Effect of ambulatory oxygen on quality of life for patients with fibrotic lung disease (AmbOx): a prospective, open-label, mixed-method, crossover randomised controlled trial

Title: Effect of Ambulatory Oxygen on quality of life for patients with fibrotic lung disease (AmbOx):

a randomized mixed-method cross-over controlled clinical trial

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Abstract

Background: In fibrotic interstitial lung diseases (ILDs), exertional breathlessness is strongly linked to health-related quality-of-life (HRQoL). Breathlessness is often associated with oxygen desaturation, but little information exists on ambulatory oxygen in ILD patients. We aimed to assess the effects of ambulatory oxygen on HRQoL in ILD patients with isolated exertional hypoxia.

Methods: AmbOx was a multi-centre, randomized, open label, mixed-method, cross-over controlled clinical trial evaluating whether ambulatory oxygen for a two-week period improved HRQoL, compared to no treatment. Patients with fibrotic ILD were recruited from three UK centres if their resting SpO2 was ≥94%, but dropped to ≤88% on a 6-minute-walk-test (6MWT). On a second 6MWT, oxygen flow was titrated to maintain SpO2>90% for > 1/2 of 6MWT duration and/or maximum flow of 6 litres/minute, to determine the appropriate oxygen flow for each patient. Participants were randomly assigned to the order of treatment using a computer-generated sequence of treatments randomly permuted in blocks of constant size (fixed size of ten).

The primary outcome, assessed on intention to treat, was the score-change on the King's Brief ILD questionnaire (K-BILD) after two weeks on oxygen compared to two weeks off oxygen. General linear models with treatment sequence as a fixed effect, assuming a gaussian family distribution and identity link function for continuous variables, and binomial family and logit function for binomial variables, were used for analysis. Patient views were explored through semi-structured topic-guided interviews with a subgroup. This study is registered with ClinicalTrials.gov, number NCT02286063.

Findings: Between 10th September 2014 and 5th October 2016, 84 patients were randomized to the trial. Of these, 41 were randomised to ambulatory oxygen first, and 43 to no oxygen, crossing to the alternative arm after two weeks. 76 (90.5%) completed the trial. Ambulatory oxygen, compared to no oxygen, was associated with improvements in total K-BILD score [mean (SD) on oxygen: 55.5 (13.8) versus 51.8 (13.6) on no oxygen, difference adjusted for order of treatment: 3.7-95%CI:1.8 to 5.6; p<0.0001)], breathlessness and activity domain [44.4 (22.6) on oxygen vs 35.8 (20.4) on no oxygen; difference: 8.6; 95%CI:4.7 to 12.5; p<0.0001], and chest symptoms domain [65.5 (25.2) on oxygen vs 57.9 (29.2) on no oxygen; difference: 7.6;95%CI:1.9 to 13.2; p=0.009)]. The most common adverse events were upper respiratory tract infections (3 (3.6%) in the oxygen arm and 1 (1.2%) in the no treatment arm. Five serious adverse events, including two deaths (one in each arm) occurred, but were considered not related to oxygen usage. Patients considered oxygen largely beneficial, with challenges including visibility, work-related issues and perceived prognostic significance.

Interpretation: Ambulatory oxygen appears to be associated with improved HRQoL in ILD patients with isolated exertional hypoxia, suggesting that it can be an effective intervention in this patient group with limited therapeutic options, although further studies are needed to confirm this finding.

AmbOx was funded by the National Institute for Health Research (NIHR) (Reference: PB-PG-0712-28073).

Introduction

Fibrotic interstitial lung diseases (ILD) are associated with markedly reduced health-related quality of life (HRQoL) and survival. In idiopathic pulmonary fibrosis (IPF), the most common and deadly of the idiopathic interstitial pneumonias (IIPs), anti-fibrotic therapy reduces decline in lung function, but does not improve HRQoL (1;2). As pulmonary fibrosis advances, exertional breathlessness is triggered by simple activities of daily life. Breathlessness is the strongest determinant of HRQoL in patients with fibrotic ILD (3) and can be difficult to manage both for patients and their informal carers.

Oxygen desaturation contributes to exercise intolerance in patients with ILD. However, limited data exist on supplemental ambulatory oxygen use in this group, with most studies performed in patients with COPD. Although improved survival was observed with the use of ≥15 h per day of supplemental oxygen in COPD patients with resting hypoxemia (4), ambulatory oxygen had no effect on mortality or HRQoL in COPD patients with isolated exertional desaturation (5). However, ILD is characterised by more frequent and severe exercise-induced desaturation (6) compared to COPD, indicating that ILD-specific studies are needed (7) . The paucity of data on ambulatory oxygen in ILD is reflected by a lack of guidance in national and international guidelines (8-10).

Both a systematic and a Cochrane review of studies specifically evaluating supplemental oxygen use during exercise tests in ILD patients were inconclusive (11;12), although two recent studies report significant benefits of high flow oxygen compared to placebo air on performance and breathlessness during cycle endurance testing in the laboratory (13;14). However, immediate benefits in the test setting do not necessarily translate into improvements in day to day HRQoL. Drawbacks include the weight of the portable oxygen equipment, logistical difficulties of replenishment, travel limitations, and the psychological and social burden of the intervention on patients and their caregivers (15;16). The effects of high flow oxygen, used in a pulmonary rehabilitation setting, on exercise performance and breathlessness are currently under investigation (17).

Research in context

We searched PubMed up to March 1st 2018 for systematic reviews and randomised controlled trials with the search terms “ambulatory oxygen”, “supplemental oxygen”, “portable oxygen”, “exercise/exertion” and “interstitial lung disease”, with no restrictions on start publication date or language. Both a 2016 Cochrane review and systematic review published in early 2017 had not found evidence of a consistent effect of supplemental oxygen during short bursts of exercise on dyspnea, with many of the reviewed studies considered of low quality as retrospective, uncontrolled or with

small numbers of patients. Two recent controlled studies published subsequently, have shown significant benefits of high flow oxygen compared to placebo air on endurance time and breathlessness during a cycle ergometer test in the laboratory setting. However, the acute effects of high flow supplemental oxygen on exercise in a laboratory setting may not translate in benefits of ambulatory oxygen to patients in their daily lives. No studies have so far investigated the effect of ambulatory oxygen on quality of life in patients with ILD.

Added value of this study

To our knowledge, the AmbOx study is the first to prospectively evaluate the effect of ambulatory oxygen on HRQoL in patients with ILD in a randomized controlled trial setting. The results of this trial, if confirmed by further studies, will enable delineation of ILD-specific guidelines for ambulatory oxygen use.

Implications of all the available evidence

The 2011 IPF guidelines, endorsed by numerous respiratory societies, did not provide guidance on the use of supplemental oxygen in patients with isolated exertional hypoxia. The 2015 British Thoracic Society guidelines state that ambulatory oxygen should not be routinely offered to patients who are not hypoxic at rest. No specific reference to ILD patients is made except to mention possible benefit of ambulatory oxygen for individual patients with severe exertional breathlessness. Given the lack of condition-specific guidelines, wide variability exists in prescribing practices of ambulatory oxygen in ILD. National and international guidelines on supplemental oxygen rely on studies performed in patients with COPD. Extrapolating data from patients with obstructive disorders to patients with fibrotic ILD is not appropriate, given the differences in the two disease processes. The AmbOx trial suggests that ambulatory oxygen improves day to day HRQoL in patients with isolated exertional hypoxia. However, further larger studies are required to confirm this finding, to enable further understanding of the predictors of longer term uptake of ambulatory oxygen, and to assess whether long term ambulatory oxygen use is associated with improvements in survival.

