life at 6 months post-randomisation, as measured by the total score on the K-BILD questionnaire

8.2.2. Secondary outcomes

All secondary outcomes are measured at 6 months post-randomisation unless otherwise stated.

8.2.2.1 Clinical

- Subscales within K-BILD (breathlessness, activity, chest symptoms)
- MRC Score
- Exercise capacity using the 6MWT or 1 minute sit to stand
- Physical activity using the IPAQ
- Sleepiness using the Epworth Sleepiness Scale
- Hospitalisations (all cause and IPF specific)
- Cough using a 6 point VAS
- Targeted adverse events
- Mortality (6 months, and from medical record only at 12 months)

- Medication use: benzodiazepines, antifibrotics; ACEis and opiates for breathlessness.
- Completion of pulmonary rehabilitation
- Scheduled and unscheduled health service use relating to IPF.

8.2.2.2 Economic

To assess the cost effectiveness of AOT compared to the standardised breathlessness advice alone at 6 months after using the trial allocation using EQ-5D-5L and scheduled and unscheduled health service use relating to IPF.

8.2.2.3 Mechanistic

Haemoglobin and haematocrit, which are measures of secondary effects of chronic hypoxia – rises in either would indicate a lack of effectiveness of AOT, or disease progression by way of development of chronic respiratory failure. They are a required safety measure as well, as development of secondary rises in either measure would be an indication for routine oxygen treatment.

Physical activity data will also be obtained via an accelerometer in a subset of 20% of trial participants (n=52; 26 participants from each trial arm), and associated processing software for how many minutes per day somebody is active in terms of intensity of exercise: sedentary; low; moderate; high. Accelerometers will be worn by the participant for 7 days after randomisation prior to commencing the trial allocation. It will then also be worn for 7 days prior to their final trial visit.

8.2.2.4 Qualitative

These are outlined in the internal pilot outcomes in section 8.1.2.

9. TRIAL PROCEDURES

The following should be performed/collected at baseline:

Clinic visit 1 (Baseline):

- Weight & Height
- Medical history
- Smoking status
- Shortness of breath (MRC dyspnoea score)
- Spirometry within the last 6 months
- Blood Gases (if saturations are <90% on air as per usual care)
- Full Blood Count (FBC/CBC) and storage of plasma for translational work
- Gas Transfer Test within the last 6 months
- Lung function tests
- Assessment of desaturation both on and off oxygen via either the 6MWT or 1 minute sit to stand
- Completion of the participant completed booklet

In addition, at the baseline visit, following randomisation, advice on breathlessness should be given to all participants, and for those randomised to the AOT arm, the oxygen prescription should be provided. For those centres taking part in the sub-study, interest by the participant in taking part in the sub-study should be ascertained.

The following should take place at the 3 week telephone follow up:

3 weeks post randomisation for AOT arm only:

- Telephone (3 weeks post randomisation) ***Completed by staff at BCTU***.

- *The timescale as to when this telephone call takes place depends on when the participant receives the AOT. Depending on site/demand, this may take 2-3 weeks following referral to the oxygen team following randomisation.*

The following should be performed at 3 months follow up:

Clinic Visit 2 (3 months) *May be conducted via video depending on local policy*

- Review prescription for Study
- Survival Check
- SAE
- Completion of EQ-5D-L
- Healthcare utilisation
- SpO2 check

The following should be performed/collected at 6 months follow up:

Clinic Visit 3 (6 months)

- Survival Check
- SAE Check
- Clinical review
- Check completion of HRQoL
- Blood Gases (if saturations are <90% on air as per usual care)
- Full Blood Count (FBC/CBC) and storage of plasma for translational work
- Recording of lung function (spirometry and gas transfer) if done as part of usual care
- Check completion of HRQoL
- Healthcare utilisation
- Weight
- Smoking status
- Shortness of breath (MRC dyspnoea score)
- Assessment of desaturation both on and off oxygen via either 6MWT or 1 minute sit to stand

9.1. Schedule of assessments

Table 2: Schedule of Assessments

Event	Pre-screening	Visit 1: Baseline	Telephone call: 3 week (done by BCTU)	Visit 2: 3 months	Visit 3: 6 months
Inclusion	X	X			
Exclusion	X	X			
Consent		X			
FVC & DLCO		X			X
6MWT on/off oxygen		X			X
Randomisation		X			
Standardised breathlessness advice		X			
Demographics		X			
Medical history		X			
Pulmonary rehabilitation date and/or completion date		X			X
Medications (including LTOT)		X			X
KBILD		X			X
MRC, cough by VAS		X			X
IPAQ		X			X
*Accelerometer**		X			X
Trial fidelity			X		
Adverse events		X		X	X
EQ-5D-5L		X		X	X
Healthcare utilisation		X		X	X
Observations including oxygen sats		X		X	X
Clinical review		X		X	X

10. Withdrawal and changes in levels of participation

Informed consent is defined as the process of learning the key facts about a clinical trial before deciding whether or not to participate. It is a continuous and dynamic process and participants should be asked about their ongoing willingness to continue participation.

Participants should be aware from the beginning that they can freely withdraw (cease to participate) from the trial at any time. A participant may wish to cease to participate in a *particular* aspect of the trial.

The changes in levels of participation within the trial are categorised in the following ways:

- **No trial intervention**: The participant would no longer like to receive the trial treatment, but is willing to be followed up in accordance with the schedule of assessments and if applicable using any central UK NHS bodies for long-term outcomes (i.e. the participant has agreed that data can be collected and used in the trial analysis)
- **No trial related follow-up**: The participant would like to withdraw from trial treatment and does not wish to attend trial visits in accordance with the schedule of assessments but is willing to be followed up at standard clinic visits and if applicable using any central UK NHS bodies for long-term outcomes (i.e. the participant has agreed that data can be collected at standard clinic visits and used in the trial analysis, including data collected as part of long-term outcomes)
- **No further data collection**: The participant is not willing to be followed up in any way for the purposes of the trial and does not wish for any further data to be collected (i.e. only data collected prior to any changes of level in participation can be used in the trial analysis)
- **Sub-study withdrawal:** The participant wishes to withdraw specifically, and only, from the sub-study (Qualitative or actigraph study).

