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Synopsis

# Ambulatory Oxygen for Pulmonary Fibrosis (OxyPuF): a randomised controlled trial and acceptability study

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## Abstract

**Introduction:** Idiopathic pulmonary fibrosis is a devastating condition of unknown cause that results in progressive, irreversible scarring of the lung, manifesting as breathlessness and dry cough. Idiopathic pulmonary fibrosis is thought to be responsible for as many as 1 in 100 deaths in the United Kingdom, killing 5300 people a year. Ambulatory oxygen therapy is commonly used in idiopathic pulmonary fibrosis to relieve exertional breathlessness, although evidence to support this strategy is lacking. This pragmatic randomised controlled trial was planned to test whether use of ambulatory oxygen therapy is beneficial in people with idiopathic pulmonary fibrosis.

**Methods:** We planned a randomised controlled trial in 260 patients with idiopathic pulmonary fibrosis who are breathless on exertion and do not meet criteria for long-term oxygen therapy, randomising in a 1 : 1 ratio between ambulatory oxygen therapy and best supportive care. Primary outcome was a quality-of-life questionnaire validated in pulmonary fibrosis, the King's Brief Interstitial Lung Disease questionnaire, measured at 6 months. We calculated our sample size based on the minimum clinically important difference of four units and standard deviation equal to 8.85 in King's Brief Interstitial Lung Disease questionnaire; assuming power of 90% and 5% two-sided significance level, thus required 130 per arm, after accounting for 20% dropout. The trials unit's web-based randomisation algorithm minimises on factors potentially influencing response to ambulatory oxygen therapy, such as severity of idiopathic pulmonary fibrosis, desaturation to < 88% present on walking, current or recent (within 6 months) pulmonary rehabilitation, and recruitment centre. Secondary outcomes included symptoms, exercise capacity and cost-effectiveness. A process evaluation included assessment of trial fidelity and acceptability of the intervention with use of qualitative research methods and arts approaches with patients and staff. Qualitative interviews were conducted with patients from the Ambulatory Oxygen for Pulmonary Fibrosis trial and the idiopathic pulmonary fibrosis patient support group Action for Pulmonary Fibrosis, and stakeholders: healthcare professionals and policy-makers. Interviews were audio-recorded, transcribed clean verbatim. Photovoice methodology was conducted with patients. A workshop prior to data collection informed and guided data collection and analysis. Traditional qualitative analysis and arts-based coproduction analysis approaches were used to produce a short film. An economic model was planned but could not occur due to early termination.

**Results:** The trial was stopped prematurely due to low recruitment. This was due to a combination of the impact of COVID-19 on research infrastructure, financial issues for sites with the payment structure for the trial and lack of equipoise which limited site recruitment. Seven out of 25 eligible, interested patients were randomised after pre-screening, implying a lack of interest among patients in the study. Baseline characteristics indicated that patients were elderly (mean age 81) and predominantly male. Qualitative work with 11 patients and 23 other stakeholders

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concluded that ambulatory oxygen therapy is desirable, acceptable and widely commissioned in the United Kingdom, such that further trials are not likely to be feasible.
**Conclusion:** Although we are not able to formally address our objectives of assessing efficacy and cost-effectiveness of ambulatory oxygen therapy in idiopathic pulmonary fibrosis, it is unlikely that conducting a randomised controlled trial is feasible due to lack of equipoise.
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## Introduction

This synopsis paper describes the methods and limited results from a pragmatic open-label blinded end-point study, where patients were to be randomised from secondary care, and which terminated early due to low recruitment. As the trial has terminated early, with much lower numbers of patients than expected, due to the slow recruitment post pandemic, limited conclusions can be drawn. In this report, we also detail some lessons learnt for future trialists who wish to study ambulatory oxygen in future.

## Background

### *What is the problem?*

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 to the frustration of sufferers, their families and their supporting clinical teams. While, 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 gender-age-physiology score, which uses FVC and transfer capacity of the lungs for carbon monoxide 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 (PR) 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.[7,8] In order to be eligible, the FVC must be between 50% and 80%, a figure based on trial data;[6] 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. The treatments slow progression of FVC decline[9] and reduce the risk of acute respiratory deteriorations,[10] which are associated with very high morbidity and mortality, as well as improving mortality longer term.[10] There is only limited evidence to suggest that there may be an improvement in cough[11] 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, they 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 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.[12] Current recommendations for long-term oxygen therapy (LTOT) for resting hypoxaemia in IPF are largely extrapolated from trials conducted in chronic obstructive pulmonary disease (COPD), where a survival benefit is well established,[13] 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;[14] use of supplemental oxygen for patients with fibrotic ILD is recommended where there is severe resting hypoxaemia or exertional hypoxaemia with attributable symptoms or exercise limitation.

Surprisingly, given the above consensus, there is very little conclusive evidence in IPF on whether oxygen is beneficial. Long-term use in marked hypoxia (LTOT) 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).[15] However, opinions of ambulatory oxygen therapy (AOT) are far less certain; one systematic review concluded no benefit,[15] noting included studies were largely observational designs prone to bias. Some studies found a small benefit on objective exercise capacity.[16–18] A small open-label, crossover randomised controlled trial (RCT; $n$ = 84) suggests use of AOT also improves HRQoL in the short term.[19] 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,[20] resulting in great variability in access. Given that this intervention is expensive and burdensome,[21] 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, that is, counselling, PR and early referral to palliative care.[22]

## *Why was this research important?*

In other conditions, in which oxygen has evidence of patient benefit when used long term (LTOT; typically ≥ 12 or ≥ 15 hours/day), such as COPD,[13,23] our systematic review has shown no consistent benefit of AOT.[24] 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 ≥ 1 in Borg score indicates it should be used in patients with desaturation on exertion of > 4%.[25] Our 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 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.[21] These factors are likely to be common to IPF patients; hence, it was important to test AOT in a pragmatic RCT, to obtain information on effects in a real-life setting and to inquire in detail about adherence and acceptability. Given that these attitudes could impact recruitment, we planned to conduct acceptability work during the pilot phase of the trial.

Selection of patients for treatment may also be important, and again there may be transferable lessons from use of AOT in COPD. In our review, two studies[26,27] 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[26–32] included a single assessment acute oxygen test for all participants as part of their protocol. All but one[31] 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[29,31–34] were carried out as part of PR. Although no benefit of long-term AOT was demonstrated, exercise capacity (particularly 6MWT) in the PR studies exceeded that of the domiciliary studies[26,27] whether patients were randomised to AOT or placebo. Furthermore, the improvement in 6MWT distance gained by PR far exceeded that gained by AOT,[32] thus supporting guidance[25] that any assessment of AOT should be made following PR. While rehabilitation is beneficial in ILD,[35] the effects tend to be sustained for a shorter period,[36] and it is recognised that any improvement in exercise capacity can be negated by the weight of the AOT if carried by patients alone.[37,38] 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, which is why our protocol accounted for this via our minimisation algorithm.

## *Why this research was conducted*

A commissioning brief was put to the National Institute for Health and Care Research (NIHR) by National Institute for Health and Care Excellence (NICE) in order to inform their next iteration of IPF guidance – this demonstrates its importance to national policy. The NICE guideline was last updated in May 2017, and its revision history indicates that it would be desirable for a trial to give indicative results by 2023; we, therefore, focused on a design which could deliver close to this time frame. The current NICE document recognises that AOT is widely used, yet with little evidence base.[6] Since pulmonary fibrosis diagnoses are rising,[2] and this group is one in whom AOT is often prescribed, they

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are a priority group for study. An adequately powered RCT such as that proposed could have evaluated whether AOT is beneficial compared to best supportive care, and thus could have informed national guidelines. If the trial was not feasible to conduct, then alternative means to source evidence supporting the intervention, or acceptance of delivery in practice, might be required. Preliminary inquiry prior to study setup demonstrated to us that prescription of AOT was already routine in many IPF services, and the data obtained during trial conduct concurred with this. The logic model for the study is shown in *Figure 1*.

## Aims and objectives

### *Our main aim was to answer the research question:*

What is the clinical and cost-effectiveness of AOT in patients with IPF?

### *Our objectives were:*

1. Determine whether HRQoL described by the King's Brief Interstitial Lung Disease (K-BILD) questionnaire is superior after AOT compared to best supportive care at 6 months after commencement of therapy.
2. Determine whether breathlessness, determined by the Medical Research Council (MRC) dyspnoea scale, is superior after AOT compared to best supportive care at 6 months.
3. Determine whether exercise capacity and physical activity, as described by the 6MWT, and a self-reported activity questionnaire [international physical activity questionnaire (IPAQ)], respectively, is superior after AOT compared to best supportive care at 6 months. Objective confirmation of physical activity was planned in a subset of approximately 20% ($n$ = 52) patients.
4. Describe relationship of AOT use to other clinical outcomes, such as mortality, admissions to hospital, progression to LTOT use and completion of PR.
5. Assess cost-effectiveness of AOT.
6. Assess the acceptability of AOT.

We were unable to address our main objective, nor most of our research questions, due to early termination of the study. Health-economic analysis was not commenced.

## Methods

### *Study population and rationale*

#### Included patients had:

- Clinically diagnosed IPF, confirmed by an ILD multidisciplinary team (MDT) within a specialist-commissioned IPF service.
- Breathlessness with MRC dyspnoea scale ≥ 2.

#### Exclusion criteria were:

- Unable to adequately consent.
- Requiring LTOT, defined by pO2 < 7.3 kPa on air twice in the stable state, or < 8 kPa in the presence of cor pulmonale, with blood gases only performed if required as part of usual care (UC).
- Unable to complete a 6MWT or 1-minute sit-to-stand test.

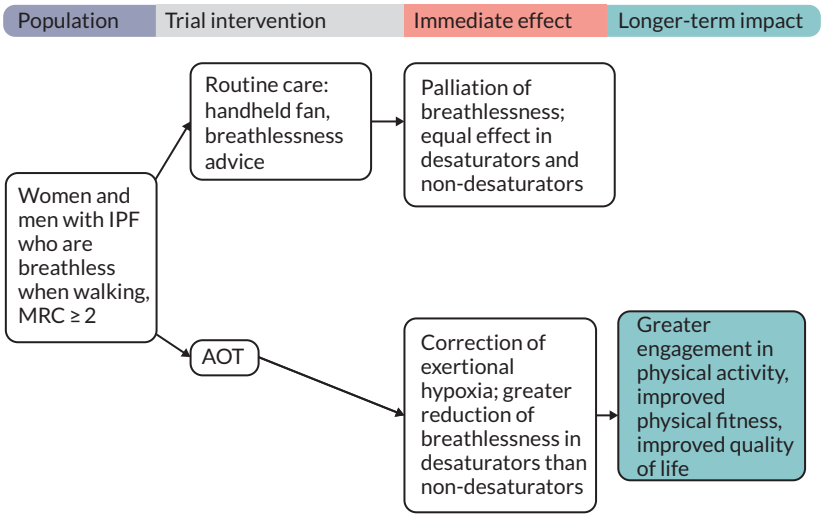


**FIGURE 1** Ambulatory Oxygen for Pulmonary Fibrosis logic model.

- Previous acidotic hypercapnic respiratory failure (AHRF) requiring non-invasive ventilation (NIV).
- Unsafe to use oxygen for other reasons (e.g. current smokers).[39]
- Life expectancy < 6 months.
- Under active lung transplant assessment or on active transplant list.