Methods

Study design

The AmbOx trial is a UK multi-centre, prospective, randomised, open label, mixed- method, controlled cross-over trial of portable ambulatory oxygen for two weeks, against no intervention for two weeks,

to evaluate whether ambulatory oxygen is associated with improved HRQoL compared to no intervention in patients with fibrotic ILD. Approval of the final clinical protocol (18) was provided by the appropriate independent Ethics Committee (NRES Ref: 14/LO/0258).

Participants

Patients were recruited from three ILD centres (Royal Brompton Hospital, Aintree University Hospital and North Bristol NHS Trust). Eligible patients had fibrotic ILD, aged >18, were not hypoxic at rest (SpO2≥ 94% on room air), but were observed to have a fall in SpO2 to ≤88% on a screening visit 6 minute walk test (6MWT). At screening, self-reported stable respiratory symptoms in the preceding two weeks were required. Patients were excluded if expected to change treatment during the course of the study. Baseline characteristics including age, gender, smoking history, ethnicity, medical history, and current medications were collected. In all patients, diagnosis of fibrotic ILD type was reached following MDT discussion. Pulmonary function tests, including FVC, FEV1 and DLCO measurements, and an echocardiogram, were performed within -6 months to +6 weeks from screening visit. The composite physiologic index (CPI) was used as a functional index of lung fibrosis severity, as previously described (19)**.** Serum brain natriuretic peptide (BNP) levels were collected within a month from the screening visit and centrally analysed. Full inclusion and exclusion criteria are listed in the appendix (Supplementary file p 1). All patients provided written informed consent before entering the study.

Procedures

Screening 6MWT

At the screening visit (-2 weeks) (Figure 1), a 6MWT was performed. If oxygen saturation dropped ≤ 88% on the first test on room air, a second test was carried out with a portable oxygen cylinder, with a mandatory 30-minute rest period after the first test. The flow rate of oxygen was up-titrated to either maintain oxygen saturation > 90% for >1/2 of the 6MWT and/or to a maximum flow rate of 6 LPM (20). Participants performed the 6MWTs in a quiet 30-m corridor, with standardised instructions and encouragement, according to *ERS*/*ATS* standards (21). Screening 6MWT (on room air) distance and end test SpO2 of randomized patients are shown in Table 1.

Oxygen versus placebo air 6MWT

At the baseline visit (Figure 1), patients reporting stable symptoms in the two-week run in period, were asked to perform two further 6MWTs: one on oxygen and one on placebo air-filled canisters, at the flow rate (either oxygen or placebo air) identified during the screening visit, with continuous flow via nasal cannulae. The order of oxygen vs placebo air filled canisters was randomised, and patients

were blinded to the content of the canisters. A rest of at least 30 minutes between tests was mandatory. One patient withdrew a few hours after being randomised and therefore did not perform the placebo controlled 6MWT. Measured parameters (WristOx2™ model 3150) included 6-minute walk distance, oxygen saturation and heart rate measured continuously, Borg dyspnoea and fatigue score before and at the end of the test (22), as well as time to recovery/baseline of heart rate, oxygen saturation, and Borg dyspnoea and fatigue scores.

Intervention: ambulatory oxygen cylinders

Lightweight oxygen gas cylinders provided ambulatory oxygen. Participants were instructed to use the cylinders during routine activities of daily living. The lightweight oxygen cylinders were provided by the relevant oxygen companies in the UK, determined by post code. Cylinder weight was similar between oxygen companies varying between 1.8 and 2.2 kg (Supplementary Table 1). Continuous oxygen flow via nasal cannulae was the standardized mode of delivery. Oxygen flow rates were determined on the basis of the entry 6MWT on oxygen. Patients were asked to report, in a dedicated trial paper diary, the number of fully and partially used oxygen cylinders at the end of each week. Median patient-reported oxygen cylinder use per week was 2.75 cylinders (range 0-14), while median oxygen flow rate was 3 LPM (range 1-6 LPM). For 47 pts, an independent report from the oxygen companies and/or domiciliary visits, was available. In the 47 patients for whom a report of the amount of oxygen used was available from both sources, the median number of weekly cylinders reported by the patients (2; range 0.5-14) was similar to the independent report (2; range 0-14), with good agreement observed (concordance correlation coefficient: 0.87) (Supplementary Figure 1, page 2). Further details on assessment of oxygen cylinder use can be found in the Appendix (Supplementary page 2).

Patients were assessed at week -2 (screening), and then at weeks zero (baseline), two (crossover) and four (last visit) (Figure 1). At week zero, after performing the placebo controlled 6MWT, patients were randomised centrally to either ambulatory oxygen or no treatment for the following two weeks, as outlined below. Following completion of the two weeks on the treatment arm (ambulatory oxygen or no intervention), patients crossed-over to the alternative treatment for a further two weeks (Figure 1). At each visit, starting from week zero, patients underwent a physical examination, adverse event assessment, and were questioned about concomitant medication. Each visit included the K-BILD (23), in addition to the other questionnaires listed below in the outcomes section. Visits at weeks two and four also included the patient's global assessment of change in breathlessness and walking ability, respectively (Supplementary file p 3).

Randomisation and masking

Participants were randomly assigned as to the order of treatment by an Interactive Web-based Randomisation System (InForm), specifically set up by Imperial College Clinical Trials Unit (ICTU). All participants had two separate randomization processes, one for order of oxygen vs placebo air during the 6MWT and one for the order of portable home oxygen versus no oxygen during the first two weeks of treatment. Participants were randomly assigned to order of treatment by using a computer-generated ("ralloc" command in STATA12 software; StataCorp LP, College Station, TX) sequence of treatments randomly permuted in blocks of constant size (fixed size of ten) to ensure that within each block the sequence of treatment was balanced. The constant block size was chosen because the trial size was relatively small. The result was a 2×2 crossover design: a 2-sequence, 2-period, 2-treatment crossover design, with sequences AB and BA. The sequences were determined a priori and the program generated the said sequence in a random order.

The randomisation list was generated by the statistician at Royal Brompton hospital. To conceal allocation, the treatment names were not included in the list which was held securely, and at a separate site, by a central organisation (ICTU), whose staff were completely independent of the trial. ICTU staff assigned participants to the trial groups (i.e. the sequence of treatment); the clinical research staff enrolling the patients and the participants were not made aware of the sequence of the treatment. The statistician who generated the randomisation list was involved in the analysis together with an independent statistician but neither of them had prior knowledge of how ICTU labelled treatments A and B. There was no formal evaluation of the success of masking the treatments.

Patients were blinded to the content of the cylinders utilised during the 6MWT, by using concealing black tape around the surface of the cylinder to cover all labelling.

Although assessors collecting the data were not blinded to the treatment arm, patients completed all study questionnaires without input from the clinical trial researchers. Data entry of primary and key secondary outcomes was performed independently at RBH, by an assessor blind to any information pertaining to the trial, including treatment with/without ambulatory oxygen.

Outcomes

Quality of life

Our main objective was to assess whether ambulatory oxygen used for two weeks in day to day life was associated with improved HRQoL: the K-BILD was selected as a validated ILD-specific HRQoL measure (23). The primary outcome of the study was the difference in K-BILD scores between oxygen and no oxygen treatment at the end of each two-week treatment period, respectively (23). The K-BILD

comprises 15 questions, each with a seven-point response scale, grouped into three domains: breathlessness and activities, chest symptoms, and psychological. The domain and total score ranges are 0-100, with lower scores indicating worse quality of life.

Key secondary outcomes to address the objective of measuring the impact of ambulatory oxygen on breathlessness during activities, included:

- patient reported global assessment of change (same, better or worse) over the previous two weeks in a) breathlessness on exertion (breathlessness global assessment) and b) ability to walk (walking global assessment) (Supplementary File p3);
- the University of California San Diego Shortness of Breath questionnaire (UCSD SOBQ) (24), a well-established tool for assessment of dyspnoea during activities;
- severity of dyspnoea in 24 activities ranked on a scale of 0 to 5, for a total range from 0 to 120, with higher scores indicating worse dyspnoea.