The details of changes of level in participation within the trial (date, reason and category of status change) should be clearly documented in the source data.

11. ADVERSE EVENT REPORTING

11.1 Definitions

Standard definitions of different types of adverse events (AEs) are listed in Table 3.

Table 3: Adverse event reporting definitions

Severity Definitions	Mild	Awareness of signs or symptoms that do not interfere with the participant's usual activity or are transient and resolved without treatment and with no sequelae.
	Moderate	A sign or symptom, which interferes with the participant's usual activity.
	Severe	Incapacity with inability to do work or perform usual activities.
Adverse Event	AE	Any untoward medical occurrence in a participant administered a medicinal product and which does not necessarily have a causal relationship with this intervention. Comment: An AE can therefore be any unfavourable and unintended sign (including abnormal laboratory findings), symptom or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product.

Adverse Reaction	AR	All untoward and unintended responses to an IMP related to any dose administered. Comment: An AE judged by either the reporting Investigator or Sponsor as having causal relationship to the IMP qualifies as an AR. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.
Serious Adverse Event	SAE	Any untoward medical occurrence or effect that: Results in death Is life-threatening* Requires hospitalisation or prolongation of existing hospitalisation Results in persistent or significant disability or incapacity Is a congenital anomaly/birth defect Or is otherwise considered medically significant by the Investigator**
Serious Adverse Reaction	SAR	An AR which also meets the definition of a SAE.
Unexpected Adverse Reaction	UAR	An AR, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator Brochure for an unapproved IMP or (compendium of) Summary of Product Characteristics (SmPC) for a licensed product). When the outcome of an AR is not consistent with the applicable product information the AR should be considered unexpected.
Suspected Unexpected Serious Adverse Reaction	SUSAR	A SAR that is unexpected i.e., the nature, or severity of the event is not consistent with the applicable product information. A SUSAR should meet the definition of an AR, UAR and SAR.
Unexpected Event	UE	The type of event that is not listed in the protocol as an expected occurrence.
Related and Unexpected Serious Adverse Event	N/A	A SAE that meets both the definition of a Related and Unexpected Event.

* The term life-threatening is defined as diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted.

** Medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in the definitions above.

11.2. Adverse event (AE) recording – general

The recording and reporting of AEs will be in accordance with the UK Policy Framework for Health and Social Care Research, the Principles of Good Clinical Practice (GCP) as set out in the UK Statutory Instrument (2004/1031; and subsequent amendments) and the requirements of the Health Research Authority (HRA) and The Medicines for Human Use (Clinical Trials) Regulations 2004 and amendments thereof. Definitions for adverse event reporting are listed in Table 3 in Section 11.

It is routine practice to record AEs in the participant's medical notes and it is also recommended that this includes the documentation of the assessment of severity and seriousness and also of causality (relatedness) in relation to the intervention(s) in accordance with the protocol.

11.3. Adverse event reporting in OXYPuF

As the use of ambulatory oxygen is part of the current standard of care for this participant population the collection of AE data is not in itself an outcome measure within the trial. Therefore AE data will not be collected although SAE data will be collected as per section 10.4.

11.4. Serious Adverse Advents (SAE) reporting in OXYPuF

For all SAEs, the PI or delegate must do one of the following:

- **Record safety reporting-exempt SAEs** in the medical notes but **not report** them to the trials office on an SAE form as per Section 0 11.4.1. Serious Adverse Events not requiring reporting to the Trial Office.

- **Report SAEs to the trial office in a non-expedited manner**. This can only be done for the pre-defined subset of SAEs as per Section 0 11.4.2 Serious Adverse Events requiring non-expedited reporting to the Trial Office.

- **Report SAEs to the trial office in an expedited manner** (within 24 hours of the site research team becoming aware of the event). All SAEs not covered by the above 2 categories must be reported as per Section 0 11.5. SAE Reporting process.

Note: when an SAE occurs at the same hospital at which the participant is receiving trial intervention or is being followed up for trial purposes, processes must be in place to make the trial team at the hospital aware of any SAEs, regardless of which department first becomes aware of the event, in an expedited manner.

11.4.1. Serious Adverse Events not requiring reporting to the Trial Office

At whatever time they occur during an individual's participation, from when intervention started to end of participant follow-up, the following are not considered to be critical to evaluations of the safety of the trial:.

1. Pre-planned hospitalisation even if >24 hours
2. Hospital admissions lasting less than 24 hours

All events which meet the definition of serious must be recorded in the participant notes, including the causality and severity, throughout the participant's time on trial, including follow-up, but for trial purposes these events do not require reporting on the SAE Form. Such events are "safety reporting exempt".

11.4.2 Serious Adverse Events requiring non-expedited reporting to the Trial Office (expected SAEs)

OXYPuF participants are likely to have significant co-morbidities and therefore the frequency of SAEs may be high. Most of the SAEs occurring in OXYPuF will be anticipated in the sense that they are recognised and accepted complications/consequences of IPF.

The events outlined in Table 4 are regarding as expected SAEs, i.e. are recognised complications/consequences of IPF. These events should be reported in the participant's medical

records and on the OXYPuF SAE Form, and will not be subject to expedited reporting i.e. within 24 hours of the event, but should be reported within 2 weeks of the site research team becoming aware of these events. As such events will, by protocol definition be unrelated, rapid assessment of causality is not required.

Table 4 Expected SAEs that do not require expedited reporting

Acidotic hypercapnic respiratory failure
Right heart failure
Polycythaemia

11.4.3. Serious Adverse Events requiring expedited reporting to the Trial Office

All SAEs not listed in section 0 must be reported to the Trial Office on a trial specific SAE form within 24 hours of the site research team becoming aware of the event.

11.5. SAE Reporting process

On becoming aware that a participant has experienced an SAE which requires reporting on an SAE form, the PI or delegate should report the SAE to their own Trust in accordance with local practice and to the Trial Office.