The patient population was drawn from hospital outpatient clinics, with the intervention used by patients in their own homes. We intended to recruit from any home oxygen assessment and review service (HOSAR) but did not set up any community oxygen providers. Patients had a clinical diagnosis of IPF, confirmed via a MDT meeting or a IPF specialist clinic, and any disease severity, with or without antifibrotic treatment. While MRC dyspnoea scale ≥ 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 antifibrotics; this plus a desire for our trial population to reflect those likely to receive the intervention in life prompted us to keep inclusion broad. Patients who have previously had AHRF represent a group in whom uncontrolled oxygen use could trigger further admissions for AHRF, thus are effectively a subgroup of those in whom it is unsafe to prescribe oxygen. Those unable to complete a 6MWT are unlikely to be sufficiently active at home to experience much biological benefit from AOT.

The commissioning brief suggested the relevant population were those with IPF who are breathless on exertion, and did not specify the criterion used in a prior RCT on AOT in IPF,[19] namely desaturation to < 88% after 6MWT. Desaturation might be a critical feature for response to AOT since oxygen does not reduce breathlessness in other settings in non-hypoxic patients (e.g. palliative care[40]); however, in real life, there is potential for 'bleed' into non-desaturators unless there is evidence of lack of benefit in this subgroup. While we hypothesised that oxygen will be less beneficial in this group, one small study has shown evidence of benefit from oxygen on exercise capacity in non-desaturators,[41] justifying their inclusion. Consequently, we planned to adhere exactly to the brief, and not require desaturation for inclusion; however, we balanced desaturators and non-desaturators between arms, and planned to enrol a maximum of 25% of patients who do not desaturate. The off-oxygen 6MWT conducted at screening would establish desaturation, and an on-oxygen 6MWT was to be used in order to allow us to adequately describe the population with regard to features that might determine response to AOT. Date of PR was also collected, since this could affect exercise tolerance and thus the primary outcome. In order to collect data around reasons for not wanting to participate, the senior trial manager contacting sites recorded reasons for declining those declining to participate in the qualitative research interviews.

## *Intervention and control*

### Ambulatory oxygen therapy

The intervention was 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% during an on-oxygen 6MWT. Current 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.[42] While 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'.[43] This standard does not specifically say that exercise duration or symptoms must decrease, so expansion of AOT provision has occurred in any patient who has had exercise testing. Consequently, we defined receipt of AOT as normal NHS care for those patients in our trial population who desaturate on exertion, such that oxygen was a research cost only in those not desaturating.

The *comparator was best supportive care for breathlessness*, specifically including use of a handheld fan to promote the sensation of air flow around the face, and advice on use of appropriate pharmacological agents (e.g. morphine, benzodiazepines). A number of interventions may palliate breathlessness, and we ensured that both groups received information on these – in particular, use of a handheld fan, as this effective palliation measure[44] in particular might mimic the effect of oxygen flow in the UC arm, thus is close to a placebo. A true placebo of medical air would have been 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. Items considered standard in the advice for the two arms is summarised in *Table 1*.

## *Outcomes*

### Primary outcome

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

**TABLE 1** Appropriate delivery of supportive care and AOT

| Breathlessness management advice | Instructions on AOT use |
|---|---|
| Print advice sheet | Print advice sheet |
| Add personalisation – patient name, general practitioner name, emergency contact details, case manager, palliative care team (as applicable) | Check safety (e.g. smoking) |
| Discuss use of a handheld fan | Explain use during activity, not rest |
| Discuss breathing techniques, including pacing with activity | Explain device (cylinder/ concentrator) |
| Discuss posture as a means of symptom relief | Explain delivery system (nasal/face mask) |
| Discuss pharmacological options to palliate severe symptoms: lorazepam, opiates | |

randomisation. We chose K-BILD as it has been specifically developed to assess HRQoL in ILD patients,[45] including the IPF group targeted by this trial. Moreover, it has been successfully used in a prior crossover trial of AOT in this patient group;[19] thus, we could be sure that it is responsive to the intervention.

### Secondary outcomes

Subscales within K-BILD (breathlessness, activity, chest symptoms); EuroQol-5 Dimensions, five-level version (EQ-5D-5L);[46] exercise capacity (6MWT); physical activity (IPAQ),[47] accelerometery in a subset of 20% of patients; hospitalisations (all-cause and IPF-specific); adverse events, classified according to Medical Dictionary of Regulatory Activities terms (including type 2 respiratory failure as a serious adverse event of special interest); disease progression [FVC and diffusing capacity for carbon monoxide (DLCO) at 6 months]; mortality (6 months, and from medical record, only at 12 months); medication use; scheduled and unscheduled health service use; completion of PR; progression to LTOT use.

We chose to use both a specific validated breathlessness score (MRC dyspnoea scale), and relevant subscale of K-BILD because the brief specified that breathlessness was an important outcome; while a subscale within a questionnaire validated in IPF obviously has value, the subscale itself is not a validated item, unlike the MRC. The core outcome data set for IPF trials advises specific assessment of cough and fatigue; our steering committee felt that these aspects were adequately covered by the K-BILD, and that further targeted questionnaires represented an unwarranted burden to patients. Activity levels were also required by the brief; we planned to objectively evaluate this in 20% of patients in both arms using the ActiGraph (ActiGraph, LLC, Pensacola, FL, USA) device, validated for use both against calorimetry and in daily life in respiratory patients.[48,49] We felt this necessary as self-reported activity by IPAQ cannot be certain to relate to actual activity, and patients had concurred with this in pre-application public and patient involvement (PPI). We chose 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.[50] We planned to describe disease progression primarily based on the change in FVC, since a clinically significant decline in this is well accepted (10%), unlike DLCO, which for some patients is a harder manoeuvre to perform; thus, there is a risk of missing data.

### *Sample size and trial duration considerations*

To detect an absolute minimum clinically important difference (MCID) of 4.0 in K-BILD between groups, assuming standard deviation (SD) of 8.85 (as reported in the study which derived it[51]) with 90% power and 5% significance level (two-sided type 1 error), a total of 104 participants per group were planned to be randomised, 208 in total. Assuming and adjusting for approximately 20% dropouts, 260 participants were required. The effect size assumed is slightly larger than that observed in a crossover trial of AOT in fibrosis patients (mean difference K-BILD 3.7[19]). 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 (see *Figure 1*), such as exercise training.[52] Furthermore, there is an argument that interventions whose benefit is less than MCID should not be supported by the NHS; since this trial aimed to inform a guideline, we need to keep this perspective in mind. While sample size could be driven down a little further by taking into account the correlation between baseline and 6-month assessment (maximum 25% but likely less), we considered this undesirable given that there is always

some uncertainty around issues such as lost to follow-up; thus, we retained contingency in our calculations.

Prevalence estimates for IPF range from 2 to 29/100,000 in Europe;[53] there were 32,500 cases of IPF in 2012 in England,[54] and NHS England has estimated that 300–800 new diagnoses will occur annually over the next 10 years,[55] meaning a population of at least 33,000 patients now in the UK. Dyspnoea typically occurs in > 90% of patients[53] and desaturation in 54%,[56] suggesting sufficient patients would be eligible (0.9 × 33,000 = 29,700, 0.54 × 33,000 = 17,820). Taking into account exclusions and other factors, we estimated an average recruitment of two patients/month/centre to be feasible across 20 centres which determined our recruitment duration. We selected 20% dropout in our sample size calculation based on 14% dropout seen in previous AOT study[19] and the likelihood that longer follow-up may mean higher dropout, for example, if patients progress over 6 months to a point that they feel unable to complete the trial, or need LTOT. Our prior trial of AOT in COPD using treatment for 12 weeks in each arm of a crossover design (NCT01722370), thus total duration similar to the study proposed here, also suggested that this precaution is required, as dropouts rose with time to around this level.

### *Randomisation*

The trials unit randomised patients in a 1 : 1 ratio using a web-based platform, with telephone support from the trials unit in normal working hours. The randomisation algorithm allowed balancing of key features between intervention and control arms, including the following minimisation criteria which centre on factors that might influence response to AOT, or influence one or more outcome measures: disease severity, as determined by FVC; desaturation to < 88% on 6MWT or 1-minute sit-to-stand test; current or recent (within 6 months) PR; antifibrotic use. In addition, recruitment site was included to adjust for any stratification effects.

### *Data collection*

Data were collected from the routine care record, study-specific source data and patient self-report, into electronic case report forms. Accelerometery data were collected by download from ActiGraph devices; patients were advised to wear it at all times for 1 week when not in water, adhering to guidance from a systematic review of appropriate accelerometer use[50] and to return it to the study team by recorded delivery post 1 week. One week prior to the final visit, these patients will be delivered (or pick up, according to patient preference) the monitor to wear similarly for 1 week prior to the final visit, returning it at that time. How well patients adhered to their AOT was primarily by self-reported data from patients on usage (time per day), as this is the only way of obtaining this in users of portable concentrators, and we wished to obtain the same data from all participants. We also planned to request information from the oxygen provider on the number of cylinders used, to give an indication of how accurate the self-reported data are, and compare time reported to time supplied in the cylinder-using patients; this aspect was not completed when the study was terminated early, as it was felt inappropriate to chase external sources for data unlikely to be informative on such a low number of participants.

### *Statistical analysis*

The trials unit conducted data management and statistical analysis, intending to compare K-BILD between arms to check our hypothesis. The primary outcome analysis was planned to be performed in the intention-to-treat population, with sensitivity analysis of per-protocol participants. A complier-average causal effect (CACE) – a form of causal inference analysis – would also have been conducted, had the trial completed. Pursuing a CACE analysis is important because patients often want to know what the effect would be if they were to take the treatment as prescribed (the patient-oriented effect),[57] and this study (1) has HRQoL as its primary outcome and (2) patients raised the stigma of AOT use in preliminary PPI work, such that it is possible adherence issues would occur. Several methods of CACE have been described for patient-oriented RCTs.[57]

Patient characteristics were summarised using mean and SD for continuous data, unless distribution is non-normal, in which case median and interquartile range (IQR) were used. Categorical data were presented as frequency counts and percentages. Linear regression models for continuous outcomes and log-binomial models for binary outcomes were planned to determine effect on outcomes, adjusted for minimisation factors and baseline values for parameters where available and relevant. The adjusted mean difference or risk ratio with 95% confidence intervals would be presented for all outcomes alongside the associated *p*-value for the primary outcome only. Due to the low number of participants randomised, these analyses were not conducted, and only summary statistics are presented for each outcome.

### *Qualitative substudy*

A qualitative interview study, utilising photovoice methodology, was conducted with patients with IPF and those who work with people with IPF. The trial applicants, and, in particular, our PPI representatives, anticipated a lack of acceptability to the trial design from healthcare

professionals (HCPs) and patients; therefore, we aimed to explore the acceptability of the trial design, including the intervention (AOT) as well as views and experiences regarding ambulatory oxygen. Traditional qualitative analysis and arts-based coproduction analysis approaches were used. Participants were recruited from across the UK. We aimed to interview up to 60 people.