To further assess the impact of ambulatory oxygen on HRQoL as well as psychological impact, additional secondary outcomes included:

- St George's Respiratory Questionnaire (SGRQ), a 50 item questionnaire developed in COPD but widely used in IPF (25), divided into three components (symptoms, activity, and impacts), with a total score ranging from 0 to 100 (higher scores indicating worse HRQoL).
- Hospital Anxiety and Depression Scale (HADS) (26) consisting of seven items for depression (HADS-D) and seven items for anxiety (HADS-A), with scores on each subscale ranging from 0 to 21. Patient scores for HADS-A and for HDAS-D ≥8 were considered to indicate presence of anxiety and depression, respectively (27;28)

Physical Activity

Accelerometer measurements

To address the question of whether ambulatory oxygen is associated with increased physical activity levels (PAL) in daily life, patients were asked to wear a SenseWear Pro Armband (SAB), a biaxial accelerometer, over the body of the triceps, for five consecutive days in each of the two-week periods (on and off oxygen respectively), for 24hours/day with the exception of time undertaken for personal hygiene requirements. Valid activity was taken as three consecutive days with a wear time of >89% per day.

Qualitative interviews

To identify patient experiences, benefits and concerns relating to using ambulatory oxygen at home, audio-recorded semi-structured interviews with a qualitatively-trained research nurse (AF) were conducted within two weeks of trial completion. Twenty-one of the 56 trial participants at the Royal Brompton site and three carers agreed to participate. Patient demographic and baseline ILD characteristics are summarised in Supplementary Table 2, p4. Semi-structured interviews following a topic guide were conducted at the hospital (N=18) or in patients' homes (N=3). Audio-recordings were transcribed, anonymised, entered into NVivo qualitative data analysis software (QSR International Pty. Ltd. Version 10, 2012) and analysed using the Framework approach: a systematic, well-recognised method for qualitative analysis that uses a process of summarisation, mapped onto framework matrices enabling generation of themes (29). Analysis and interpretation were conducted by an analytic team (SF, AF, MF, EAR), with credibility of interpretation facilitated through review by a patient panel.

Statistical analysis

Sample size calculation for the RCT

The RCT sample size of 80 was calculated to be sufficient to detect a significant difference in the K-BILD score between the two arms of the study. The power calculations were based on an MCID of 8, available at the time of the protocol design, observed in a cohort of 57 ILD patients across a wide range of disease severity, with mean K-BILD total score of 62 (SD:23) (30) and an expected within-subject correlation of 0.8.

Analysis

The primary outcome was the difference in K-BILD score on oxygen compared to no oxygen. We used a generalised linear model assuming a gaussian family distribution and identity link function, with the difference in HRQoL as the dependent variable and treatment sequence as a fixed effect (31). In a two period crossover, it is impossible to separate carryover (be it pharmacological or psychological) from treatment by period interaction (32). Given these uncertainties, we took the a priori decision to adjust for order of treatment (18), as this takes into account the possibility of a difference in effect according to treatment sequence. However, the unadjusted analysis of the primary outcome, where sequence is omitted, can be found in the supplementary file (supplementary table 4, p5). As there were no obvious differences between baseline variables according to order of treatment, and none of the baseline variables were linked to the primary outcome (supplementary file, p6), we did not adjust for

baseline variables. The study was considered positive if statistical significance at the level of 0.05 (two tailed) was achieved. The same model was used to analyse differences in SGRQ and UCSD SOBQ scores, as well as 6MWT parameters, except for the difference in dyspnoea/fatigue and the respective recovery times on 6MWT, that were analysed using the Koch method for the two-period cross over design (33). Conditional logistic regression, with sequence as an interaction term, was used to analyse the effects of oxygen on the presence of anxiety or depression, as defined by a HADS score ≥8 (27;28). To analyse the determinants of the decision to continue on ambulatory oxygen at trial completion, binary distribution and logit family were assumed (logistic regression). To compare the proportion of patients with an improvement versus a worsening in K-BILD scores>MCID, a 2x2 chi2 test was used.

An intention to treat analysis was performed with all the patients entered in the study for whom data were collected, regardless of compliance with treatment. Missing items due to post-processing incidents (lost questionnaire pages, patient input errors, etc) were less than 1% and were considered as occurring completely at random. We therefore performed the analyses both as complete case analysis (omitting missing data), and after replacing missing data with multiple imputation, using 20 replicates imputed by multivariate normal regression over the baseline value of that parameter, the value of global assessment, and the order of treatment. There were no noticeable or significant differences in the results, and we therefore only report the results of the complete case analysis without imputing data. Analysis was performed using Stata 12 software (StataCorp LP, College Station, TX). This trial is registered with ClinicalTrials.gov, number NCT02286063.

Role of the funding source

This manuscript presents independent research funded by the National Institute for Health Research (NIHR) under its Research for Patient Benefit (RfPB) Programme (Grant Reference Number PB-PG-0712-28073). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health. EAR was involved in all stages of study development and delivery, had full access to all data in the study, and had final responsibility for the decision to submit for publication.

Results

Baseline characteristics

Between 26th August 2014 and 22nd September 2016, a total of 269 patients were screened. Of these, 84 were randomized between 10th September 2014 and 5th October 2016 (Figure 2). Of these, 41 patients were randomised to ambulatory oxygen first, and 43 to no oxygen first, of whom 37 and 39,

respectively, completed the trial (Figure 2). Baseline characteristics of the 84 randomised patients are summarised in Table 1. Mean age (SD) was 67.9 (10.4) yrs, 26/84 (31%) patients were women and 53/84 (63%) had a history of smoking. The most frequent diagnosis was IPF (49 patients; 58%). Other diagnoses included fibrotic HP (n=13/84; 15.5%), CTD associated ILD (n=8/84; 9.5%), fibrotic NSIP +/- OP (n=6/84; 7.1%) unclassifiable ILD (n=3/84; 3.6%), fibrotic sarcoidosis (n=2/84; 2.4%), pleuroparenchymal fibroelastosis (n=1/84; 1.2%) and interstitial pneumonitis with autoimmune features (n=1/84; 1.2%). On average, patients had moderate-severe disease, with DLCO of 38.5% (9.3%) and mean composite physiologic index (CPI) of 52.9 (8.4). Mean K-BILD total score was 50.5 (11.2). A summary of other HRQoL questionnaire scores is provided in Table 1.

Compared to patients with non-IPF ILD, patients with IPF were older, more likely to be men, and more likely to be ex-smokers. Baseline lung function, questionnaire scores and 6MWT parameters were similar between patients with and without IPF (Supplementary Table 3, p 5).

Placebo controlled 6MWT (oxygen cylinders against placebo air cylinders)

Compared to the 6MWT performed on placebo air, the median Borg dyspnoea score at the end of the test on supplemental oxygen fell from a median value of 3 (IQR 2.0 to 5.1) to 2.1 (IQR 0.7 to 3.4) $p < 0.0001$) (Table 2). Supplemental oxygen improved the mean 6MWT distance by 18.5 meters (p=0.001) compared to placebo air (Table 2). Compared to placebo air, oxygen was associated with a significant reduction in the dyspnoea and fatigue recovery time (Table 2).