To report an SAE to the Trial Office, the PI or delegate must complete, date and sign the OXYPuF SAE form. The completed form together with any other relevant, appropriately anonymised, data should be submitted to the Trial Office using the information below in accordance with the timelines given in Section 0 and 0.

To report an SAE, submit the SAE Form to:

oxypuf@trials.bham.ac.uk

Where an SAE Form has been completed by someone other than the PI initially, the original SAE form must be countersigned by the PI to confirm agreement with the causality and severity assessments.

On receipt of an SAE form, the Trial Office will allocate each SAE a unique reference number and notify the site via email to the site as proof of receipt. The site and the Trial Office should ensure that the SAE reference number is quoted on all correspondence and follow-up reports regarding the SAE and filed with the SAE in the ISF.

If the site has not received confirmation of receipt of the SAE or if the SAE has not been assigned a unique SAE identification number within 1 working day of reporting, the site should contact the Trial Office.

11.5.1. Assessment of causality of an SAE

When completing the SAE form, the PI (or, throughout this section, a medically qualified delegate) will be asked to define the nature of the seriousness and causality (relatedness; see table 5) of the event.

In defining the causality the PI must consider if any concomitant events or medications may have contributed to the event and, where this is so, these events or medications should be reported on the SAE form. It is not necessary to report concomitant events or medications which did not contribute to the event.

As per table 5, all events considered to be 'possibly', 'probably', or 'definitely' related to the intervention will be reported by the trial office as 'related'; all events considered at site to be 'unlikely' or 'unrelated' to the intervention will be reported by the trials office as 'unrelated'. The same categorisation should be used when describing AEs and protocol-exempt SAEs in the source data.

Table 5: Categories of causality

Category	Definition	Causality
Definitely	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.	Related
Probably	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.	
Possibly	There is some evidence to suggest a causal relationship. However, the influence of other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events or medication)	
Unlikely	There is little evidence to suggest there is a causal relationship. There is another reasonable explanation for the event (e.g., the participant's clinical condition, other concomitant events or medication).	Unrelated
Not related	There is no evidence of any causal relationship.	

On receipt of an SAE Form, the Trial Office will forward it, with the unique reference number, to the Chief Investigator (CI) who will independently* review the causality of the SAE. An SAE judged by the PI or CI to have a reasonable causal relationship ("Related" as per Table 5) with the intervention will be regarded as a related SAE (i.e., SAR). The severity and causality assessment given by the PI will not be downgraded by the CI. If the CI disagrees with the PI's causality assessment, the opinion of both parties will be documented, and where the event requires further reporting, the opinion will be provided with the report.

*Where the CI is also the reporting PI an independent clinical causality review will be performed.

11.5.2. Assessment of expectedness of an SAE by the CI

The CI will also assess all related SAEs for expectedness with reference to the criteria in table 6.

Table 6: Categories of expectedness

Category	Definition
Expected	An adverse event that is consistent with known information about the trial related procedures or that is clearly defined in the relevant safety information found in the Baywater Medical Oxygen SmPC.
Unexpected	An adverse event that is not consistent with known information about the trial related procedures.

If the event is unexpected (i.e., it is not defined in the approved version of the Reference Safety Information (RSI)) it will be classified as a Suspected Unexpected Serious Adverse Reaction (SUSAR).

The CI will undertake review of all SAEs and may request further information from the clinical team at site for any given event(s) to assist in this.

11.5.3. Provision of SAE follow-up information

Following reporting of an SAE for a participant, the participant should be followed up until resolution or stabilisation of the event. Follow-up information should be provided using the SAE reference number provided by the Trial Office. Once the SAE has been resolved, all critical follow-up information has been received and the paperwork is complete, a copy of the final version of the completed SAE form must be submitted to the Trial Office and the original kept in the ISF.

11.6. Reporting SAEs to third parties

The independent Data Monitoring Committee (DMC) may review any SAEs at their meetings.

The Trial Office will report details of all SARs (including SUSARs) to the MHRA, Research Ethics Committee (REC), and University of Birmingham (UoB) Research Governance Team (RGT) annually from the date of the Clinical Trial Authorisation, in the form of a Development Safety Update Report (DSUR).

Additionally, the Trial Office will report a minimal data set of all individual events categorised as a fatal or life threatening SUSAR to the MHRA, REC, and UoB RGT within 7 days of being notified. Follow-up information will be provided within an additional 8 days.

All other events categorised as SUSARs will be reported within 15 days of being notified.

Details of all SUSARs and any other safety issue which arises during the course of the trial will be reported to the PIs. A copy of any such correspondence should be filed in the ISF and Trial Master File (TMF).

11.7. Urgent Safety Measures

The Clinical Trials Regulations make provision for the Sponsor and PIs to take appropriate Urgent Safety Measures to protect a research participant from an immediate hazard to their health and safety. This measure can be taken before seeking approval from the competent authorities (MHRA in the UK) and ethics committees of all member states concerned.

If any urgent safety measures are taken, the Trial Office shall immediately, and in any event no later than 3 days from the date the measures are taken, give written notice to the REC and the MHRA of the measures taken and the reason why they have been take

12.DATA HANDLING AND RECORD KEEPING

12.1 Source data

Source data is defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. In order to allow for the accurate reconstruction of the trial and clinical management of participants, source data will be accessible and maintained.

Some data variables may be entered directly onto the CRF, these are clearly identified and detailed below in Table 7.

Table 7: Source data in OXYPuF

Data	**Source**
Participant Reported Outcomes	The original participant-completed CRF is the source and will be stored with the participant's trial record at the trial office.
Lab results	The original lab report (which may be electronic) is the source and will be kept and maintained, in line with normal local practice. Information will be transcribed onto CRFs.
6MWT	The 6 minute walk test or the 1 minute sit to stand test results will be directly transcribed onto the CRF. The CRF is the source data
Clinical event data	The original clinical annotation is the source document. This may be found on clinical correspondence, or electronic or paper participant records. Clinical events reported by the participant, either in or out of clinic (e.g., phone calls), must be documented in the source documents.
Health economics data	Often obtained by interview directly with the participant for transcription onto the CRF. The CRF is source data.
Qualitative interviews	Interviews will be recorded and transcribed clean verbatim for analysis. The recording is the source.
Recruitment	The original record of the randomisation is the source. It is held on BCTU servers as part of the randomisation and data entry system.
Withdrawal	Where a participant expresses a wish to withdraw, the conversation must be recorded in the participants medical records.