*Patients*: In order to gain a breadth of experiences of IPF and its treatment, and to avoid recruitment bias towards those who were willing to participate in the trial, we undertook two parallel recruitment methods:

a. Patients enrolling in the Ambulatory Oxygen for Pulmonary Fibrosis (OxyPuF) trial could opt to have their contact details made available to the qualitative research team. We aimed to speak to about 10 patients from each arm.
b. Further recruitment of up to 20 people with IPF was also undertaken via patient support groups. We worked closely with our local branch of the patient support group Action for Pulmonary Fibrosis (APF), attending meetings and inviting participation. We worked with the research manager to add details of our study to the APF website inviting participation. We worked with the branch group co-ordinator to circulate information about the study and met with branch leads online. Finally, we invited the research manager and chair from APF to join us at our monthly Trial Management Group (TMG) meetings so we could discuss recruitment. The purpose of these interviews was to provide a broad range of perspectives; numbers of potential interviewees were to be guided by gaps in the data and were therefore not specified.

Due to the challenges of collecting data from those who decline participation in trials, we did not seek permission to recruit patients this way; instead, we felt that we would get more representative views from alternative channels, that is, patient support group members.

*Healthcare professionals*: all those who declined to participate in the trial were invited to participate in the qualitative interviews by the trial manager. These e-mail invitations were revised in collaboration with the qualitative and trials' team when recruitment proved challenging. The qualitative team e-mailed all HCPs involved in the study, inviting them to participate. Participants identifying other team members who had participated in the trial were asked to pass on details of the study to their colleagues. We attended the Interstitial Lung Disease Interdisciplinary Network (ILD-IN) conference, where we spoke about the study and invited participation. We also sent out invitations to participate via their mailing list twice. One participant gave us a list of 14 HOSARs across their geographical area (spanning one city and several counties). We contacted all of these by phone and/or e-mail. This participant also gave us e-mail details of all seven colleagues in their local ILD-IN branch. We e-mailed all of these and also all HCPs known to us in the field, inviting participation. Where participants identified challenges in obtaining AOT for their IPF patients, we contacted their local integrated care board (ICB) (these are local boards responsible for commissioning patient services in the local population) and invited them to participate. We also liaised with APF, who had a programme of work identifying areas where AOT was not available for their members. We did not invite the teams in setup to participate as the criteria had been to speak to staff about trial recruitment which they had not been involved in. We kept the principal investigator (PI) appraised of all activities throughout and took advice on how we could improve recruitment.

A purposive sampling frame was created:

*Patients:* we aimed to select a demographically diverse sample (e.g. age, gender, ethnicity, length of time using $O_2$) of patient participants. Follow-up interviews were offered to explore changes in their experience of IPF.

*Healthcare professionals:* we aimed to speak to a range of clinical and non-clinical staff, including relevant policy-makers and stakeholders (providers) concerned with the delivery of care to IPF patients.

## Data collection

To maintain COVID resilience in this particularly vulnerable group, interviews were conducted remotely [e.g. telephone, Zoom (Zoom Video Communications, San Jose, CA, USA) or Teams (Microsoft Corporation, Redmond, WA, USA)]. Informed consent was collected verbally. Photovoice methodology was used to prompt discussion during the interviews; participants were invited to take and share photographs (without people's faces) to aid discussion as to how their experience had changed during the trial. Providers were also given this option, but none took it up. Semistructured topic guides (see *Appendix 1*) based on existing literature and theories on attitudes to and practices around AOT in IPF, along with data from our patient and public workshop, guided the interviews and were refined iteratively. Interviews were approximately 30–60 minutes long. Interviews were audio-recorded and transcribed intelligent/clean verbatim.

### Data analysis

Data were analysed in two ways: using traditional qualitative analysis and through arts-based, collaborative methods with patients, members of the public and professional arts practitioners.

*Traditional analysis:* a coding framework was agreed within the research team and data coded using NVivo 12 (QSR International, Warrington, UK). Data were analysed using the framework method.[58]

*Collaborative arts-based analysis*: to ensure that the patient voice remained central to the analysis, and to inform the brief of the planned short film(s), participants and members of our PPI group were included as co-researchers in the analysis stage through a series of online and in-person data workshops to cocreate the film content. The workshops were co-facilitated by the qualitative research team and professional scriptwriters who had full access to the anonymised qualitative data set. The filmmaker was present and participated in these workshops. Where permissions had been given, a selection of participants' photos and quotes were included in these workshops and emergent themes discussed. The scriptwriters then prepared draft scripts. The draft film scripts were then workshopped in a subsequent online discussion, which also included a clinical perspective (AT: project PI). Once finalised, professional actors were appointed and the filmmaker began the filming. We held a hybrid workshop with a soft launch of the film in February 2024. This was attended by the cocreators and guests from APF; we used feedback from this workshop to create the necessary scaffolding for the film and website from where it is housed.

The methods listed here follow what is detailed in the trial protocol (https://fundingawards.nihr.ac.uk/award/NIHR131149) and the statistical analysis plan (SAP). A summary of the OxyPuF trial can be found in *Appendix 2*.

## Results

### *Research design: lessons learnt*

This study was planned as a pragmatic RCT, as a withdrawal of intervention study, on the basis that most centres we inquired with prior to application said that they routinely prescribed AOT to IPF patients. Nevertheless, sufficient sites ($n$ = 16 named collaborators) stated they had equipoise regarding its utility to enable us to identify participating hospitals at the point of application. We have divided our lessons learnt into categories, to enable other studies to pick up on our themes.

### *Recruitment: lessons learnt*

#### Regulatory delays

The grant was activated on 1 November 2020. Due to the delays experienced with getting regulatory approval, the 6-month pilot phase began on 1 September 2022, ending on 28 February 2023. Regulatory delays occurred within the governance department of the sponsor, because COVID studies were prioritised for approval versus non-COVID, and with the Medicines and Healthcare products Regulatory Agency (MHRA) and sponsor where debate occurred about whether this was a Clinical Trial of an Investigational Medicinal Products (CTIMP) or not. Drug removal studies where a product is already in use in the NHS and the intervention removes it (like ours) had most recently been classed as non-CTIMP in the experience of our trials unit.[59] However, in this case, OxyPuF ended up classed as a CTIMP after these discussions, which necessitated numerous changes to the draft protocol and planning of the study, and impacted study finances. We had worked with our lead NHS site to cost AOT using flow rates prescribed to their patients, and our lead NHS trust agreed that this was a drug removal study. The effect of this was that there were difficulties in some sites delivering the trial, because those who interpreted the classification of CTIMP strictly asked for money to be given for the intervention (even though they were usually giving it in routine care); this had not been included in the study budget, because it was a drug removal study. Views on whether AOT should be funded by the study differed country-wide, so some sites were able to deliver it despite classification. Drug removal studies have been classified both as CTIMP[60] and non-CTIMP[59] by UK regulators for trials within our trials unit – the lesson learnt for us at study design stage is that since classification is not assured, investigators may need to cost the study as if it were a CTIMP, irrespective of routine practice. However, this would have had huge implications on the cost of our application; because our study would not have prescribed AOT to nearly 50% of the participants, many of whom would likely have required high flow rates or usage (as modelled in the grant application budget), it was hugely cost saving to the NHS. An alternative would be for NIHR to work with the MHRA to determine whether a single approach to such studies is possible, which can then be reflected in costing guidance for trialists.

#### Site recruitment

Thirteen sites declined upfront to take part mainly due to lack of capacity, but three sites also cited a lack of equipoise, and a further three said they would not open without additional financial support (in the form of

remuneration for research nurse time) from the trial. This leads us to our second lesson for study design, which is that payment structures within the NHS may not be adequately set up to deliver cost-saving studies, at least of oxygen therapy, which is commissioned and provided differently to more standard medications. Oxygen in the community is generally supplied by an outside provider, whereas other more standard medicines (tablets, inhalers, etc.) can be supplied by the hospital pharmacy. In the NIHR payment structure, the cost of study delivery [as determined by the Schedule of Events Cost Attribution Tool (SoECAT)] is balanced against the net cost of the intervention and control to the NHS. The end result for our study was of a putative cost saving to the NHS of not giving AOT to patients in the study, accruing to the clinical department in which routine care is given. However, the delivery costs are borne by the research and development (R&D) department. Theoretically, NHS trusts should balance their costs internally, but since the savings are putative and the costs of delivery are real, some trusts then stated that they could not deliver the study because they would not have received payment for doing the trial. We had attempted to account for this in our application by including a fixed payment to sites for each participant recruited, even though this is not in the normal costing model; however, it was removed at contracting stage.

The lesson that could be learnt from this is that at application delivery, costs should be included elsewhere from the SoECAT, but not as a per-patient payment. Another possible conclusion is that cost-saving studies should be allowed leeway to facilitate delivery, in recognition of the fact that internal NHS finance systems were not always able to manage the concept. While some drug removal studies have been managed adequately, it is possible they were classed as non-CTIMPs [our Clinical Trials Unit (CTU) has experience of this,[59] and notably, this study also failed to recruit, albeit probably for very different reasons] or involved simpler or more standard medications than ours, where internal absorption of costs was easier within the trust.

During setup for the study, it became apparent that many sites were limited by social distancing requirements at the time in performing 6MWT, largely because many sites previously conducted them in hospital corridors, which were not wide enough to allow distancing and transit of other patients. We, therefore, included an alternative 1-minute sit-to-stand test to overcome this issue.

Five centres had been initiated, and a further seven were in setup at the time of termination, with four out of five active sites having recruited at least one patient. Across the five centres, it took on average 146 days to set them up. The majority of those sites in setup had been in receipt of the Local Information Pack for over 8 months but were still yet to confirm capacity and capability. This suggested that NHS R&D capacity was a significant limiting factor; post-COVID recovery and financial issues described previously are likely the main contributors here.

### Recruitment of participants

Seven patients were recruited prior to termination of the study at the end of the pilot phase due to low recruitment rate. Sixty-three participants were pre-screened, and 18/25 participants approached declined to participate. The remaining seven were randomised. Sites generally used a combination of initial approach by the medical team, with follow-up by research nurses, to drive recruitment.

Seventy-two per cent of patients were recruited in the last 2 months of the pilot phase, and the average recruitment was 0.23 patients/month of site activity, being well below the 0.5 patients/month determined to be a stop criterion in the pilot phase. Measures to improve recruitment included increasing the number of sites and increasing the duration of the recruitment phase. These scenarios were modelled – if the recruitment rate remained 0.23 and one new site was recruited per month it, it would take a further 46 months to recruit. If we were able to increase participant and site recruitment rates to one recruit per site per month and two new sites per month, it would still take a further 22 months; this seemed unlikely given the pre-screen and response to contact rates at the initial five sites. All scenarios would require a total of 33 sites to open to the trial in order to recruit to the same size. Given the issues encountered with site setup, it was therefore deemed unfeasible to continue the trial. The study flow chart is shown in *Figure 2*.