Primary outcome

Ambulatory oxygen used during daily activities for two weeks was associated with a statistically significant improvement in the total K-BILD score [on oxygen: 55.5 (SD:13.8) vs no oxygen: 51.8 (13.6) - adjusted mean difference between supplemental oxygen and no oxygen of 3.7: 95% C.I. 1.8 to 5.6] (Table 3 and Figure 3). In K-BILD subdomains, the largest improvement was seen in the "breathlessness and activity" domain [44.4 (22.6) on oxygen vs 35.8 (20.4) on no oxygen; difference=8.6; 95% C.I. 4.7 to 12.5)], followed by the "chest symptoms" score [65.5 (25.2) on oxygen vs 57.9 (29.2) on no oxygen; difference=7.6; 95% C.I. 1.9 to 13.2)], while the difference in the "psychological" domain was not statistically significant [55.2 (19.6) on oxygen vs 52.8 (19.6) on no oxygen; difference=2.4; 95% C.I.-0.6 to 5.5) (Table 3 and Figure 3). The difference in the K-BILD total score was similar regardless of the order of the intervention, although there was a non-significant trend towards a greater effect in patients first randomised to air rather than oxygen (Supplementary Table 4, p5). After the two weeks of ambulatory oxygen, 13/74 (17.6%) had an improvement in the

total K-BILD score>8, the previously defined MCID threshold (30), compared to 2/74 (2.7%) of patients with a worsening K-BILD score by>8, p=0.003). None of the baseline demographic characteristics, smoking history, diagnosis of IPF, baseline HRQoL questionnaire scores, baseline lung function tests, screening 6MWT distance and end test desaturation, presence of raised PASP on echo, presence of RV dilatation, or BNP levels significantly affected the primary outcome (change in K-BILD total score) (Supplementary Table 5, p6). In particular, no correlation was observed between the primary outcome and the K-BILD score at baseline (supplementary Figure 2, p7). The difference in primary outcome remained significant after adjusting for study site.

Secondary outcomes

Pre-defined major secondary outcomes included the patient reported global assessment of change in breathlessness and walking ability, and the UCSD-SOBQ. At the end of the two weeks assigned to ambulatory oxygen, the majority of patients reported improved breathlessness [better:52/76 (68.4%) - same:23/76 (30.3%) - worse:1/76 (1.3%)], compared to the two weeks on no oxygen [better 1/76 (1.3%) – same:57/76 (75%) - worse:18/76 (23.7%) (p<0.0001)]. (Figure 4 panel A). Similar results were observed when asked about change in the ability to walk (Figure 4 panel B) (p<0.0001). Significant improvements were observed at the end of the two weeks on ambulatory oxygen compared to no oxygen on the UCSD SOBQ (adjusted difference: -8.0; 95% CI -12.4 to -3.6, p<0.0001) (table 3b).

Among additional secondary outcomes, the SGRQ total score improved significantly on oxygen (adjusted difference -3.6; 95% CI -6.7 to -0.6, p=0.018) (Table 3b), with the largest difference observed in the activity domain (-7.5; 95%CI-12.4 to -2.5, p=0.003) (Table 3b). No significant differences were observed in the numbers of patients meeting HDAS score thresholds for depression (≥8) or for anxiety ((≥8) on the two weeks on oxygen compared to no oxygen (Table 3c).

Sensewear Armband (SAB) data

SAB measurements met the criteria outlined in the methods section in both periods of the trial in only 41 patients. SAB activity data is provided in Supplementary Table 6 (p7). According to established thresholds (35) for physical activity levels (PAL), 28/41 (68.3%) individuals were very inactive (PAL <1.4), and only two individuals could be categorised as active (PAL>1.7). Although activity levels and step counts were numerically higher on ambulatory oxygen, this was not statistically significant.

Impact of Oxygen induced changes in 6MWT parameters on the primary outcome

The relationship between changes in 6MWT parameters on oxygen versus placebo air and the primary outcome were evaluated. Of the O2-induced changes in 6MWT parameters, only oxygen induced reduction in highest heart rate recorded during the 6MWT was loosely associated with the primary outcome (p=0.052) (Supplementary table 7, p8).

Decision to continue on supplemental oxygen

At the end of the trial period, the majority of patients (51/76, 67%) chose to continue using ambulatory oxygen. On univariable analysis, baseline clinical parameters associated with this decision included younger age [64.8 (10.3) vs 73.0 (8.6); OR:0.89 (95% C.I.:0.83-0.96); p=0.002], and more severe lung function impairment [CPI 54.9 (8.4) vs 49.1 (7.1); OR: 1.1 (95% C.I.:1.03-1.17); p=0.008] (Table 4), with both age and CPI remaining independently predictive on bivariate analysis (p=0.009 and p=0.037, respectively).

Among the outcomes of the trial, on univariable analysis, the most significant determinants of the decision to continue on O2 were the patient's global assessment of change in breathlessness (OR 4.1, 95% C.I.:1.8-9.4; p=0.001) and in walking ability (OR 3.2, 95% C.I.: 1.5–6.9; p=0.003) (table 5). On multivariate analysis, the patients' global assessment in the change in breathlessness (or in a separate model the assessment in change walking ability) remained the strongest determinant of the decision to continue on oxygen; younger age also remained independently predictive (Supplementary Tables 8 and 9, p8).

Adverse events

Five serious adverse events were recorded during the trial; three (including one death) in the two weeks on oxygen and two (including one death) in the two weeks of no oxygen. All adverse events were classified as unrelated to the trial. Details can be found in the Appendix (Supplementary Table 10, p9).

Qualitative interviews

Seven themes arose from the interviews: (1) attitudes towards using ambulatory oxygen, (2) benefits of ambulatory oxygen, use of ambulatory oxygen (3) indoors and (4) outdoors, (5) challenges faced, (6) supply of oxygen and (7) support given. Illustrative patient quotes are provided for each theme in Table 6.

Attitudes towards using ambulatory oxygen

Whilst most patients reported initial apprehension, attitudes changed for many as they experienced improved exercise tolerance and quality of life; these patients continued with oxygen post-trial (N=16). Six, who were initially frightened or shocked at the prospect of ambulatory oxygen, continued with these negative attitudes; most stopped oxygen post-trial (N=5).

Benefits of ambulatory oxygen

Nearly all patients experienced benefits from ambulatory oxygen, including being less breathless when walking or doing daily activities, not having to stop as much when doing activities, and reduced cough. They reported their quality of life as improved as they 'could do more'. Other patients reported less 'chest tightness', reduced fatigue, increased energy, less dizziness, and feeling that supplemental oxygen provided a 'boost' when they were 'feeling low'. All three carers reported their spouses benefited and continued with ambulatory oxygen post-trial. Only one patient reported little benefit from using ambulatory oxygen.

Use of ambulatory oxygen indoors and outdoors

Ambulatory oxygen was reportedly helpful indoors with tasks that required some exertion such as housework, DIY jobs and going upstairs. Most used ambulatory oxygen outdoors to go for walks, do gardening, go shopping, go on social outings, walk to work and get to and from public transport. Some reported feeling more confident to go on outings. However, the amount of oxygen used outdoors varied, with some patients using it most times they went out and some rarely or not at all because of the particular challenges involved in using it outside of the home.

Challenges faced

Cylinders were cumbersome or awkward to carry for some patients, and two of the three carers found the cylinders heavy. A few patients and one carer also worried that cylinders would run out; this could be a particular challenge if away from home. Workplace challenges were encountered for three of the four patients who worked, including an initial reluctance amongst employers to accommodate oxygen use. Visibility of the ambulatory oxygen was also a concern for some. However, most patients used ambulatory oxygen despite these concerns because of the benefits perceived.

Oxygen had prognostic significance for four patients as it made them question if their illness was getting worse. One carer saw oxygen therapy as "*a sign that he is being even more not well*" but she realised it was making him feel better, so she was happy for him to continue (Carer16a, wife).

The patients who did not continue with ambulatory oxygen post-trial reported more of these challenges than patients who continued with it.

Supply of ambulatory oxygen and support given

A few patients and one carer reported feeling shocked at the first delivery. However overall, there were very few problems reported with the oxygen delivery and supply, with patients reporting receiving good support and information. All patients and carers seemed to particularly gain from the support related to oxygen use provided by the research co-ordinator throughout the trial, suggesting the importance of ensuring such support where ambulatory oxygen is prescribed outside of a study setting in daily clinical practice.