12.2 Case Report Form (CRF) completion

The CRFs will include (but will NOT be limited to) the following Forms (see Table 8).

Table 8: Case report forms in OXYPuF

Form Name	**Schedule for submission**
Consent CRF	At the point of randomisation
Randomisation CRF	At the point of randomisation
Actigraph CRF	At the point of randomisation

Baseline and follow-up CRFs including participant reported outcome measures	As soon as possible after each assessment time point
Serious Adverse Event CRF *paper CRF only*	If expedited: emailed within 24 hours of site research team becoming aware of event If non-expedited: emailed within 4 weeks of site research team becoming aware of event
Change of status CRF	As soon as possible after the point of reduced participation or death

A CRF is required and should be completed for each individual participant. The data held on the completed original CRFs are the sole property of the respective PIs whilst the data set as a whole is the property of the Sponsor and should not be made available in any form to third parties except for authorised representatives or appropriate regulatory authorities without written permission from the Sponsor.

Data reported on each CRF will be consistent with the source data and any discrepancies will be explained. All missing and ambiguous data will be queried. Staff delegated to complete CRFs will be trained to adhere to the **OXYPuF Work Instruction on CRF completion** which can be found in the **OXYPuF ISF**.

The delegated staff completing the CRF should ensure the accuracy, completeness and timeliness of the data reported. This will be evidenced by signing and dating the CRF.

The following guidance applies to data and partial data:

- Only CRFs provided by the Trial Office should be used.
- Original completed CRFs or true copies should be sent to the Trial Office with copies filed in the ISF.
- Entries should be made in dark ink and must be legible.
- Any errors should be crossed out with a single stroke, the correction inserted and the change initialled and dated.
- Time format – all times should be in accordance with the 24hr clock
- Rounding conventions – rounding should be to the nearest whole number: If the number you are rounding is followed by 5, 6, 7, 8, or 9, round the number up. **Example**: 3.8 rounded to the nearest whole number is 4. If the number you are rounding is followed by 1, 2, 3 or 4, round the number down. **Example**: 3.4 rounded to the nearest whole number is 3
- Trial-specific interpretation of data fields – where guidance is needed additional information will be supplied
- Entry requirements for concomitant medications (generic or brand names) – generic names should be used where possible
- Missing/incomplete data – should be clearly indicated – all blank fields will be queried by the Trial Office
- Repeat laboratory tests – the data used to inform clinical decisions should always be supplied. If a test is repeated it is either to confirm or clarify a previous reading. Confirmatory tests should use the original test values.
- Protocol and GCP non-compliances should be reported to the Trial Office on discovery.

For the OXYPuF trial, all CRFs (with the exception of SAE forms and Participant completed questionnaires), will be completed electronically at site via eCRFs directly onto the OXYPuF database <include link>. **SAE forms are completed via paper CRF only at site.** Electronic CRFs (eCRFs) and paper CRFs should only be completed by those who are delegated to do so as evidenced on the **OXYPuF Trial Signature and Delegation log**.

Data should be submitted within a 2 week period of the schedule. If the data has still not been received within 2 weeks then the trial manager will directly contact the site via email to ascertain the reason for the delay. At 8 weeks from expected submission if the data still has not been received this may be escalated to the site's senior management and can trigger a monitoring visit.

In all cases it remains the responsibility of the PI to ensure that the CRF (electronic and paper) has been completed correctly and that the data are accurate. This will be evidenced by the signature of the PI.

12.3 Participant completed questionnaires

Participant completed questionnaires are completed by participants and are completed using paper questionnaires.

Questionnaires should generally be completed by the participant alone but physical assistance in completing the form can be given by the research staff or the participant's friends and relatives where appropriate. In such circumstances, questions are to be read to the participant verbatim and responses must not be led by the person assisting with the form completion. This requirement must be made clear when the participant's friends and relatives are providing the assistance. Participants should be encouraged to respond to all questions but can refuse to answer any, or all, of the questions should they wish. Where a questionnaire is returned to the local research staff, in person, with some questions unanswered, research staff should clarify with the participant that they have chosen not to respond specifically to the unanswered questions and that they have not simply missed them in error.

These questionnaires should be completed in clinic at baseline. For follow up questionnaires, these can be sent out to the participant via post and then returned to the trials office either directly via a self-addressed envelope or returned to the trials office by the site if a participant completes the questionnaires in clinic.

12.4 Data Management

Processes will be employed to facilitate the accuracy and completeness of the data included in the final report. These processes will be detailed in the trial specific Data Management Plan and include the processes of data entry, data queries and self-evident corrections on trial data.

Data entry will be completed by the sites via a bespoke BCTU trial database. The data capture system will conduct automatic range checks for specific data values to ensure high levels of data quality. Queries will be raised using data clarification forms (DCFs) via the trial database, with the expectation that these queries will be completed by the site within 30 days of receipt. Overdue data entry and data queries will be requested on a monthly basis.

12.5 Self-evident corrections

The below self-evident corrections will be permitted by the Trial Office:

Contingent fields: When a response to a question determines, to a degree, the response required by a second question, then conflicts in the responses can be resolved by the data entry clerk. E.g., Has the person had procedure "x"? If yes, state type. If the response to the first question is "no", yet the type of procedure is stated, it is self-evidently true that the initial response was incorrect.

Changes to administrative notes and reference numbers: When new information becomes available such that a reference number does not accurately reflect the sequence of CRFs received e.g., an SAE form is received for an incident which occurred prior to an already reported incident, then it is appropriate to change the reference number provided no DCFs have been raised using the original number. Similarly, any notes relating to the participant care

which have an impact on the administration process, but not the data fields themselves, can be changed as appropriate.