#### *Patient characteristics*

Baseline characteristics are summarised by group in *Table 2* and appeared well balanced between groups. Patients were generally considerably older than an average IPF patient in the published antifibrotic drug trial literature, where average age was around 65.[9,61] They were predominantly male, which is typical in IPF, and were exclusively white. Notable areas for future trialists are: (1) 6MWT was chosen as not feasible to complete for 3/7 participants, suggesting that our addition of 1-minute sit-to-stand test was valuable; (2) most participants had spirometry performed in the recent past, despite post-pandemic limitations; and (3) very few had completed PR. While there was missing data in some fields, such as desaturation timing and location of PR, it is not clear if this was truly unavailable data in the main record, or from

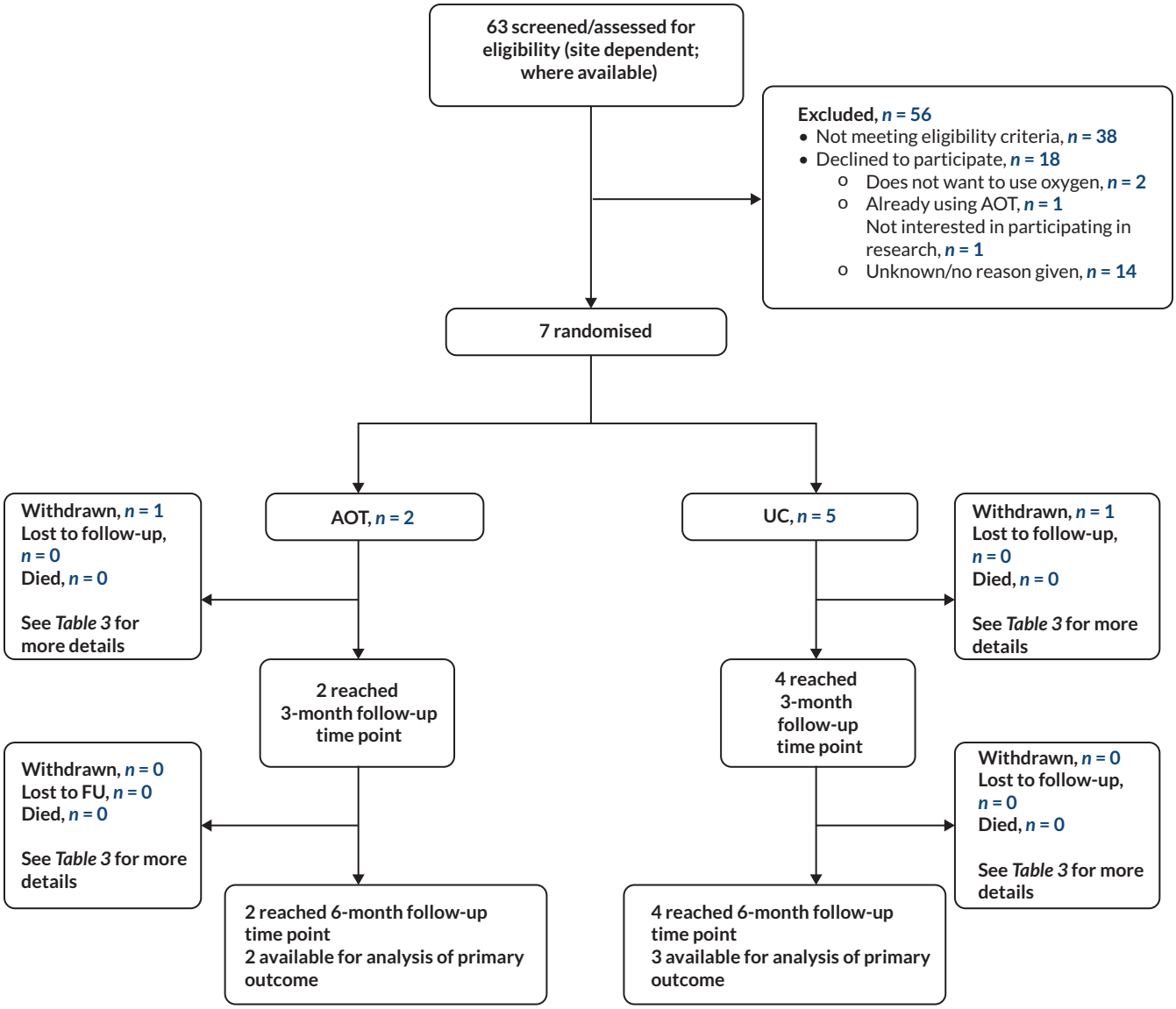


**FIGURE 2** Consolidated Standards of Reporting Trials diagram.

patient recall, or whether we would have been able to obtain it had the trial continued. There was one recruit to the accelerometery substudy, with data returned for baseline. Feedback from the participant reported easy use of the accelerometer with clear instructions. However, with the trial proceeding to close early, it was not feasible to continue with this as planned, nor to make interpretations of the limited data obtained.

### *Outcomes*

Seven participants completed 6-month follow-up, and data for the primary outcome are shown in *Table 3*. K-BILD scores were generally higher at baseline in the UC group, and the breathlessness component appeared lower both in comparison to UC and to follow-up (from baseline) in the AOT patients; however, with such small numbers, we cannot ascribe meaning to this.

### *Qualitative substudy*

Between October 2022 and October 2023, 11 patients were interviewed (trial and support group members) and with 23 HCPs [policy-makers, research nurses, respiratory clinical nurse specialists (CNSs), ILD nurses, respiratory doctors and patient representatives]. Three of the patients were interviewed twice, totalling 37 interviews in all.

Five of the seven patients from the trial agreed to be contacted by the qualitative team, one of whom declined to participate. Two further patients expressed an interest in the study at the local face-to-face group support meeting but chose not to leave contact details and did not make further contact with the qualitative team. Due to difficulties recruiting IPF patients, we included two patients with auto-immune-related disease. One patient died shortly after being interviewed. Characteristics of the

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**TABLE 2** Baseline characteristics by group

| | AOT N = 2 | UC N = 5 | Total N = 7 |
|---|---|---|---|
| ***Minimisation variables*** | | | |
| *Desaturation to < 88% on 6MWT or equivalent exercise test* | | | |
| Yes | 1 (50%) | 1 (20%) | 2 (29%) |
| No | 1 (50%) | 4 (80%) | 5 (71%) |
| *Current or recent (within 6 months)* PR | | | |
| Yes | 0 (–) | 0 (–) | 0 (–) |
| No | 2 (100%) | 5 (100%) | 7 (100%) |
| *Current antifibrotic use* | | | |
| Yes | 2 (100%) | 1 (20%) | 3 (43%) |
| No | 0 (–) | 4 (80%) | 4 (57%) |
| *Centre* | | | |
| Queen Elizabeth Hospital Birmingham, University Hospitals Birmingham NHS Foundation Trust | 1 (50%) | 1 (20%) | 2 (29%) |
| Imperial College Healthcare NHS Trust | 0 (–) | 1 (20%) | 1 (14%) |
| North Tees and Hartlepool NHS Foundation Trust | 1 (50%) | 0 (–) | 1 (14%) |
| Royal Devon University Healthcare NHS Foundation Trust | 0 (–) | 3 (60%) | 3 (43%) |
| ***Demographic and baseline variables*** | | | |
| *Age (years)* | | | |
| Mean (SD) | 85.4 (6.5) | 79.2 (5.2) | 81.0 (5.8) |
| Range | 80.8–90.0 | 70.5–84.0 | 70.5–90.0 |
| *Ethnic group* | | | |
| White (British/Irish/other) | 2 (100%) | 4 (100%) | 6 (100%) |
| Black/Black British (Caribbean/African/other) | 0 (–) | 0 (–) | 0 (–) |
| Asian/Asian British (Indian/Pakistani/Bangladeshi/other) | 0 (–) | 0 (–) | 0 (–) |
| Chinese | 0 (–) | 0 (–) | 0 (–) |
| Other | 0 (–) | 0 (–) | 0 (–) |
| Unknown/missing | 0 | 1 | 1 |

**TABLE 2** Baseline characteristics by group (*continued*)

| | AOT<br>*N* = 2 | UC<br>*N* = 5 | Total<br>*N* = 7 |
|---|---|---|---|
| *Sex* | | | |
| Male | 2 (100%) | 4 (80%) | 6 (86%) |
| Female | 0 (0%) | 1 (20%) | 1 (14%) |
| *Weight (kg)* | | | |
| Mean (SD) | 78.2 (1.1) | 76.5 (11.6) | 77.0 (9.5) |
| Median (IQR) | 78.2 (77.4–79.0) | 80.0 (72.3–85.0) | 79.0 (72.3–85.0) |
| Range | 77.4–79.0 | 58.3–86.8 | 58.3–86.8 |
| *Height (cm)* | | | |
| Mean (SD) | 178.0 (2.8) | 172.0 (6.3) | 173.7 (6.0) |
| Median (IQR) | 178.0 (176.0–180.0) | 171.0 (167.0–178.0) | 176.0 (67.0–179.0) |
| Range | 176.0– 180.0 | 165.0–179.0 | 165.0–180.0 |
| ***Lung function*** | | | |
| *Spirometry performed in the last 6 months?* | | | |
| Yes | 2 (100%) | 3 (75%) | 5 (83%) |
| No | 0 (%) | 1 (25%) | 1 (17%) |
| Missing | 0 | 1 | 1 |
| *If yes:* | | | |
| FVC (%) | | | |
| Mean (SD), *n* | 64.0 (11.3), 2 | 71.7 (21.4), 3 | 68.6 (16.7), 5 |
| Median (IQR) | 64.0 (56.0–72.0) | 84.0 (47.0–84.0) | 72.0 (56.0–84.0) |
| Range | 56.0–72.0 | 47.0–84.0 | 47.0–84.0 |
| DLCO (%) | | | |
| Mean (SD), *n* | 38.5 (3.5) | 49.3 (12.9) | 45.0 (11.0) |
| Median (IQR) | 38.5 (36.0–41.0) | 53.0 (35.0–60.0) | 41.0 (36.0–53.0) |
| Range | 36.0–41.0 | 35.0–60.0 | 35.0–60.0 |

continued

This synopsis should be referenced as follows: Adams RL, Maher A, Gale N, Crawshaw A, Thickett D, Turner AM. Ambulatory Oxygen for Pulmonary Fibrosis (OxyPuF): a randomised controlled trial and acceptability study [published online ahead of print July 2 2025]. *Health Technol Assess* 2025. https://doi.org/10.3310/TWKS4194

DOI: 10.3310/TWKS4194



**TABLE 2** Baseline characteristics by group (*continued*)

| | AOT<br>*N* = 2 | UC<br>*N* = 5 | Total<br>*N* = 7 |
|---|---|---|---|
| *Physical capacity test* | | | |
| 6MWT | 2 (100%) | 2 (40%) | 4 (57%) |
| 1-minute sit-to-stand test | 0 (–) | 3 (60%) | 3 (43%) |
| *If 6MWT:* | *n = 2* | *n = 2* | *n = 4* |
| Distance walked (*m*) | | | |
| Mean (SD), *n* | 330.0 (42.4), 2 | 225.0 (21.2), 2 | 277.5 (66.5), 4 |
| Median (IQR) | 330.0 (300.0–360.0) | 225.0 (210.0–240.0) | 270.0 (225.0–330.0) |
| Range | 300.0–360.0 | 210.0–240.0 | 210–360 |
| *Time to first instance below 88% saturation (minute)*[a] | *n = 1* | *n = 0* | *n = 1* |
| Mean (SD), *n* | 2.0 (–), 1 | – | 2.0 (–), 1 |
| Median (IQR) | 2.0 (2.0–2.0) | – | 2.0 (2.0–2.0) |
| Range | 2.0–2.0 | – | 2.0–2.0 |
| *If 1-minute sit-to-stand test:* | *n = 0* | *n = 3* | *n = 3* |
| Repetitions | | | |
| Mean (SD), *n* | – | 16.3 (2.5), 3 | 16.3 (2.5), 3 |
| Median (IQR) | – | 16.0 (14.0–19.0) | 16.0 (14.0–19.0) |
| Range | – | 14.0–19.0 | 14.0–19.0 |
| *Time to first instance below 88% saturation (minute)*[a] | *n = 0* | *n = 1* | *n = 1* |
| Mean (SD), *n* | – | 0.95 (–) | 0.95 (–) |
| Median (IQR) | – | 0.95 (0.95–0.95) | 0.95 (0.95–0.95) |
| Range | – | 0.95–0.95 | 0.95–0.95 |
| ***MRC grade*** | | | |
| *Shortness of breath category* | | | |
| Category 0, no dyspnoea | 0 (–) | 0 (–) | 0 (–) |
| Category 1, slight degree of dyspnoea | 0 (–) | 0 (–) | 0 (–) |
| Category 2, moderate degree of dyspnoea | 0 (–) | 1 (25%) | 1 (17%) |