Discussion

To our knowledge, this is the first randomised controlled study to assess the effects of ambulatory oxygen on day to day health-related quality of life in patients with fibrotic ILD. Ambulatory oxygen was associated with improvements in the total KBILD score, the primary outcome of the trial, and in its subdomains of "breathlessness and activity" and "chest symptoms", but not the "psychological symptoms" domain. Ambulatory oxygen was also associated with improvements in the pre-specified key secondary outcomes, including the UCSD SOBQ and in the global assessment of change in breathlessness and walking ability. Analysis of the qualitative interviews revealed that almost all interviewed patients considered oxygen beneficial, although challenges included visibility, the perceived prognostic significance and work-related issues.

The mean improvement in the K-BILD total score was below the previously reported MCID estimate of 8 (30). This MCID was originally calculated in a relatively small cohort of 57 ILD patients, with on average milder disease than patients recruited to AmbOx, who had disease severe enough to cause desaturation to ≤88% on exertion. In more advanced ILD, there is likely to be a reduced ability to see major differences because of the severity of the disease and the confounding effect of complications and co-morbidities. Analysis of a subsequent larger study of a group of ILD patients limited to the same sort of magnitude as the patients included in AmbOx, revealed an MCID for the K-BILD total score of 4.0 (range 3.7-4.2) , although this was published in a conference abstract (34), and not in a peer reviewed manuscript. The average difference of 3.7 observed in the K-BILD total score is therefore at the lower estimate of this recently revised MCID for clinically important change, and further studies are needed to confirm whether ambulatory oxygen is associated with a change that is clinically meaningful to patients. Nonetheless, the K-BILD difference was > MCID of 8 in 17% of patients, and > 4 in more than a third of patients [27/74 (36.5%)], a significant observation particularly considering that there are currently very few, if any, treatments that improve quality of life in progressive pulmonary fibrosis. The findings of the qualitative interviews at the end of the study also support a

clinically significant benefit, as most interviewed patients described symptomatic improvement in a number of areas, despite the challenges posed by ambulatory oxygen. Taken together, these observations suggest that the difference observed in the K-BILD total score reflects a change that is relevant in patients' daily lives, although further studies are clearly needed to confirm the clinical importance of our findings.

Within K-BILD, the most marked effect of ambulatory oxygen was seen for the K-BILD breathlessness and activity domain, with an average difference of 8.6, well above recently revised MCID of 6 for this subdomain (34). We note that the KBILD total score amalgamates items relating to general quality of life and lung-specific symptoms. It is quite likely that an intervention may improve some domains more than others, particularly if it is only used during exertion. The breathlessness and activity domain includes four questions focused on breathlessness during exertion and while carrying weights, as well as how often the lung condition leads to avoidance of tasks or interferes with the patient's job/daily tasks. Ambulatory oxygen would be expected to mostly impact on breathlessness and activities, and it is therefore not surprising that the largest effect was seen in this domain rather than in the K-BILD total score, which also includes a number of questions on the patient's psychological response to their illness, not necessarily affected by a short-term intervention used only during activities. The marked effect seen in the breathlessness and activities domain is particularly relevant to patients with pulmonary fibrosis, as breathlessness has been consistently shown to be the symptom most strongly linked to quality of life (3).

The real clinical significance of an intervention may be better captured by an individualised judgement of the involved patients than by a "one size fits all" MCID. In this regard, it is interesting to note that 57/76 patients reported improved breathlessness at the end of the two weeks on oxygen, compared to only 1 patient out of 76 at the end of the two weeks with no oxygen, as assessed by the global assessment of change question, one of the pre-specified key secondary outcomes.

Ambulatory oxygen was also associated with improvement in the other pre-determined main secondary outcome, the UCSD SOBQ. The average adjusted difference of 8 observed for the UCSD SOBQ score was higher than the MCID reported for COPD patients (>4) (36). Although the MCID has not been tested in ILD, the finding of a significant difference in the UCSD SOBQ, a questionnaire dedicated to breathlessness across a range of activities, further suggests a clinically beneficial effect of ambulatory oxygen. Although oxygen was associated with a trend towards reduced numbers of patients with HADS scores suggestive of depression, this was not statistically significant, a finding not surprising in view of the limited duration of the intervention, and in keeping with the non-significant findings for the K-BILD psychological domain. The improvements seen in the SGRQ total score, although significant, were less marked than those seen with the K-BILD or UCSD SOBQ. The impact on

the domain investigating breathlessness with activities was again the strongest, in keeping with the findings for the K-BILD subdomain “breathlessness and activity”, thereby increasing the confidence in this result. It is also notable that most patients chose to continue using ambulatory oxygen beyond the trial.

Despite improved breathlessness and quality of life scores, we observed no significant differences in step counts or physical activity levels during the two weeks assigned to ambulatory oxygen. However, the analysis of the Sensewear activity data was hampered by the technical/logistical difficulties encountered by patients, such that only little more than half of patients completing the study had analysable data according to our inclusion criteria. This may have limited our power to detect an effect, and further studies focused on the effects of ambulatory oxygen on activity levels are needed before any definitive conclusion can be drawn.

This study has a number of potential limitations. The study design did not include a placebo arm, although this was a carefully reached decision. Ambulatory oxygen cannot be administered without the concomitant weight of the oxygen delivery device, as the intervention is a combination of possible benefits from oxygen and the disadvantage of canister weight. In a recent COPD study, the weight of the oxygen system was reported as a key negative issue by 93% of study participants (37). Cylinder weight was also a consistent issue identified in our qualitative interviews. The negative effects of a “placebo” air filled cylinder mean that a positive result of an oxygen arm against an air-filled canister arm would be clinically difficult to interpret. The ‘placebo’ would be actively harmful to study participants, and carrying an air-filled canister would be expected to lead to reduced exercise tolerance. As such, we concluded that use of an air-filled cylinder arm would not inform the real-life comparison between oxygen plus cylinder weight and no intervention. In view of the absence of a placebo arm, independent checks on the amount of oxygen used by patients were made. The good agreement between self-reported number of cylinders and independent report by oxygen companies and/or specialist nurse home visit suggests reliability of self-reported use of oxygen cylinders in this study. The cross over design does not allow to exclude a potential carryover effect of oxygen in patients randomised to start on oxygen first, which could be related to a longer than expected biological carryover effect of oxygen on tissues, a psychological carry over effect, or to differences in the perception of change depending on whether there is improvement or worsening, as suggested by Redelmeier DA et al (38).

Although data entry of the primary and key secondary outcomes was performed independently by an assessor blind to any trial information, and the questionnaires were filled in by patients independently, the researchers collecting the questionnaires were not blinded to treatment, and may

have introduced bias. Another limitation of the study is that in view of its short duration, the potential for long-term harm of supplemental oxygen via oxidative stress in the lungs (39), or conversely of a benefit of oxygen on the oxygen radical production induced by intermittent periods of hypoxia was not assessed (40). Future studies on supplemental oxygen in ILD including measurements of oxidative stress markers are needed to further evaluate these possibilities (41).