12.6 Data security

UoB has policies in place, which are designed to protect the security, accuracy, integrity and confidentiality of Personal Data. The trial will be registered with the Data Protection Officer at UoB and will hold data in accordance with the Data Protection Act (2018 and subsequent amendments). The Trial Office has arrangements in place for the secure storage and processing of the trial data which comply with UoB policies.

The Trial Database System incorporates the following security countermeasures:

Physical security measures: restricted access to the building, supervised onsite repairs and storages of back-up tapes/disks are stored in a fire-proof safe.

Logical measures for access control and privilege management: including restricted accessibility, access controlled servers, separate controls of non-identifiable data.

Network security measures: including site firewalls, antivirus software and separate secure network protected hosting.

System management: the system will be developed by the Programming Team at the Trial Office, and will be implemented and maintained by the Programming Team.

System design: the system will comprise of a database and a data entry application with firewalls, restricted access, encryption and role based security controls.

Operational processes: the data will be processed and stored within BCTU.

System audit: The system will benefit from the following internal/external audit arrangements:

1. Internal audit of the system
2. Periodic IT risk assessment

Data Protection Registration: UoB's Data Protection Registration number is Z6195856.

12.7 Archiving

All records created by following trial procedures and all documents listed in guidance relating to the conduct of the trial must be retained and archived for the specified period.

The TMF will be stored at BCTU for at least 3 years after the end of the trial. Long-term offsite data archiving facilities will be considered for storage after this time; data will be stored securely and confidentially for at least 25 years. BCTU has standard processes for both hard copy and computer database legacy archiving.

It is the responsibility of the PI to ensure all essential trial documentation and source documents (e.g. signed ICFs, Investigator Site Files, participants' hospital notes, copies of CRFs etc.) at their site are securely retained for at least 25 years. Archiving will be authorised by BCTU on behalf of UoB following submission of the end of trial report. No documents should be destroyed without prior approval from the BCTU Director or their delegate.

13. QUALITY CONTROL AND QUALITY ASSURANCE

13.1 Site set-up and initiation

The CI is required to sign a UoB CI agreement to document the expectations of both parties. The UoB CI agreement document must be completed prior to participation. The CI is required to sign a Clinical Trials Task Delegation Log which documents the agreements between the CI and BCTU. In addition all PIs will be asked to sign the necessary agreements including a Site Signature and Delegation log between the PI and the Trial Office and supply a current CV

and GCP certificate. All members of the site research team are required to sign the **Site Signature and Delegation Log**, which details which tasks have been delegated to them by the PI. The Site Signature and Delegation Log should be kept up to date by the PI. It is the PI's responsibility to inform the Trial Office of any changes in the site research team.

Prior to commencing recruitment, each recruiting site will undergo a process of initiation, either a meeting or a teleconference, at which key members of the site research team are required to attend, covering aspects of the trial design, protocol procedures, adverse event reporting, collection and reporting of data and record keeping. Sites will be provided with an ISF containing essential documentation, instructions, and other documentation required for the conduct of the trial.

13.2 Monitoring

The central and on-site monitoring requirements for this trial have been developed in conjunction with the trial specific risk assessment and are documented in the trial specific monitoring plan.

13.2.1 On-site monitoring

For this trial, all sites will be monitored in accordance with the trial risk assessment and monitoring plan. Any monitoring activities will be reported to the Trial Office and any issues noted will be followed up to resolution. Additional on-site monitoring visits may be triggered. PIs and site research teams will allow the OXYPuF trial staff access to source documents as requested. The monitoring will be conducted by BCTU/UoB staff.

13.2.2 Central monitoring

The Trial Office will check received ICFs and CRFs for compliance with the protocol, data consistency, missing data and timing at a frequency and intensity determined by the Data Management Plan. Sites will be sent DCFs requesting missing data or clarification of inconsistencies or discrepancies.

13.3 Audit and inspection

The Investigator will permit trial-related monitoring, audits, ethical review, and regulatory inspection(s) at their site and provide direct access to source data/documents. The investigator will comply with these visits and any required follow-up. Sites are also requested to notify the Trial Office of any relevant inspections or local audits.

13.4 Notification of Serious Breaches

In accordance with the Medicines for Human Use (Clinical Trials) Regulations 2004 and its amendments, the Sponsor of the trial is responsible for notifying the licensing authority in writing of any serious breach of the conditions and principles of GCP in connection with that trial or of the protocol relating to that trial, within 7 days of becoming aware of that breach. For the purposes of this regulation, a "serious breach" is a breach which is likely to affect:

- the safety or physical or mental integrity of the participants of the trial;
- the scientific value of the trial.

Sites are therefore requested to notify the Trial Office of any suspected trial-related serious breach of GCP and/or the trial protocol as soon as they become aware of them. Where the Trial Office is investigating whether or not a serious breach has occurred, sites are also requested to co-operate with the Trial Office in providing sufficient information to report the breach to the MHRA where required and in undertaking any corrective and/or preventive action

Sites may be suspended from further recruitment in the event of serious and persistent non-compliance with the protocol and/or GCP, and/or poor recruitment.

14. END OF TRIAL DEFINITION

The end of trial will be 6 months after the last data capture, including DCFs. This will allow sufficient time for the completion of protocol procedures, data collection and data input. The Trial Office will notify the REC and RGT within 90 days of the end of trial. Where the trial has terminated early, the Trials Office will inform the MHRA and REC within 15 days of the end of trial. The Trials Office will provide the REC and RGT with a summary of the clinical trial report within 12 months of the end of trial

15. STATISTICAL CONSIDERATIONS

15.1 Sample size

To detect an absolute minimum clinically important difference (MCID) of 4.0 points in the K-BILD Total score between groups, assuming a standard deviation of 8.85 as reported in the study which derived it (55), with 90% power and 5% significance level (2-sided type I error), a total of 104 participants per group will be needed to be randomised, 208 in total. Assuming and adjusting for approximately 20% dropouts, 260 participants will need to be recruited. The MCID of 4 being used here is slightly larger than the effect size in a crossover trial of AOT in fibrosis patients (mean difference K-BILD 3.7 (17)), however this tested HRQoL at 2 weeks, effects may grow with time, particularly if patients are more able to participate in activity or therapeutic interventions beneficial over 6 months, such as exercise training (56).