**TABLE 2** Baseline characteristics by group (*continued*)

| | AOT *N* = 2 | UC *N* = 5 | Total *N* = 7 |
|---|---|---|---|
| Category 3, moderately severe degree of dyspnoea | 2 (100%) | 3 (75%) | 5 (83%) |
| Category 4, severe degree of dyspnoea | 0 (–) | 0 (–) | 0 (–) |
| Category 5, very severe degree of dyspnoea | 0 (–) | 0 (–) | 0 (–) |
| Missing | 0 | 1 | 1 |
| ***PR*** | | | |
| *Has the participant completed* PR*?* | | | |
| Yes | 1 (50%) | – (%) | 1 (14%) |
| No | 1 (50%) | 5 (100%) | 6 (86%) |
| *If yes:* | *n = 1* | *n = 0* | *n = 1* |
| Rehabilitation setting | | | |
| Face-to-face | 1 (100%) | – | 1 (100%) |
| Virtual | 0 (–) | – | 0 (–) |
| *Time since most recent PR completed (days)* | *n = 1* | *n = 0* | *n = 1* |
| Mean (SD), *n* | 379 (–), 1 | – | 379 (–), 1 |
| Median (IQR) | 379 (379–379) | – | 379 (379–379) |
| Range | 379–379 | – | 379–379 |

a Only in those who saturated below 88%.

This synopsis should be referenced as follows: Adams RL, Maher A, Gale N, Crawshaw A, Thickett D, Turner AM. Ambulatory Oxygen for Pulmonary Fibrosis (OxyPuF): a randomised controlled trial and acceptability study [published online ahead of print July 2 2025]. *Health Technol Assess* 2025. https://doi.org/10.3310/TWKS4194

**TABLE 3** Primary outcome summary statistics

| | AOT *N* = 2 | UC *N* = 5 | Total *N* = 7 |
|---|---|---|---|
| ***K-BILD***[a] | | | |
| *Baseline* | | | |
| Psychological score | | | |
| Mean (SD), *n* | 49.5 (16.3), 2 | 44.8 (14.0), 5 | 46.1 (13.4), 7 |
| Median (IQR) | 49.5 (38.0–61.0) | 41.0 (41.0–44.0) | 41.0 (38.0–61.0) |
| Range | 38.0–61.0 | 30.0–68.0 | 30.0–68.0 |
| Breathlessness and activities score | | | |
| Mean (SD), *n* | 69.0 (43.8), 2 | 35.6 (13.5), 5 | 45.1 (26.6), 7 |
| Median (IQR) | 69.0 (38.0–100.0) | 40.0 (27.0–40.0) | 40.0 (27.0–53.0) |
| Range | 38.0–100.0 | 18.0–53.0 | 18.0–100.0 |
| Chest symptoms score | | | |
| Mean (SD), *n* | 86.5 (19.1), 2 | 68.2 (18.5), 5 | 73.4 (19.2), 7 |
| Median (IQR) | 86.5 (73.0–100.0) | 73.0 (54.0–85.0) | 73.0 (54.0–85.0) |
| Range | 73.0–100.0 | 44.0–85.0 | 44.0–100.0 |
| Total score | | | |
| Mean (SD), *n* | 58.5 (16.3), 2 | 49.2 (9.8), 5 | 51.9 (11.4), 7 |
| Median (IQR) | 58.5 (47.0–70.0) | 50.0 (45.0–50.0) | 50.0 (45.0–64.0) |
| Range | 47.0–70.0 | 37.0–64.0 | 37.0–70.0 |
| *6 months* | | | |
| Psychological score | | | |
| Mean (SD), *n* | 60.5 (29.0), 2 | 44.7 (4.0), 3 | 51.0 (17.1), 5 |
| Median (IQR) | 60.5 (40.0–81.0) | 44.0 (41.0–49.0) | 44.0 (41.0–49.0) |
| Range | 40.0–81.0 | 41.0–49.0 | 40.0–81.0 |
| Breathlessness and activities score | | | |
| Mean (SD), *n* | 35.5 (17.7), 2 | 38.7 (16.0), 3 | 37.4 (14.5), 5 |
| Median (IQR) | 35.5 (23.0–48.0) | 38.0 (23.0–55.0) | 38.0 (23.0–48.0) |
| Range | 23.0–48.0 | 23.0–55.0 | 23.0–55.0 |
| Chest symptoms score | | | |
| Mean (SD), *n* | 72.0 (39.6), 2 | 66.7 (11.0), 3 | 68.8 (21.5), 5 |
| Median (IQR) | 72.0 (44.0–100.0) | 73.0 (54.0–73.0) | 73.0 (54.0–73.0) |
| Range | 44.0–100.0 | 54.0–73.0 | 44.0–100.0 |
| Total score | | | |
| Mean (SD), *n* | 54.5 (17.7), 2 | 50.0 (4.4), 3 | 51.8 (9.7), 5 |
| Median (IQR) | 54.5 (42.0–67.0) | 52.0 (45.0–53.0) | 52.0 (45.0–53.0) |
| Range | 42.0–67.0 | 45.0–53.0 | 42.0–67.0 |

a K-BILD domain and total scores have a range of 0–100, where 100 represents the best health status.

participants are shown in *Table 4*. None of our patients from the patient support groups were persons who were clinically eligible for AOT but had chosen not to use it.

Three HCPs directly involved in the trial were recruited from two different sites; five others were recruited through other methods from sites which were subsequently green-lighted. Therefore, we had representation from three of the five green-lighted sites. One participant was a respiratory nurse consultant from a non-specialist centre whose story was quite different from that of the specialist, tertiary centres. All our personal contacts agreed to participate. We approached two ICBs, both of whom agreed to talk to us. We spoke with all those in APF involved in the programme, exploring access to AOT for IPF patients. See *Table 4* for participant characteristics.

In addition to the 14 HOSARs contacted, we sent direct e-mails and/or phone calls to 60 additional HCPs. These included contacts given to us by colleagues or participants, and nurses from the ILD-IN. Three of the teams who declined participation in the trial agreed to be contacted by the qualitative substudy. One of these teams initially agreed an interview date but was then advised not to participate by their local managers and R&D department. The other two teams did not respond to our attempts to contact them. Therefore, we were unable to interview any of the teams who declined to participate in the main trial. Two members of staff directly involved in site setup from green-lighted sites declined participation, one stating that this was because the trial was no longer running. Attempts were made to discuss the importance of the interviews with the team, but they asserted that they did not want to participate. The other site did not respond to our attempts to make contact. We approached six sites in setup; none responded to our invitations to participate in the qualitative substudy. The three sites who were unable to proceed with setup because of funding issues were not approached as we could not offer remuneration for their time either.

**TABLE 4** Characteristics of qualitative study participants

| | Patients | HCPs |
|---|---|---|
| **Total** | **11** | **23** |
| Male | 8 | 4 |
| Age range | 36–85 | 26–75 |
| Not White British | 2 | 3 |
| Using AOT | 6 | N/A |
| ILD patients | 2 | N/A |
| Trial | 4 | 3 |
| Consultant | N/A | 2 |
| CNS | N/A | 1 |
| Intervention | 1 | N/A |
| Control | 3 | N/A |
| Support group/ILD-IN[a] | 7 | 11 |
| Oxygen nurses | N/A | 1 |
| Clinical other | N/A | 2 |
| Patient representatives | N/A | 3 |
| Policy-makers (from ICBs) | N/A | 2 |
| CNS[b] | N/A | 2 |
| Consultant[b] | N/A | 2 |
| Follow-up interviews | 3 | 0 |

N/A, not applicable.
a Patients recruited from APF support group, CNSs recruited from ILD-IN.
b Contacts known to team.

In the sites who actively recruited, staff responsible for screening did not respond to our invitations to participate, despite close liaison with their colleagues. In one case, we were informed that the person in question was too busy, and a second person from the same site was too busy to meet with us before leaving the trust. Three people from the ILD-IN made initial contact with us but then did not actually arrange an interview. Only one person from a HOSAR agreed to be interviewed (this was local to the trial team); other HOSARs, including others local to the trial team, did not respond.

We made multiple attempts to contact people, using various methods in case our non-NHS e-mails were being blocked. The trial PI and colleagues, including the lead qualitative co-applicant, were kept fully informed and guidance taken as to how best to proceed.

## Experiences of living with idiopathic pulmonary fibrosis

The narratives that participants shared about the photos they had taken about life with IPF were focused on the following themes:

1. **Navigating their fundamentally changed everyday lives.** Participants described how their lives were very different in many practical ways, for example, uncertainty around side effects of antifibrotics and safety limits around oxygen use. Perceived oxygen soak into clothing limited ability to participate in cooking both indoors and outdoors. Participants understood the importance of keeping active, but for some, the lockdown during the COVID-19 pandemic had negatively affected this.

   *[I will have to give up barbecuing when unable to manage it without oxygen; otherwise I would be] dancing with death [because your clothes, skin and facial hair become] soaked in oxygen … and therefore become much more combustible.*

   *OXP7*

2. **Coping with what they had given up since being diagnosed.** Participants describe the emotional impact of what they had given up in their lives, and how their worlds had shrunk, for example, no more foreign holidays. A number were extremely reluctant to accept things which would identify them as different, frail or disabled, for example, oxygen, disabled parking badges and mobility scooters.

   *Wouldn't go on holiday in case too far away from bathroom.*

   *P2*

3. **Living with uncertainty about the future.** Underpinning participant accounts was a strong sense of uncertainty about their future, and one particular feature of these narratives was acknowledgement that they had already lived beyond the 3–5 years given in their initial prognosis. This was both a relief and a worry as they wondered how close their death was. Holding support groups at the local hospice was an unwelcome reminder of what was to come, as was AOT. Hence, most of our patients were, or had been, extremely reluctant to accept it; fear of becoming dependent on oxygen was a factor in this. The main exception to this was someone who was relatively well from a IPF point of view but had another condition that was unpredictable and not responding to treatment.

   *I think oh blimey, because originally when you followed it up, it was like you'd got 3–5 years…, and to be honest, I'm over that hill at the moment, because they say you could wake up one day and that's it, and I do know that's the problem.*

   *P1*

4. **Pushing the boundaries and living well with** IPF**.** Finally, we were struck by our patients' incredibly resilient attitude towards their disease, the language being noticeably different from, for example, COPD patients whom we have interviewed and the literature regarding cancer patients. Several told stories explaining how they pushed the boundaries of their limitations, for example, still using exercise bikes in the last weeks of life and taking breaks while going upstairs instead of using AOT. This is a theme that we explored further in the arts-based analysis.