The beneficial effect of supplemental oxygen on breathlessness could reside in the stimulation of the upper airway mucosa receptors by the high air flow rather than the oxygen per se (42;43). In the study by Abernethy et al (30), no difference was seen in the effects on dyspnoea on breathless patients with chronic lung diseases but not hypoxic at rest, between ambient air vs oxygen via nasal cannulae at a flow of 2 LPM delivered continuously over a seven-day period. However, in their mostly COPD cohort, only 6% of patients had interstitial lung disease, oxygen was provided regardless of activities, was not titrated to optimize oxygen saturation on exertion, and the breathlessness scores appear to have been measured at rest. Conversely, Leach et al (20) compared 6MWT distance and breathlessness scores of patients with severe lung disease, between walking tests performed using a sham cylinder containing air at a flow rate of 4 LPM, or oxygen at flow rates of 2, 4 and 6 LPM, in random order. All patients, including ILD patients, analysed separately, experienced a significant worsening in distance walked and in visual breathlessness scores when they carried the extra weight of the cylinder, despite the nasal cannulae air flow of 4 LPM, while distance walked and breathlessness score progressively improved with increasing O2 flow rates. On the other hand, in a recent meta-analysis, short term supplemental oxygen during short bursts of exercise was associated with improvements in exercise performance but with inconsistent effects on breathlessness (11). The current study included a 6MWT on oxygen against placebo air, the latter provided at the same flow of the supplemental oxygen, titrated to the needs of the individual patient. We found that breathlessness was significantly improved by oxygen compared to placebo air, with a median decrease in the Borg breathlessness score by approximately one unit, although the acute effects of oxygen may not necessarily translate into beneficial effects in day to day life. Furthermore, it is possible that the effects of oxygen on reducing the sensation of breathlessness may not solely be due to improved oxygenation in peripheral tissues. Nevertheless, taken together, these data suggest that the benefit observed with supplemental oxygen in this study is dependent on oxygen itself rather than the effect on the nasal mucosa receptors of high flows of air, although further studies directly comparing the two modalities, with a placebo air arm, will be useful. One such study is currently under way (ACTRN12617000054314) comparing ambulatory oxygen with placebo air, and should usefully integrate the findings of AmbOx.

In AmbOx, ambulatory oxygen improves quality of life in patients with ILD who experience significant desaturation on exercise. The captured experiences of patients and carers in this mixed methods study adds to our knowledge on patients' and carers' experiences of ambulatory oxygen in their private and public social worlds. Patients mostly reported improvement of symptoms and their quality of life, supporting the quantitative findings of the AmbOx trial. However, even if oxygen improved symptoms, patients and their carers did experience physical and psychosocial challenges in using ambulatory oxygen, as also recently reported (15;16). In AmbOx, approximately a third of patients decided not to continue using ambulatory oxygen at the end of the trial. This finding suggests that the challenges associated with supplemental oxygen use need further assessment. From our qualitative findings, most patients were initially concerned about using oxygen, although the benefits experienced meant that most became more positive and opted to continue. However, a few patients had a persistently negative attitude towards ambulatory oxygen, and declined to use it post trial, despite all but one patient reporting symptomatic benefits during the trial. Interestingly, among the challenges reported by patients who decided not to continue were the prognostic significance attributed to having oxygen prescribed, challenges encountered in the workplace and concerns about social stigma, suggesting these as areas for potential intervention.

We identified younger age as a strong predictor of adopting ambulatory oxygen in the longer term. Whether this is related to higher motivation to remain active in younger patients, or other factors, will also require further study. The strong correlation between the global assessment of change, i.e. the simple question on whether patients had noticed a change in breathlessness and/or walking ability after the two weeks on ambulatory oxygen and longer-term continuation, suggest that a trial period of two weeks may be useful to assess whether the benefits provided by ambulatory oxygen overcome the burden associated with its use in the individual patient. This would allow clarification of the many questions that arise from oxygen use, and may help focus resources on patients who are most likely to continue to use the oxygen long term. We also propose to undertake an economic evaluation to assess the cost-effectiveness of ambulatory oxygen in improving patient HRQoL, in order to inform the value of implementing it more widely (18).

In conclusion, ambulatory oxygen was found to attenuate exertional hypoxia and dyspnoea on a 6MWT, and appeared to improve HRQoL in fibrotic ILD, a group of diseases associated with life changing respiratory symptoms, with limited beneficial interventions. Whether other compressed gases, including air, can provide similar benefits, and whether the changes observed with ambulatory oxygen are sufficient to be clinically meaningful to patients, will require further study. Despite the downsides of supplemental oxygen, the majority of patients opted to continue with the ambulatory

oxygen, suggesting an overall positive effect in the majority of patients. Nevertheless, further studies are needed to better assess the effects of ambulatory oxygen and ultimately allow the development of guidelines for its use specific to patients with ILD.

Author Contributions

EAR, PS, AUW, MF, DV and LS participated in the design and planning of the study. EAR supervised the study. DV, LM, SC, ADL, PS, CH, AF, EL, VA, LGS, HA, AS, MP, JB, FC, PMG, PLM,GM, MK, VK, AC, AM, AMR participated in recruitment and data collection from patients. VT monitored the study and supervised data entry. SF, MF and AF collected and analysed qualitative interviews. MB was the independent data enterer for the primary and secondary outcome. MJP and NSH contributed to the Sensewear Armband data analysis. MJP, MB, CB, CJWS, SSB, TMM, JAW, PC, NSH and AUW contributed to the analytical approach. PS and WB performed the statistical analysis. EAR wrote the manuscript with input from all authors.

Declaration of interests

EAR has received consultancy or speaker fees from Hoffman La Roche, Boehringer Ingelheim, and Mundipharma outside of the submitted work. TMM has, via his institution, received industry-academic funding from GlaxoSmithKline R&D and UCB and has received consultancy or speaker fees from Apellis, Astra Zeneca, aTyr Pharma, Bayer, Biogen Idec, Boehringer Ingelheim, Galapagos, GlaxoSmithKline R&D, Indalo, Pliant, ProMetic, Roche, Samumed and UCB. PLM and his employing institution has received speaker fees from Roche outside the remit of the submitted work. AMR reports grants and personal fees from Hoffman La Roche, outside the submitted work. PMG reports personal fees and other from Boehringer Ingelheim, personal fees and other from Roche Pharmaceuticals, outside the submitted work. SSB reports personal fees from Patara, other from Chiesi, personal fees from Novartis, other from Boehringer, outside the submitted work. MF and JW report grants from National Institute for Health Research (NIHR) Research for Patient Benefit, during the conduct of the study; MK reports personal fees from Roche, personal fees from Intermune, outside the submitted work. AUW reports lecture and/or advisory board fees from Boehringer Ingelheim, Roche, Bayer, outside the submitted work. The other authors declare no conflict of interest.

Acknowledgments

We would like to thank John Tayu Lee for his contribution to the study protocol. We would also like to thank the logistical support provided by the Royal Brompton Hospital Clinical Research Facility.

Table 1 Baseline characteristics of randomised patients

	O2 first N=41	No O2 first N=43	Total N=84
Female sex,N (%)	15 (36.6)	11 (25.6)	26 (30.95)
Age -yrs, mean (SD)	68.9 (11.4)	66.8 (9.5)	67.9 (1.4)
Body mass index, mean (SD)	28.5(5.1)	28.3 (4.6)	28.4 (4.8)
Smoking status, N (%)			
Ex-smoker	29 (70.7)	24 (55.8)	53 (63)
Lung function, mean (SD)			
FVC, % predicted	71.1 (18.9)	75.1 (19.5)	73.1 (19.2)
FEV1, % predicted	73.6 (21.0)	76.8 (19.4)	75.2 (20.2)
DLCO, % predicted	39.8 (10.2)	37.3 (8.2)	38.5 (9.3)
Composite Physiologic Index, mean (SD)	52.4 (9.1)	53.5 (7.7)	52.9 (8.4)
Screening 6MWT on air			
Distance meters, mean (SD)	377.1 (122)	367.7 (104.7)	372.4 (113.0)
SpO2, mean (SD)	84.4 (4.1)	85.7 (3.5)	85.1 (3.9)
Dilated RV on echo, N (%)	6/38 (15.8)	4/40 (10)	10 /78 (12.8)
BNP (ng/L), median (IQR)	38 (24 - 61)	29 (17 - 50)	34 (20 - 57)
IPF, N (%)	23 (56.1)	26 (60.5)	49 (58.3)
KBILD baseline total score, mean (SD)	51.2 (8.4)	49.7 (13.4)	50.5 (11.2)
Breathlessness	33.8 (13.6)	34.9 (18.8)	34.4 (16.3)
Chest symptoms	57.4 (16.6)	55.3 (22.8)	56.3 (19.9)
Psychological	52.1 (10.8)	48.1 (16.7)	50.1 (14.1)
SGRQ total score, mean (SD)	50.8 (15.1)	51.9 (18.1)	51.4 (16.6)
Symptoms	55.2 (21.9)	56.6 (21.4)	55.9 (21.5)
Activity	69.0 (16.3)	66.6 (19.2)	67.8 (17.8)
Impact	38.7 (18.1)	41.7 (20.6)	40.2 (19.3)
UC-SDSOBQ score, mean (SD)	51.5 (21.2)	48.8 (24.5)	50.1(22.8)
HDAS anxiety, N (%)	9 (22)	15 (34.9)	24 (28.6)
HDAS depression, N (%)	7 (17.1)	13 (30.2)	20 (23.8)

Data are mean (SD), N (%), or median (IQR) unless otherwise specified.