15.2 Analysis of outcomes

A separate Statistical Analysis Plan will be produced and will provide a more comprehensive description of the planned statistical analyses. A brief outline of the planned analyses is given below. The primary comparison groups will be composed of those randomised to AOT and standardised breathlessness advice versus those randomised to standardised breathless advice alone. In the first instance, all analyses will be based on the intention to treat principle, i.e. all participants will be analysed in the intervention group to which they were randomised irrespective of adherence to randomised intervention or protocol deviations. For all outcomes, appropriate summary statistics and differences between groups, e.g., mean differences will be presented, with 95% confidence intervals (95% CI) and p-values from two-sided tests also provided. Where possible, intervention effects will be adjusted for the minimisation variables listed in section 6.4.1, and also baseline K-BILD score. These variables will be treated as fixed effects, apart from centre which will be included as a random effect. No adjustment for multiple comparisons will be made. Statistical significance will be set to $p<0.05$ (two sided) and all model estimates will be supported with 95% CI. All analysis will be done in STATA (version 14.0 or higher).

15.2.1 Primary outcome

The primary outcome K-BILD will be assessed based on whether AOT is superior to usual care, and will follow an intention to treat analysis.

K-BILD recording over 6 months, will be analysed using mixed effects GEE to calculate an adjusted mean difference between groups, and corresponding 95% CI. The p-value relating to the intervention group parameter as generated by the model will be presented

15.2.2 Secondary outcomes

Patient characteristics will be summarised using mean and standard deviation (SD) for continuous data.

Continuous secondary outcomes (e.g., K-BILD subscales, VAS for cough) will be analysed as per the primary outcome.

Categorical outcomes (e.g, Hospitalisations, Adverse events, Mortality) will be presented as frequency counts and percentages. Frequency of hospitalisations and adverse events will be analysed using Poisson regression techniques. Binary outcomes (Scheduled/Unscheduled health services use, Completion of pulmonary rehabilitation, Progress to LTOT) will be analysed using log-binomial regression model to calculate the adjusted relative risk and 95% confidence interval. Mortality data, will be analysed using Cox proportional hazard techniques given the assumptions of proportionality are met, and an adjusted hazards ratio with a 95% confidence interval will be presented.

Regarding safety, the total number of patients experiencing SAEs will be given by intervention group along with a descriptive table of the events, and statistical significance will be determined by a chi-square test.

15.2.3 Planned subgroup analyses

Subgroup analyses will be limited to the same variables used in the minimisation algorithm (see section 6.4.1.), desaturation at baseline, 6MWT or 1 minute sit to stand and performed on the primary outcome only. The effects of these subgroups will be examined by including an intervention group by subgroup interaction parameter in the regression model, which will be presented alongside the effect estimate and 95% confidence interval within subgroups. The results of subgroup analyses will be treated with caution and will be used for the purposes of hypothesis generation only.

15.2.4 Missing data and sensitivity analyses

Every attempt will be made to collect full follow-up data on all study participants; it is thus anticipated that missing data will be minimal. Participants with missing primary outcome data will not be included in the primary analysis in the first instance. This presents a risk of bias, and sensitivity analyses will be undertaken to assess the possible impact of the risk. In brief, this will include the imputation process for the primary outcome which will utilise patient recorded characteristics like age, gender and also centre. A cycle of 50 imputations will be considered and pooled results from these will be used (62). Full details will be included in the Statistical Analysis Plan.

15.3 Planned final analyses

The primary analysis for the trial will occur once all participants have completed the 6 month assessment and corresponding outcome data has been entered onto the trial database and validated as being ready for analysis. This analysis will include data items up to and including the 6 month assessment and no further.

16. HEALTH ECONOMICS

A separate Health Economics Analysis Plan will be produced and will provide a more comprehensive description of the planned analyses. A brief outline of these analyses is given below.

16.1 Economic evaluation

The economic evaluation will assess the cost-effectiveness of AOT versus standardised breathlessness advice alone in patients with IPF. The evaluation will take the form of an incremental cost-utility analysis to estimate cost per quality adjusted life year (QALY), from an NHS perspective over 6 months follow-up using patient level data on costs and outcomes from the trial. Additional analysis will be undertaken from a broader societal perspective.

16.2 Data Collection

Health care resource use information will be collected on IPF-related primary care visits, visits to other health care professionals, prescribed medications, LTOT and hospital admissions (A&E, length and nature of inpatient admissions) using a healthcare utilisation CRF at 3 and 6 months. Information on wider costs of informal care and productivity losses will also be collected. The cost of AOT and the breathlessness advice time will be determined within the trial, as will other interventions such as antifibrotics and pulmonary rehabilitation. Unit costs from standard UK sources, for example NHS Reference costs will be sought for all health care resource use items. In order to calculate QALYs, the EQ-5D-5L questionnaire will be administered to patients at baseline, 3 and 6 months. The crosswalk value set will be applied to patient responses to obtain utility scores, in line with current NICE recommendations.

16.3 Analysis

QALYs will be calculated using responses to the EQ-5D-5L, using the "area under the curve" (AUC) approach. Unit costs will be applied to all health care resource use items, and mean resource use (for each category of health care usage) and mean total costs will be calculated for all trial participants. As cost data is likely to have a skewed distribution, the nature of the distribution of costs will be explored, and if the data is not normally distributed, a non-parametric comparison of means (using bootstrapping) will be undertaken. Multiple imputation will be used to impute all missing values for the EQ-5D and total cost estimates for non-responders.

A cost-consequence analysis will initially be reported, describing all the important results relating to categories of resource use, costs and consequences (across the full range of clinical outcomes). Incremental cost-utility analysis will then be undertaken to estimate the incremental cost per QALY gained, with adjustment for baseline covariates. The robustness of the results will be explored using sensitivity analysis. This will explore uncertainties in the trial based data itself, the methods employed to analyse the data and the generalisability of the results to other settings. Cost-effectiveness acceptability curves will also be produced to reflect the probability the intervention will be cost effective at different cost per QALY willingness to pay thresholds.