   *You've just got to learn to go with the flow, and just accept whatever is just about to happen.*

   *P2*

## Acceptability and utility of ambulatory oxygen therapy

Both HCPs and patients believed that AOT was a valuable tool for IPF patients once they started to desaturate beyond a certain level, enabling them to maintain levels of activity that they would not otherwise be able to achieve. One trial participant on initial receipt of his AOT did not think that it benefited him very much; however, 6 months later, he was unable to manage without it. Patients explained that AOT enabled them to do a wide range of things from simply walking up the stairs to using all terrain trekkers to accompany family on countryside walks, to walk the dog, contribute to household chores, after eating a meal and managing inclines.

> *The oxygen is really useful, because it does actually offer some relief … without the oxygen I think I'd be in considerable trouble … I can do things, … I can move about, I can do all sorts of things which otherwise, and I can say well am I going to do now … it makes things more feasible.*
>
> *P6*

> *[T]hey need high flow in order to work, to walk, to get to the shops, to get around the houses and to maintain activities that they enjoy. Not, we don't give it so that they can improve their survival, it's not about survival, it's about activity.*
>
> *H2*

Generally, patients talked positively about advice they had received regarding breathing exercises (both those within and outside of the trial). This was stated in relation to both advice they had received during the course of their usual treatment for their disease, as well as the advice sheet received by trial participants. Trial participants in the control arm received an advice sheet only. Participants in the intervention arm received an advice sheet and AOT.

> *The OxyPuF breathlessness advice sheet, I found quite useful, because really I wasn't breathing properly, and I think there's a lot of logic there. So now I do tend to use breathing techniques suggested in there, and it does make it easier. I say easier, it does, if I was to ignore the stairs and just climb up it, I'd be breathless at the top, so I have to concentrate on my breathing, and I can generally negotiate it more efficiently doing that as opposed to not.*
>
> *P4*

> *The breathing exercises I've really found difficulty in sticking with them. I don't think they've had much affect, and I'm supposed to be honest, I've reached the stage I'm no longer doing those now, because in the early stages I couldn't see any improvement developing.*
>
> *P8*

However, both patients and HCPs were frustrated by the failure to improve technology related to AOT, primarily in relation to oxygen concentrators. For example, IPF patients need different rates of oxygen flow depending on what they're doing, for example, a task that requires exertion versus slower-paced tasks. Patients have to walk over to the concentrator to change the oxygen flow; the activity of walking across to the concentrator in itself requires a higher litreage so many patients do not bother, instead struggling on with a lower amount. A simple remote control would resolve this. Similarly, the switches on a portable concentrator required patients to take off and open the backpacks in order to adjust the quantity needed, for example, to go up an incline. Again, patients would often not bother because it was too difficult. Locating the switch in a position that could be reached without having to take off the backpack would be much more user-friendly. Batteries for portable concentrators were also an issue:

> *[T]heir guide tells you … you should have 9 hours of battery time on setting 2, which is the lowest setting. But I'm getting 5½ on setting 2, so I don't know if that's because I have a high resp rate or because the battery is past its best … they say you should let the battery run down before you charge it, but it takes 8 hours to charge the battery. So if I want to use it a couple of days in a row but for short bits, then I would have to recharge it when it's at least half empty to make sure I have enough charged to use it the following day.*
>
> *P11*

## Organisation and clinical management of ambulatory oxygen therapy for idiopathic pulmonary fibrosis

### *Healthcare professional perspectives*

All the nurses we spoke to were quick to point out that AOT is not in itself a solution to breathlessness and that there are many more management options to consider before making such an offer. HCPs not involved in trial recruitment talked about how resistant patients were to the idea of AOT Nurses would manage this by starting the conversation about AOT early as a means of preparing the patient for it and opening up the discussion. They were passionate about encouraging patients to accept AOT as a means of opening up their world and enabling them to do more. Suggesting that patients simply try AOT, initially for a short period, during which time they could opt to use it at home if they wanted was a common way of introducing AOT. Some of the doctors we spoke to seemed to have a lower threshold for referring patients for AOT assessment than nurses; the belief that IPF patients' hypoxia could lead to organ damage was one rationale given – nurses had mixed views on this, and one was setting up a study which would explore this further. Challenges described included not having enough staff to meet patient needs and the time taken up by trying to arrange AOT for patients whose local HOSAR did not offer AOT assessments for IPF patients.

> *The problem is getting patients to, those who are prescribed it, is getting them to engage with the oxygen. The number of times you often have patients say, 'Oh*

> *well I try and make do', or, 'Try and do without it', and it's trying to help them to realise that they're prescribed it because it's felt that it would be a benefit for them for instance going up the stairs. Whereas they say, 'Oh well I'll just try and go up the stairs without it, I don't want to be reliant on it', … [I] encourag[e] them to do things at home with the oxygen first, like going out into the garden, going up the stairs and things like that, to give them the confidence of using the oxygen before they then have to start thinking about using it out in the public.*
>
> *H10*

The nurse from a local centre explained how stressed and breathless the hour-long journey to tertiary centres made IPF patients feel, along with the struggle to find their way, over some distance, within an unfamiliar hospital. In addition, their tertiary and local follow-ups invariably ended up occurring within 2 weeks of each other, meaning that patients had long periods of time without follow-up, factors which in turn affected patient access to AOT.

> *They accept their lot, … they understand that it is a terminal diagnosis, … there is a certain fatalism about … where they start, and therefore how they engage with healthcare. … So when do you say to your clinician, 'I'm getting short of breath, … I need oxygen?' I've had a chap recently just buy it from China because he thought … then I don't have to worry the NHS.*
>
> *H4*

Timely access to AOT was also impeded by oxygen assessment services not understanding IPF patients' particular needs.

> *[The] local … private company … commissioned to deliver our oxygen assessment service … work off KPIs … they have to see their patients within 14 days … But ambulatory oxygen is not part of that. So they can go to somebody's house, do an oximetry when they're sat quietly, so their sats are 94, they need … to go somewhere for their 6-minute walk test. … So that can be another 6-week wait, … unless the patient is particularly vocal about saying, 'But I can't get up the stairs', … if I write, say if I write on the referral form oxygen saturations absolutely plum normal when sat, however walk them down the corridor in the outpatient department they desaturated at 82, it still doesn't mean to say somebody's going to walk them round their house, or walk them up their stairs. Because for them that's not a formal ambulatory oxygen assessment.*
>
> *H4*

### *Patient perspectives*

Patients spoke very highly of the companies responsible for delivering oxygen. They felt that they had been well informed about the health and safety risks related to oxygen. And they valued the fact that they could get their oxygen delivered to any part of the country when going away, although one person had only recently discovered that this was possible. Although it is possible to fly with oxygen, and arrange for delivery abroad, our patients had not taken this up due to the costs, including medical insurance, assessments and general organisational challenges involved. From a clinical perspective, patients generally wanted their IPF to be monitored more frequently by the specialist team, and better access to their general practitioners.

> *You're not seen enough in that way, that's how I felt, I thought a lot could happen in 12 months, even though I do suppose you know that things are changing.*
>
> *P1*

## Engagement with research

Patients were very motivated to participate in research generally, including OxyPuF, despite their concerns about commencing AOT – as a little-known disease, they were extremely motivated to contribute to the body of knowledge around IPF.

> *I will go for anything and everything that will hopefully enhance my quality of life.*
>
> *P2*

One patient said they were already participating in another IPF study and would not want to do more than one at a time; another was keen to use AOT if it would ease their symptoms but was currently not eligible – their symptoms being primarily due to other chronic conditions. Generally speaking, patients not in the trial and not currently using AOT found it hard to hypothesise whether they would be willing to be randomised to the intervention arm. Those we spoke to who were currently using AOT were so dependent on it, it would not have been clinically appropriate for them to have had it removed; they found it hard to think back to their pre-AOT days and consider whether or not they would have found it acceptable to volunteer for the trial. Their responses were focused around convincing us of the importance of AOT; this is well captured under the theme 'Policy issues'. They also expressed implicit trust in their clinicians, believing that they would not invite them to participate in anything that was not clinically appropriate for them.

We asked those ILD-IN nurses not participating in the trial if they would be willing, hypothetically, to randomise patients to no AOT. Some expressed initial concern that this might be counter to normal practice in those who met the standard criteria for home oxygen and that they would have further concerns at the prospect of removing AOT from anyone who currently had it in situ; however, they decided that if a patient had agreed to participate in the study, this would not be a problem. They anticipated that the study might be attractive to those who were on the cusp of needing AOT, that is, those who felt they were able to manage without AOT but who were increasingly limiting their activities in order to cope, those who were reluctant to start AOT without good reason. What was key to these nurses was that there be clear guidelines as to eligibility in the study protocol, with the option that patients could withdraw if they had been randomised to no AOT and subsequently needed it.

We also explored whether it was possible to have equipoise for the trial. There was some variation in attitudes to this. HCPs who were responsible for recruiting to the trial did not express concerns about recruiting their annual quota of patients which ranged from 2 to 10 per year. Staff whom we interviewed were responsible for consenting, randomising and delivering care according to the trial protocol. They were not responsible for recruiting patients, and we were not successful in our attempts to include those involved in recruitment in the qualitative interviews. One clinician (not in the trial) explained that as AOT was typically only needed in the last 18 months of a IPF patient's life, they felt that withholding it for 6 months (for the purposes of OxyPuF's control arm) would have an unacceptably negative impact on the last stages of their life, that it would result in 6 months of quality life experience lost. It would also be extremely difficult to collect 12-month follow-up data due to patients' poor prognoses. Staff not participating in the trial wondered about eligibility criteria and why if someone who was clinically eligible for AOT might then not receive it and how acceptable the trial would be to patients who were resistant to AOT and those who wanted it. Some reflected that they could not imagine anyone currently on AOT being willing to risk giving it up by participating in the trial, but it was assumed that the recruitment criteria would not allow patients' quality of life to be reduced, believing this to be unethical. Generally speaking, HCPs considered that the lack of data supporting AOT in IPF was problematic and therefore felt that this was a much-needed research.

> *With the lack of data and the data we've got about progression with the TLC decline and the prognosis, and there's lots of other factors, possibly I would [say I'm in equipoise], yeah. … no one coerces patients, … I would go with patient choice at the end of the day, and with research to back that up, and we don't have that, so that's why I don't really go hard in to sell something that patients don't need. There are other ways to manage it, so if we've tried everything else it's, I don't know, it's the concept of giving something makes the healthcare professionals feel better … Maybe if we saw the harm it did in the airways by giving 8 or 15 litres in the nose, … killing cilias on the way, I don't know.*
>
> *H14*

## Policy issues

Two of the HCPs whom we interviewed reported that they could not get AOT for IPF patients from their local HOSAR. We approached both of the ICBs responsible for commissioning in their area; both were very concerned to hear that there were IPF patients in their areas who could not obtain AOT locally. They were keen to explore this further and explained that there were no commissioning policies in place, preventing the provision of AOT to IPF patients. In one area, it was explained that the local HOSAR was a fairly new service and that they had not yet had the opportunity to recruit and train staff to assess IPF patients for AOT; therefore, the ICB had agreed that such provision be made by the tertiary centres. CNSs in tertiary centres typically refer patients back to their local centres for all assessments; trying to arrange for these assessments to be conducted in the tertiary centres was time-consuming, as the CNSs had no experience of making such arrangements. The same challenges followed when it came to prescribing and arranging for equipment delivery. It was so time-consuming that the CNSs were unable to offer the usual telephone support to other IPF patients.