6MWT= six-minute walk test. SpO2= peripheral transcutaneous oxygen saturation. RV= right ventricle. IPF= idiopathic pulmonary fibrosis- FVC=forced vital capacity (expressed as percent of predicted values). FEV1=forced expiratory volume in 1 second. DLCO=diffusing capacity of the lung for carbon monoxide. BNP= brain natriuretic peptide. KBLD=King's Brief Interstitial Lung Disease Questionnaire. UC-SDSOBQ= University of California Shortness of Breath Questionnaire. SGRQ=St George's respiratory Questionnaire. HADS:Hospital Anxiety and Depression Scale: N(%) of cases with anxiety and depression scores≥8 are presented (27;28)

Table 2. Effects of oxygen vs placebo air on 6-minute walk test parameters

	Oxygen	Placebo air	Difference between oxygen vs placebo air	P value
	Mean (SD)		Mean difference (95% C.I)	
SpO2, end of test	90.6 (5.7)	84.7 (4.7)	5.9 (4.8-7.0)	<0.0001
Min SpO2	88.9 (4.3)	82.9 (4.4)	5.9 (4.8-7.1)	<0.0001
Distance walked	373.2 (89.9)	354.7 (97.8)	18.5 (10.9-26.1)	0.001
Heart rate end of test	99.9 (14.3)	102 (18.3)	-2.2 (-4.9- to 0.6)	0.12
Max heart rate	104.4 (13.8)	108.9 (15)	-4.5 (-6.2 to -2.8)	0.01
SpO2 recovery time (s)	117 (101)	217.7 (124)	-101 (-129 to -73)	<0.0001
Heart rate recovery time	163.7 (138.7)	191.9 (145.3)	-28.2 (-67.9 to 11.5)	0.06
	Median (IQR)		Median difference (IQR)	
Borg dyspnoea score	2.1 (0.7 to 3.4)	3 (2.0 to 5.1)	-1.6 (-2.1 to -1.1)	<0.0001
Borg fatigue score	0.0 (0.0 to 1.4)	0.1 (0.0 to 2.6)	-0.4 (-1.1 to -0.2)	<0.0001
Borg dyspnoea score recovery time (s)	112 (72 to 164)	171 (114 to 229)	-49 (-99 to -1)	0.0008
Borg fatigue score recover time (s)	0 (0 to 82)	0 (0 to 174)	-14 (-64 to -0.5)	<0.0001

Data are presented as mean (SD), or median (IQR), as indicated. Differences between treatment with oxygen vs placebo air are presented as mean (95% C.I.) or median (IQR), as indicated.

SpO2= trans-cutaneous arterial oxygen saturation; s=seconds

Table 3a. Quality of life scores after two weeks on and two weeks off ambulatory oxygen

PRIMARY OUTCOME	On oxygen	No Oxygen	Mean between treatment difference	P value
K-BILD* (N=74)				
Total score	55.5 (13.8)	51.8 (13.6)	3.7 (1.8 to 5.6)	<0.0001
Breathlessness and Activities score	44.4 (22.6)	35.8 (20.4)	8.6 (4.7 to 12.5)	<0.0001
Chest Symptoms score	65.5 (25.2)	57.9 (29.2)	7.6 (1.9 to 13.2)	0.009
Psychological Symptoms score	55.2 (19.6)	52.8 (19.6)	2.4 (-0.6 to 5.5)	0.12

Data are adjusted mean (SD) and mean difference (95% CI) for order of treatment KBLD=King's Brief Interstitial Lung Disease Questionnaire. *Higher scores reflect better quality of life. Recently reported minimal clinically important difference estimates for the KBILD scores are: total score: 4 (range 3.7-4.2); breathlessness and activities: 6 (5.6 – 6.5); psychological: 5.4 (4.6-6.9). and chest symptoms: 0.5SD:8.9 (34)

Table 3b. Shortness of breath and quality of life scores after two weeks on and two weeks off ambulatory oxygen

	Oxygen	No Oxygen	Mean between treatment difference	P value
UCSD-SOBQ * (N=72)				
Total score	41.0 (30.5)	49.1 (34.1)	-8.0 (-12.4 to -3.6)	<0.0001
SGRQ * (N=72)				
Total score	48.7 (25.3)	52.4 (25.0)	-3.6 (-6.7 to -0.6)	0.018
Activity score	61.5 (27.3)	68.9 (25.2)	-7.5 (-12.4 to -2.5)	0.003
Symptoms score	53.3 (30.7)	54.9 (31.9)	-1.7 (-6.6 to 3.3)	0.51
Impacts score	39.7 (28.6)	41.8 (28.8)	-2.1 (-5.6 to 1.3)	0.22

Data are adjusted mean (SD) and mean difference (95% CI) for order of treatment except otherwise stated. KBLD=King's Brief Interstitial Lung Disease Questionnaire. UCSD SOBQ= University of California San Diego Shortness of Breath Questionnaire. SGRQ=St George's Respiratory Questionnaire.

* Lower scores reflect better quality of life

Table 3c. Anxiety and depression scores after two weeks on and two weeks off ambulatory oxygen

HADS (N=70)	Oxygen	No Oxygen	OR (95% C.I.)	P value
HADS anxiety score≥ 8 N (%)	**16 (22.9)**	**18 (25.7)**	**0.6 (0.14-2.5)**	**0.47**
HADS depression score ≥8, N (%)	**10 (14.3)**	**18 (25.7)**	**0.14 (0.02-1.16)**	**0.14**

N (%) of cases with anxiety and depression scores≥8. OR (95% C.I)= Odds Ratio, conditional logistic regression.

Table 4. Relationship between baseline clinical parameters and patient decision to continue on O2 at the end of trial.

	Decision to Continue O2 (N=51)	Decision not to continue O2 (N=25)	OR (95%CI	P value *
Age	64.8 (10.3)	73.0 (8.6)	0.89 (0.83-0.96)	0.002
Males (%)	34 (66.7%)	17 (68%)	0.94 (0.34-2.6)	0.91
Ex-smokers	28 (55%)	19 (76%)	0.62 (0.36-1.06)	0.08
BMI	29.0 (5.2)	27.8 (4.3)	1.05 (0.95-1.17)	0.31
IPF (%)	26 (51%)	18 (72%)	0.52 (0.19-1.45)	0.22
FVC % predicted	68.2 (18.5)	83.6 (16.5)	0.95 (0.92-0.98)	0.003
FEV1 % predicted	70.8 (19.9)	84.6 (18.5)	0.96 (0.94-0.99)	0.011
DLCO % predicted	37.3 (9.1)	40.54 (9.8)	0.96 (0.91-1.02)	0.17
KCO % predicted	74.4 (16.4)	68.1 (15.5)	1.02 (0.99-1.06)	0.12
CPI	54.9 (8.4)	49.1 (7.1)	1.1 (1.03 -1.17)	0.008
BNP levels (ng/L)	31 (20.25 - 50)	40 (19.25 - 66.5)	0.99 (0.99-1.01)	0.59

* Logistic regression, univariable analysis. Data are mean (SD), median (IQR), or N (%).