There is a high probability that patients' disease will progress to the point that treatment might change (e.g. from AOT to LTOT) over a relatively short time frame. However, if trial data indicates that few patients progress in this way then we will construct a decision model, using trial data and estimates from the published literature, extrapolating trial results over a 5 year time horizon, with discounting of costs and outcomes at 3.5%.

17. SUB-STUDIES

The qualitative sub-study is designed to assess the acceptability of the trial intervention. This will be conducted in the pilot phase of the study.

The data from the objective physical sub-study will be received by BCTU and anonymised data passed for analysis to the Sportex team at UoB.

18. TRIAL ORGANISATIONAL STRUCTURE

18.1 Sponsor

The Sponsor for this trial is University of Birmingham (UoB).

18.2 Coordinating centre

The trial coordinating centre (Trial Office) is Birmingham Clinical Trials Unit (BCTU), based at UoB.

18.3 Trial Management Group

The Trial Management Group (membership detailed in the Administrative Information section) will monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself.

18.4 Trial Steering Committee

A Trial Steering Committee (TSC), comprising independent and non-independent members, will be established for the OXYPuF trial and will meet as required depending on the needs of the trial. Membership and duties/responsibilities are outlined in the TSC Charter. In summary, the role of the TSC is to provide oversight of the trial. The TSC will monitor trial progress and conduct, and provide advice on scientific credibility. The TSC will consider and act, as appropriate, upon the recommendations of the Data Monitoring Committee (DMC). The TSC will operate in accordance with a trial specific TSC Charter.

18.5 Data Monitoring Committee

The role of the independent DMC is to monitor the trial data, and make recommendations to the TSC on whether there are any ethical or safety reasons as to why the trial should not continue or whether it needs to be modified. To this end, data on safety outcomes and (where appropriate) primary and major secondary outcomes will be supplied to the DMC during the trial. Reports will be supplied in confidence.

The DMC will operate in accordance with a trial specific DMC Charter which will define the membership, roles and responsibilities of the DMC. The DMC will meet at least annually as a minimum. Additional meetings may be called if needed e.g., recruitment is faster than anticipated or a safety issue is identified.

18.6 Finance

The National Institute for Health Research (NIHR) is funding this trial. Clinical Research Network (CRN) support will be sought. Excess cost for the trial remains part of NHS costs.

19. ETHICAL CONSIDERATIONS

The trial will be conducted in accordance with the UK Policy Framework for Health and Social Care Research and applicable UK Acts of Parliament and Statutory Instruments (and relevant subsequent amendments), which include, but are not limited to, the Medicines for Human Use Clinical Trials 2004, Data Protection Act 2018; Human Tissue Act 2004; Mental Capacity Act 2005.

This trial will be carried out under a Clinical Trial Authorisation in accordance with the Medicines for Human Use Clinical Trials regulations and according to the Principles of GCP as set out in the UK Statutory Instrument (2004/1031; and subsequent amendments).

The protocol will be submitted to and approved by the REC prior to the start of the trial. All correspondence with the MHRA and/or REC will be retained in the TMF/ISF, and an annual progress report will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given by the REC, and annually until the trial is declared ended. A trial-specific risk assessment and monitoring plan will be developed before submission to the REC and will be reviewed regularly during the trial.

Before any participants are enrolled into the trial, the PI at each site is required to obtain the necessary local approval.

It is the responsibility of the PI to ensure that all subsequent amendments gain the necessary local approval. This does not affect the individual clinicians' responsibility to take immediate action if thought necessary to protect the health and interest of individual participants.

20. DATA PROTECTION AND CONFIDENTIALITY

Personal data and sensitive personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the Data Protection Act 2018 (and subsequent amendments). Personal data categories that will be collected and analysed include: name, date of birth, NHS number, telephone number, email and postal address, health information, medical history.

Participants will only be identified by their unique trial identification number and partial date of birth on CRFs and on any correspondence with the Trial Office. Where a trial is collecting consent forms for central review, the participant needs to acknowledge that their informed consent form may be transferred and stored at the University of Birmingham. Participants will acknowledge the transfer and storage of their informed consent form to the Trial Office. This will be used to perform central monitoring of the consent process.

In the case of specific issues and/or queries from the regulatory authorities, it will be necessary to have access to the complete trial records. Representatives of the OXYPuF trial team and sponsor may be required to have access to participants' notes for quality assurance purposes, but participants should be reassured that their confidentiality will be respected at all times. The Trial Office will maintain the confidentiality of all participant data and will not disclose information by which participants may be identified to any third party.

21. FINANCIAL AND OTHER COMPETING INTERESTS

There are no financial or other competing interests related to the results of this trial. Members of the TSC and DMC are required to provide declarations on potential competing interests as part of their membership of the committees. Authors are similarly required to provide declarations at the time of submission to publishers.

22. INSURANCE AND INDEMNITY

UoB has in place Clinical Trials indemnity coverage for this trial which provides cover to UoB for harm which comes about through the University's, or its staff's, negligence in relation to the design or management of the trial and may alternatively, and at UoB's discretion provide cover for non-negligent harm to participants.

With respect to the conduct of the trial at Site and other clinical care of the patient, responsibility for the care of the patients remains with the NHS organisation responsible for the Clinical Site and is therefore indemnified through the NHS Litigation Authority.

UoB is independent of any pharmaceutical company and as such it is not covered by the Association of the British Pharmaceutical Industry (ABPI) guidelines for participant compensation.

23. POST-TRIAL CARE

Following completion of the trial (6 months following an individual's recruitment) patients will be managed according to the standard clinical care that is deemed appropriate by their responsible clinician – this could be with or without AOT.

24. ACCESS TO FINAL DATASET

The final dataset will be available to members of the Trial Management and co-applicant group who need access to the data to undertake the final analyses.

Requests for data generated during this study will be considered by BCTU. Data will typically be available six months after the primary publication unless it is not possible to share the data (for example: the trial results are to be used as part of a regulatory submission, the release of the data is subject to the approval of a third party who withholds their consent, or BCTU is not the controller of the data).