> *It is definitely commissioned. It's part of the standard contract for home oxygen. And if the clinician considers it to be required.*
>
> *H23*

During the period of data collection, the APF team involved in the programme exploring access to AOT for IPF patients had not identified additional ICBs that we should contact. We did not obtain any additional reports of difficulties obtaining AOT from the ILD-IN.

We asked patients what they would think if AOT was no longer available to IPF patients. Patients felt really strongly about the importance and benefits of AOT in IPF. The depth of feeling was captured by one patient's use of evocative imagery on the matter:

> *I would say one thing, take all [policy-makers] put them into a gas chamber, seal it, let them have a bottle of oxygen each, seal it, and when they start to get breathless and the oxygen is going, say, 'If you don't put the oxygen on you're going to die'. Because that's exactly how it is for us who have the lung disease. … I cannot understand the mentality of an organisation that turns round and says there is no evidence. The evidence is there plain for anybody to see, it is common knowledge that the body needs oxygen that's why you have lungs, and you have the blood there to transport the oxygen round to the rest of the body so all, have they never done any anatomy whatsoever?*
>
> *P7*

## Arts-based analysis and film themes

The workshops with patients, detailed in *Methods*, were very informative in planning (*Figure 3*).

The film draws out key themes in the interviews to create four short 'archetypal' voices that share elements of IPF. Each stands alone (and can be shared on social media, for instance, independently), but they also work as a whole film telling the story of IPF – from the experiences of diagnosis and living with IPF through to the final film with is the voice of a carer when their mother has passed away. The films use voiceover and images (evoking the photovoice methodology) and are intended to be informative, funny and moving, suitable for both a patient and clinical audience.

The four segments of the film are centred around four characters:

### *1. Jaswinder*

We meet Jaswinder in her house in the morning, where her ambulatory oxygen enables her to get dressed, go downstairs and make *aloo paratha* for her lunch guest. Jaswinder has had IPF for a few years now, and has had to give up some of her activities, including work and involvement in her local Sikh community, but she is sustained by family, friends, music and reading. We see her becoming very anxious as she waits for the weekly delivery of her oxygen cylinder, though she knows that the supplier never lets her down.

### *2. Len*

On a late summer's morning, we meet Len, sitting in his garden. This is the place he loves to be, his pride and joy. Today is not such a good day, as he is struggling with his medication and its side effects. Len is a working class man from the Black Country. He is down-to-earth, full of warmth and humour, and a lover of daffodils. We see Len trying to make the very best of his life with IPF.

### *3. Steve*

Steve loves trees and taking his dog, Marcus Aurelius, for a walk. The park is his favourite place to be. Steve has IPF now, but he used to be in the army and was very fit, so he is determined to reach his goal of walking 2.5 miles every day, which the oxygen in his backpack enables him to do. But today he tells Marcus Aurelius (named after the Roman Stoic philosopher) that he is hard put to keep his emotions under control, because he has just heard that ambulatory oxygen might not always be freely available to those who need it.

### *4. Beverley*

Beverley invites us into her office at the University of Cardiff at the end of a busy working day before having to rush off to pick up the kids. Constantly 'on the go', she is juggling her work and family, while also trying to come to terms with her mother's death. She tells with love and warmth the story of her mother's journey with IPF, capturing her independence and her dignity.

The film and website from where it is housed were launched as a hybrid public event at a local arts centre in July 2024. All those involved in the project, national and local APF members and colleagues were invited. All invitees were

**FIGURE 3** Activities during the data workshops to cocreate themes and characters for the films.

encouraged to further circulate the invitation. The film was also advertised to the public on the centre's events' site. The film can be viewed here: www.birmingham.ac.uk/ipf

## Discussion

Early termination of the trial means that we were not able to answer our primary research question. However, the qualitative substudy enabled us to conclude that AOT is both acceptable and desirable for patients, and that lack of equipoise may well have been an underlying factor driving slow recruitment. Further evidence on AOT use also does not appear to be required by commissioners, such that the value of another attempt at a trial to the NHS is questionable. This is evidenced within the qualitative work, where two commissioners stated it was routinely commissioned and the national ILD-IN network reported no difficulties in accessing AOT for their patients in any place in the UK. Admittedly, this contrasts with some healthcare systems then requesting payment for oxygen from the trial, despite it being routinely available; however, we think this is related to the classification of the study as a CTIMP, as described in the *Results* section on site recruitment.

Idiopathic pulmonary fibrosis patients live with a huge level of uncertainty around their condition, prognosis and treatments, and without curative treatments, they and their healthcare providers are highly motivated to provide interventions that might manage symptoms and improve HRQoL. Living well with IPF continues to be a challenge, and it was widely accepted by HCPs and patients that AOT enables patients to live well for longer during those last stages of life. While both patients and HCPs were motivated to engage in research around this relatively rare condition, there were significant challenges of conducting research around the use of AOT in IPF. Equipoise is very hard for this research question given the widespread belief from HCPs and patients that oxygen can be helpful. While we recruited a very limited number of patients to the trial, it is difficult to draw many conclusions about the population; it is notable that they were a lot older than in typical IPF trials. There are two possible reasons for this: (1) it could be because there is currently an active drug trial landscape in IPF, which commonly set an upper age limit within their protocols. This might explain some of the difficulty in recruitment; if younger patients, eligible for both a new drug trial and for OxyPuF might have been more inclined to choose these other trials for perceived benefit reasons, since AOT was being provided routinely (confirmed by our qualitative work, via commissioners), which might mean they could be in a drug trial and get AOT anyway. This is not something our study was set up to explore; hence, this is a speculative conclusion. (2) The IPF population may be older than the classical literature; as diagnostic techniques improve, the population ages, and awareness rise, so prevalence rises as well.[62] This brings lessons for those running trials in IPF – to be generalisable, populations need not include restrictive upper age limits, but if your trial has no age limit and other concurrent ones do, then it may be that yours is also not generalisable.

Our results suggest that investment into oxygen research might be better focused on things such as improving oxygen technology, which, it was felt, has not kept up with many everyday technologies in terms of ease of use and portability. It was also noted that other support, such as breathing exercises, were also important to support people with IPF, and studies of implementation or access to this could be relevant. It would be easy to label the participants in the qualitative study with IPF as stoical or resilient; however, these data suggest that what appears at face value to be stoicism may actually be a coping mechanism in itself, that is, the stoicism functions as a 'balm' for the pain of accepting the life-shortening diagnosis of IPF, and resilience is necessary to cope with the changes. Rather than idealising these as personal 'qualities' that patients have, it is important also to focus on how we can best create networks of practical and emotional support for patients.

Clinicians recognise the limitations of treatment and management of IPF and are cognisant of the changing prognoses, with some patients living longer than expected after diagnosis with IPF.[62] AOT is largely considered to be an important tool that they have available to them to support their patients, and their narratives around the decision to refer patients for AOT are suggestive of good stewardship of medical technologies and a clear understanding of when AOT can be of use in IPF (i.e. whether breathlessness is a result of hypoxia or not).

We recognise that the qualitative data here are of limited generalisability because the sample did not include the breadth of participants we had hoped; for example, we were not able to include people who withdrew from the study because they found the intervention unacceptable (no one met this criteria), people outside of the study who were unable to access or did not want AOT despite being eligible for it, or patients invited to participate in the study who declined to do so. Regarding this latter point, our experience of trying to recruit patients who decline participation in other trials has not been successful (papers and report currently under review). With hindsight, we

could have invited those in setup to participate in the interviews; however, given our experience with those HCPs who were not actively involved in recruiting patients, it is likely that this would not have been a good use of resource. Rather, we focused on recruiting staff through the ILD-IN network who had not participated in the trial. Maybe the importance of participation in qualitative substudies by all those connected to the study at the different sites needs greater emphasis when inviting sites to participate and at site setup, backed up with some site visits by the qualitative team to gain a good understanding of the recruitment process as this seems to vary from one site to another. Appropriate site-level remuneration is also important for HCPs' time.

### *Recommendations*

This trial is limited in the recommendations it can make due to the exceedingly limited recruitment. Although the focus of our research was not on the policy decision-making process, but on the acceptability and utility of AOT in clinical situations, much of the data spoke to issues of policy – especially the variable access to AOT for people with IPF in practice, which is important to address. Our partners, the patient group APF, are now working with the NHS clinical reference group responsible for developing a ILD care pathway which includes provision of AOT. A critical part of this process is a 'deep dive' which APF are undertaking. This involves exploring access to AOT for their members and identifying the sticking points for them and the staff allied to APF. Our researchers have been able to make a contribution to this. This close work with a patient organisation was a strength of the study.

When ICBs consider making special arrangements with HOSARs for AOT or other oxygen provision, thorough exploration as to the feasibility of these arrangements is needed with tertiary centres. Tertiary centres need appropriate resources to enable them to manage such arrangements efficiently. The changing clinical understandings of IPF, particularly around prognosis, would be another area for future research, as it was not something we were able to explore in any depth in this study and are likely extremely relevant to issues of clinical management of IPF and the future role that AOT would play in that.

## Patient and public involvement

A patient who had IPF was included in our study team but unfortunately died during the term of the grant. We also worked with APF, the main charity supporting patients with IPF, and carers. APF members assisted with review of the trial protocol and patient-facing materials and were involved in our TMG. We also worked with APF to help shape the qualitative elements of the study, along with the local Respiratory Patient Advisory Group. We consulted with them on study design, patient information and interview topic guides. Members from their networks also participated in some of the arts-based activities detailed below. In summary, their guidance influenced:

- Trial design pre-application
  - Our APF partners were concerned that patients would not be willing to risk being randomised into the control arm of the trial. Therefore, a qualitative substudy was included to explore, among other things, acceptability of the trial design to patients.
  - Our PPI partners agreed that self-reported activity by IPAQ cannot be certain to relate to actual activity and that therefore there was validity in objectively evaluating activity in 20% of patients from both arms using the ActiGraph device.

- Qualitative patient recruitment
  - We worked closely with APF to identify ways in which we could increase recruitment rates into the qualitative study.

- Qualitative patient interviews
  - 'Stigma' was included in the qualitative topic guide because it was raised as an issue by our PPI representatives.

- Quantitative analysis
  - Concern was expressed that participants may not adhere to the intervention because of the stigma associated with AOT. This influenced the SAP, and CACE analysis was chosen.

- Qualitative analysis
  - Participants and members of our PPI group were included in the analysis stage through a series of online and in-person data workshops to cocreate the film content.

The qualitative data collection was also informed by arts-based public engagement that we undertook early in the study, after the study materials had been designed, but prior to the qualitative data collection. We held a free workshop with IPF patients and members of the public in an open access location in Birmingham city centre ('The Exchange'). In the workshop, we explored participants' experience of IPF and living with breathlessness through

creative approaches (*Figure 4*). Content focused around the symptoms of IPF and the experience of breathlessness and was designed by an independent arts facilitator in discussion with patient representatives from APF. Content from this workshop was used to inform and guide our data collection and analysis; for example, we were alerted to three themes: the reaction of others to IPF symptoms, for example, coughing; the fact that IPF may not be patients' only or biggest concern; and the degree to which IPF patients' experiences vary. Patients and members of the public were further involved at the analysis stage as described in the methods.

## Equality, diversity and inclusion

While every attempt was made to include diverse participants, this was not achieved with regard to race. However, this may have been due to early termination. We worked with community groups, NIHR infrastructure PPI and engagement leads and networks (e.g. PILAR) to ensure we were promoting the study at sites in inclusive ways.