Only scientifically sound proposals from appropriately qualified Research Groups will be considered for data sharing. The request will be reviewed by the BCTU Data Sharing Committee in discussion with the CI and, where appropriate (or in absence of the CI) any of the following: the Trial Sponsor, the relevant Trial Management Group (TMG), and independent TSC.

A formal Data Sharing Agreement (DSA) may be required between respective organisations once release of the data is approved and before data can be released. Data will be fully de-identified (anonymised) unless the DSA covers transfer of participant identifiable information. Any data transfer will use a secure and encrypted method.

25. PUBLICATION PLAN

All publications and presentations, including abstracts, relating to the main trial will be authorised by the OXYPuF Trial Management Group. The results of the analysis will be published in the name of the OXYPuF Collaborative Group in a peer reviewed journal (provided that this does not conflict with the journal's policy). All contributors to the trial will be listed, with their contribution identified as determined by the trial publication policy. If requested, trial participants will be sent a summary of the final results of the trial, which will contain a reference to the full paper.

All publications using data from this trial to undertake original analyses will be submitted to the Trial Management Group for review before release. To safeguard the scientific integrity of the trial, data from this trial will not be presented in public before the main results are published without the prior consent of the Trial Management Group. A study site may not publish results of a study until after a coordinated multicentre publication has been submitted for publication.

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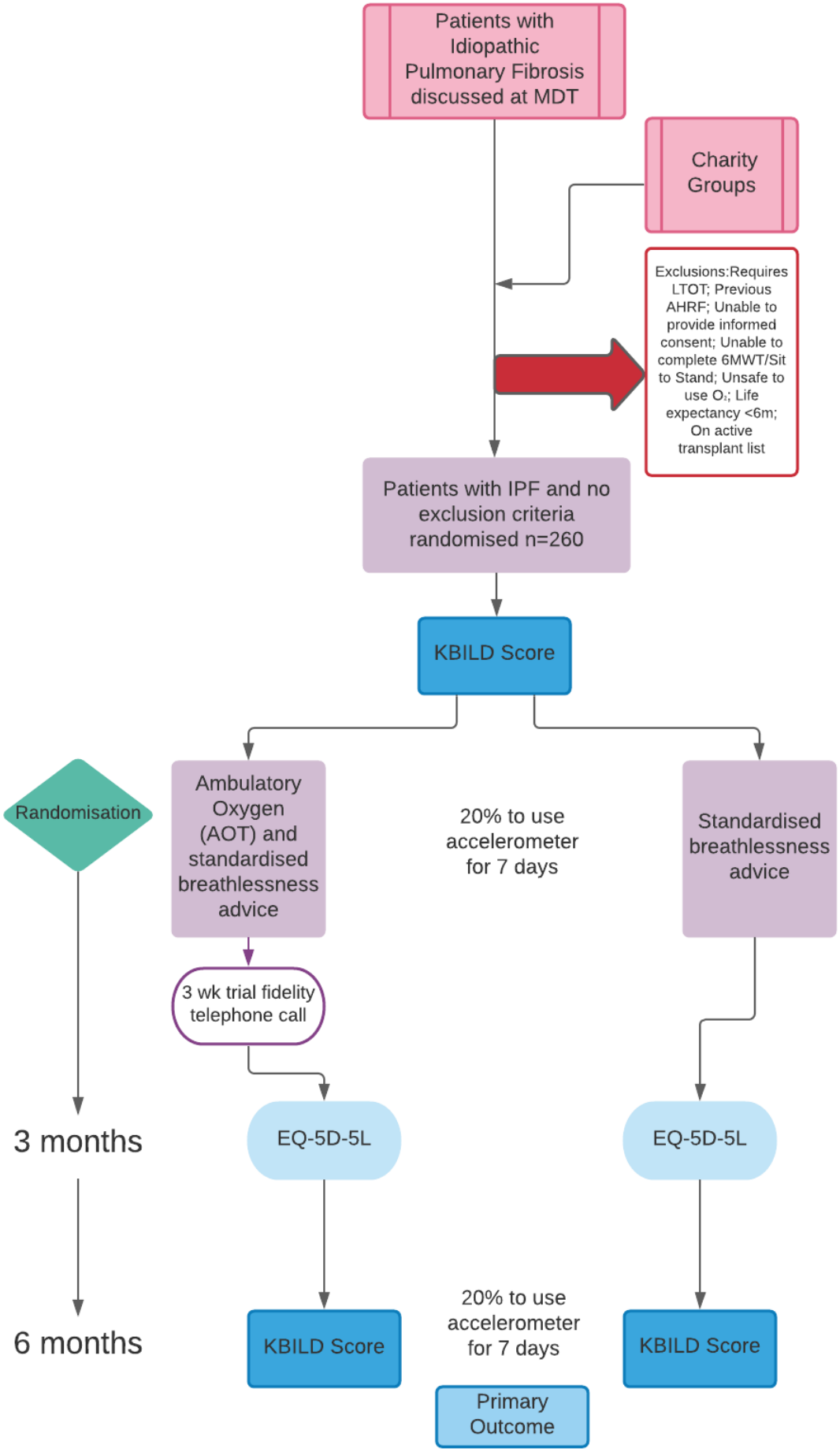
27.APPENDIX


Patients with Idiopathic Pulmonary Fibrosis discussed at MDT
Charity Groups
Exclusions:Requires LTOT; Previous AHRF; Unable to provide informed consent; Unable to complete 6MWT/Sit to Stand; Unsafe to use O2; Life expectancy <6m; On active transplant list
Patients with IPF and no exclusion criteria randomised n=260
KBILD Score
Randomisation
Ambulatory Oxygen (AOT) and standardised breathlessness advice
20% to use accelerometer for 7 days
Standardised breathlessness advice
3 wk trial fidelity telephone call
3 months
EQ-5D-5L
EQ-5D-5L
6 months
KBILD Score
20% to use accelerometer for 7 days
KBILD Score
Primary Outcome