## Conclusion

Ambulatory oxygen therapy is acceptable to use by patients with IPF, and further RCTs of AOT are not likely to be feasible. If further evidence is considered desirable on clinical efficacy by NICE, then alternative means of data collection, such as from routine care data of patients who accept (or not) AOT might be utilised, accepting all the caveats that such a design comes with.

## Additional information

### *CRediT contribution statement*

**Rachel L Adams** (https://orcid.org/0000-0002-1798-3854): Data curation (qualitative), Formal analysis (qualitative), Visualisation (qualitative), Writing – original draft (qualitative).

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**Alice M Turner** (https://orcid.org/0000-0002-5947-3254): Conceptualisation (equal), Funding acquisition (equal), Methodology (equal), Supervision (lead), Writing – original draft (lead).

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**FIGURE 4** Crafting activities from the public workshop to inform and guide our data collection.

## Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to anonymised data may be granted following review.

## Ethics statement

OxyPuF studies were reviewed by the Health and Social Care Research Ethics Committee B (22/NI/0053) and all participants gave informed consent.

## Information governance statement

The University of Birmingham is committed to handling all personal information in line with the UK Data Protection Act (2018) and the General Data Protection Regulation (EU GDPR) 2016/679. Under the Data Protection legislation, University of Birmingham is the Data Controller and we process personal data in accordance with their instructions. You can find out more about how we handle personal data, including how to exercise your individual rights and the contact details for our Data Protection Officer here: www.birmingham.ac.uk/privacy.

## Disclosure of interests

***Full disclosure of interests:*** Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at https://doi.org/10.3310/TWKS4194.

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This synopsis was published based on current knowledge at the time and date of publication. NIHR is committed to being inclusive and will continually monitor best practice and guidance in relation to terminology and language to ensure that we remain relevant to our stakeholders.

## Publications

Film entitled, 'Living with idiopathic pulmonary fibrosis (IPF)' available at: www.birmingham.ac.uk/ipf.

## Trial registration

This trial is registered as EudraCT 2021-003535-29 and ISRCTN16366011.

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## List of abbreviations

| | |
|---|---|
| 6MWT | 6-minute walk test |
| AHRF | acidotic hypercapnic respiratory failure |
| AOT | ambulatory oxygen therapy |
| APF | Action for Pulmonary Fibrosis |
| CACE | complier-average causal effect |
| CNS | clinical nurse specialist |
| COPD | chronic obstructive pulmonary disease |
| CTIMP | Clinical Trial of an Investigational Medicinal Products |
| CTU | Clinical Trials Unit |
| DLCO | diffusing capacity for carbon monoxide |
| EQ-5D-5L | EuroQol-5 Dimensions, five-level version |
| FVC | forced vital capacity |
| HCP | healthcare professional |
| HOSAR | home oxygen assessment and review service |
| HRQoL | health-related quality of life |
| ICB | integrated care board |
| ILD | interstitial lung disease |
| ILD-IN | Interstitial Lung Disease Interdisciplinary Network |
| IPAQ | international physical activity questionnaire |
| IPF | idiopathic pulmonary fibrosis |
| K-BILD | King's Brief Interstitial Lung Disease |
| LTOT | long-term oxygen therapy |
| MCID | minimum clinically important difference |
| MDT | multidisciplinary team |
| MHRA | Medicines and Healthcare products Regulatory Agency |
| MRC | Medical Research Council |
| NICE | National Institute for Health and Care Excellence |
| NIHR | National Institute for Health and Care Research |
| NIV | non-invasive ventilation |
| OxyPuF | Ambulatory Oxygen for Pulmonary Fibrosis |
| PI | principal investigator |
| PPI | public and patient involvement |
| PR | pulmonary rehabilitation |
| R&D | research and development |
| RCT | randomised controlled trial |
| SAP | statistical analysis plan |
| SD | standard deviation |
| SoECAT | Schedule of Events Cost Attribution Tool |
| TMG | Trial Management Group |
| UC | usual care |

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## Appendix 1 Qualitative topic guides

The OxyPuF trial: Ambulatory Oxygen for Pulmonary Fibrosis

## Ambulatory Oxygen for Pulmonary Fibrosis qualitative study

### *Interview topic guide (healthcare professionals)*

1. **Professional role:**
   - What is your current role?
   - Could you describe key responsibilities of your role in relation to IPF?
   - What is your involvement (if any) with the OxyPuF trial?

2. **Experiences of managing patients with IPF:**
   - In your experience, what are the current trends and patterns of experience for patients with IPF?
   - How do these differ from patients with other respiratory conditions – is there a difference in gender/age/ethnicity/socioeconomic group/education. If so, in what way?

- Are there any other disabilities patients have, for example, vision, deafness, mobility and so forth?
- How do you manage patients across the primary/secondary care interface? What about social care?
- What do you think are the roles of home-based and community-based care?
- Where are the biggest problems in the system from your perspective?
- What are your views on using information and communication technologies to help patients manage their condition at home? Has this changed since the COVID-19 pandemic?

3. **Alternative treatments for patients with IPF:**
   a. Treatment options and acceptability:
      - Can you talk me through your decision-making process around which treatments to offer patients with IPF?
      - What are your views on prescribing ambulatory oxygen?

   b. **Psychological:**
      - What support is available to self-manage the psychosocial needs of patients with IPF (anxiety, depression, social isolation)?
      - How do patients express these needs? (I.e. are they open to discuss emotional needs?)
      - How do patients handle the stigma associated with their condition and/or the treatments required (including ambulatory oxygen)?

   c. **Cultural/demographic:**
      - How do you relate to patients from different cultural or demographic backgrounds? *(Age, gender, ethnicity, etc.)*
      - Are there any challenges in supporting self-management in these different groups? *(Differences in health beliefs, health literacy, etc.)*

4. **Closing comments:**
   - Do you have any further comments about the use of ambulatory oxygen for patients with IPF?
   - Do you have any further comments about the OxyPuF trial?

The OxyPuF trial: Ambulatory Oxygen for Pulmonary Fibrosis

## Ambulatory Oxygen for Pulmonary Fibrosis qualitative substudy

### *Topic guide*

**Interview structure:**

1. **Review of the photos taken by the participants, and an explanation for each one.**
2. **Follow-up of any topics not yet covered:**

**Topics in bold**

*Possible questions to prompt discussion in italics*

a. Experiences of being diagnosed with, self-management of and treatments for IPF (with a focus on ambulatory oxygen):
   - *Firstly, how long have you been living with IPF? Can you tell me about how you were diagnosed?*
   - *What treatments were you offered? How do you feel about them?*
   - *Could you talk me through your daily routine from when you wake up in the morning?*
   - *Can you share the photos you have taken about your experience of living with IPF?*
   - *How do you feel about the medical treatments that you have been prescribed?*
   - *Have you ever had oxygen treatments? (In the hospital or at your home.)*
   - *Have you ever used ambulatory oxygen* (i.e. *that you can carry around with you in everyday life)? If not, how would you feel about it if it was recommended to you? [Use leaflet or prompt images if they don't know what it is.) If so, how did you feel about using it the first time, and how do you feel about it now?*
   - *How do you currently do to self-manage your condition/look after yourself?*
   - *What are the main issues you face when managing your condition at home* (e.g. *effects of physical activity)?*
   - *How do you feel about using technology (such as mobile phones and apps) in your daily life to help manage your condition?*

b. Material/embodied aspects of the experience:
   - *What are some of the symptoms you experience when trying to manage your condition? [*E.g. *breathlessness or any other symptoms such as cough, wheeze, phlegm (sputum), anxiety or depression.]*
   - *How does that make you feel? (I.e. any psychological impact?)*

- *What is the difference between 'good day' and 'bad day'? Tell me more on what a bad day would look like.*
- *How do you feel that your* IPF *has affected your relationship with your body? Have your expectations and experiences of your body changed? For example, sporty prior to* IPF *diagnosis and unable to do tasks that were previously easier to do. Think more about certain behaviours or practices. Could you tell me more in what way this might have been?*
- *Have you had to make many changes in your home? For example, medical equipment, moving rooms to different floors.*

c. Impact on personal, family and community life.
- *How has your condition (IPF) impacted your family life and friends (social networks)?*
- *How has it impacted you in terms of going out and about?*
- *Do you experience any discrimination or stigma as a result of your condition or the treatments that you need to use to manage it (such as ambulatory oxygen)?*
- *Do any of your family or friends act in a carer role for you? Do you have a paid carer?*
- *Are there any cultural factors that might have influenced how you manage/feel about your condition? That is, religious beliefs, ethnicity. If yes, in what way?*
- *How familiar are you with social media platforms (digital technology) to network/keep in touch with people?*
- *Has this changed given the current COVID-19 situation? (dependence on technology to for social connections due to social distancing measures).*

3. **Closing comments**
- Do you have any further comments about living with IPF?
- (If relevant), do you have any further comments about participating in the OxyPuF trial?

## Appendix 2 Ambulatory Oxygen for Pulmonary Fibrosis trial summary

| OxyPuFrial | |
|---|---|
| Objectives | To determine whether AOT is clinical and cost-effective in patients with IPF |
| 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 |
| Total number of participants | 260 consenting adults diagnosed with IPF confirmed via a MDT meeting or a IPF specialist |
| Sample size assumptions | To detect an absolute MCID of 4.0 points in the K-BILD total score between groups, assuming a SD of 8.85 with 90% power and 5% significance level (two-sided type 1 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 |
| Eligibility criteria | Inclusion<br>• Aged 18 or over<br>• Clinically diagnosed IPF, confirmed by a ILD MDT linked to an NHS specialist-commissioned IPF service<br>• Breathlessness with MRC dyspnoea scale ≥ 2<br>• Willing and able to comply with completion of questionnaires out to 6 months post randomisation<br>• Able to complete a 6MWT or 1-minute sit-to-stand test<br>• Able to use oxygen safely in the opinion of the local investigator<br>Exclusion criteria<br>• Unable to provide informed consent<br>• Requires LTOT, defined by need for resting oxygen in the opinion of the local investigator<br>• Life expectancy < 6 months<br>• On the active transplant list<br>• Previous AHRF requiring NIV |

| OxyPuFrial | |
|---|---|
| Interventions | **Intervention arm:** AOT and standardised breathlessness advice<br>**Control arm:** standardised breathlessness advice |
| Primary outcome measure | Primary outcome<br>Total K-BILD score at 6 months |
| Secondary outcome measures | Secondary outcomes at 6 months after randomisation unless otherwise stated<br>1. Subscales within K-BILD (breathlessness, activity, chest symptoms)<br>2. Exercise capacity using the 6MWT or 1 minute sit to stand<br>3. MRC dyspnoea scale<br>4. Physical activity using the IPAQ<br>5. Sleepiness using the Epworth Sleepiness Scale<br>6. Hospitalisations (all cause and IPF specific)<br>7. Cough using a 6-point visual analogue scale (VAS)<br>8. Targeted adverse events<br>9. Mortality (6 months, and from medical record only at 12 months)<br>10. Medication use: benzodiazepines, antifibrotics; ACEis and opiates for breathlessness<br>11. Completion of PR<br>12. Acceptability of AOT<br>13. Cost-effectiveness (using EQ-5D-5L, and scheduled and unscheduled health service use relating to IPF) |
| Funder | NIHR |