Table 5 Relationship between primary and major secondary outcomes and the decision to continue on O2

Change in outcome variables on O2 (adjusted for order of treatment)	Decision to Continue O2 (N=51)	Decision not to continue O2 (N=25)	OR (95% C.I.)	P value*
K-BILD total change	3.7 (6.5)	1.5 (4.8)	1.06 (0.98 to 1.17)	0.16
K-BILD breathlessness change	9.7 (13.4)	3.4 (8.3)	1.05 (1.002 to 1.097)	0.04
K-BILD chest symptoms change	7.1 (17.2)	2.8 (18.9)	1.01 (0.99 to1.04)	0.35
K-BILD psychological change	2.8 (9.0)	0.13 (10.5)	1.03 (0.98 to 1.09)	0.27
San Diego SOBQ	-5.9 (141.1)	-1.1 (13.9)	0.97 (0.94 to 1.01)	0.18
Global change breathlessness (patient reported)	1.1 (0.6)	0.48 (0.7)	4.1 (1.8 to 9.4)	0.001
Global change walking ability (patient reported)	1.08 (0.7)	0.52 (0.8)	3.2 (1.5 to 6.9)	0.003
SGRQ total change	-2.4 (10.2)	-2.8 (7.4)	1.01 (0.95 to 1.06)	0.85
SGRQ chest symptoms	-0.7 (14.3)	-3.3 (17.1)	1.01 (0.98 to 1.05)	0.50
SGRQ activity	-4.5 (16.8)	-6.71 (12.9)	1.01 (0.98 to 1.04)	0.56
SGRQ impact	-1.4 (11.7)	-1.4 (8.1)	1.00 (0.96 to 1.05)	0.95
HADS anxiety change	-0.83 (2.4)	-0.33 (1.9)	0.92 (0.72 to 1.17)	0.49
HADS depression change	-0.7 (2.5)	-0.42 (1.4)	0.96 (0.76 to 1.22)	0.65

*Logistic regression, univariable analysis, OR=Odds Ratio; data are mean (SD)

Table 6 Illustrative patient quotes for the themes derived from qualitative interviews

Theme	Illustrative quote	Patient
Attitudes to using ambulatory oxygen	"*Initially I thought 'it is going to be strange'…a bit self-conscious with tubes hanging out of your nose and face and having to carry it around but I had got to the stage where in my job I was so incapacitated. I was beginning to think that I was going to have to leave my job and that would have broken my heart and when I got the oxygen all of a sudden it has all changed. I can do what I used to do. I can walk up the stairs and talk to somebody when I get to the top. I can even sit and sing now, I couldn't sing for ages.*	Patient 09, male, 62 years
	"*I only went on the oxygen because of this trial. I didn't want it to be honest with you. It frightened me. No, I didn't like the idea of it, but I thought because I am getting more attention, better help, I will give it a go.*"	Patient 17, female, 54 years
Benefits of ambulatory oxygen	"*Freedom. Being able to do things I haven't been able to do for such a long time. It made me feel less tired. It made me feel less breathless. My cough wasn't so bad. I could do things without having to stop. It taught me how much this disease has stopped me from doing things. It's not because I don't want to do them, I'd love to do them, and it's the fact that I physically, because of the breathlessness, can't do it."*	Patient 20, female, 52 years
	"It was definitely helpful because when I am normally hoovering I have to take it steady or perhaps stop for a couple of minutes, then I carry on and do it. With oxygen I could just do the whole lot."	Patient 18, male, 70 years
Use of ambulatory oxygen indoors	*"Playing with the grand kids is the same. I can carry on with it before I would not have been able to do very much…breathing is a lot easier."*	Patient 08, male, 70 years
Use of ambulatory oxygen outdoors	"*If I was digging I would have to stop after ten minutes to have a breather but with oxygen I could carry on and carry on."*	Patient 08, male, 70 years
	"I didn't cough quite as much and gasp for breath and I did go out more whereas when I'm not on oxygen I tend to avoid going out."	Patient 21, female, 65 years
Challenges of using ambulatory oxygen	*"Although you are benefiting from the oxygen, having to carry a heavy cylinder kind of defeats the object a little bit."*	Patient 02, male, 57 years
	"I had to have a full health and safety risk assessment before I was allowed to take it into work, then every time I left the office, I had to take the oxygen with me – so that was very difficult."	Patient 10, female, 52 years
	"*I just felt embarrassed for having these tubes running up my nose and from a tank on my back. If it was a pill nobody notices it, but with a cylinder on your back and a plastic tube up your nose it is much more visible*."	Patient 16, male, 69 years
	"*End of the road, you get the oxygen and you think because the last eight years I never had oxygen but then, all of a sudden, you get the oxygen and you feel 'is it time? Is it time I am going to go?' It is that feeling.*"	Patient 03, male, 68 years
Supply of ambulatory oxygen	*"The first day the oxygen arrived to the house I felt terrible. I was expecting one bottle of oxygen, he brought eight […] it knocked me back a bit."*	Patient 03, male, 68 years
	"It was good, they gave me leaflets to explain everything and they explained as well. They explained everything: how to use it and if any problems call them."	Patient 11, male, 53 years
Support given	*"Research co-ordinator has been very good and has explained everything, she has been wonderful."*	Patient 05, female, 69 years

Figure 1.

Figure 2.

Figure 3.

Figure 4.

Figure Legends

Figure 1: Trial Flow Diagram. After a two-week run in period, patients were randomised to each arm of the study (ambulatory oxygen or no oxygen). On the same day of randomisation, two 6MWTs were performed, on oxygen and on placebo air, in random order, with a separate randomisation list. After two weeks, patients crossed over to the alternative arm for a further two weeks. At each visit patients filled in all the required questionnaires. At the crossover and end visit, patients handed in the Sensewear Armbands. At the end of the trial, a subgroup of patients and carers underwent qualitative interviews.

Abbreviations: 6MWT= 6-minute walking test, SaO2= oxygen saturation, KBILD= King's Brief Interstitial Lung Disease questionnaire, SGRQ= St George's Respiratory Questionnaire, SDSBQ= San Diego Shortness of Breath Questionnaire, HDAS= Hospital Anxiety and Depression Scale, SAB= Sensewear Armband.

Figure 2. Trial profile. The serious adverse events are listed in the supplementary file (page 9).

Figure 3. Mean Difference (red circles – error bars are 95% CI) adjusted for order of treatment in K-BILD subdomains (Breathlessness and Activities, Chest Symptoms, Psychological Symptoms) and K-BILD total score, between ambulatory oxygen and no oxygen.

Figure 4. Numbers of patients reporting: improved-same-worse breathlessness and walking ability at the end of the two weeks on ambulatory oxygen (blue) vs no oxygen (green). The wording of the questions is provided in the supplementary file (page 3).

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Supplementary file:

Inclusion criteria

- A diagnosis of fibrotic lung disease, including idiopathic pulmonary fibrosis, fibrotic non-specific interstitial pneumonia, fibrotic hypersensitivity pneumonitis, fibrotic organising pneumonia and non-classifiable fibrotic ILD. Patients with fibrotic sarcoidosis or CTD-associated fibrotic ILD were included provided there was no significant musculo-skeletal involvement.
- Patients whose oxygen saturation (SaO2) at rest on room air was ≥94% and fell ≤ 88% on a baseline 6MWT.
- Patients with stable symptoms (no changes in medications and no chest infections) and treatment during the period of four weeks prior to being randomised into the study, including the two week run in period.

Exclusion criteria

- Age <18 or >99 years
- Patients expected to change treatment over the time course of the study
- Patients hypoxic at rest (Oxygen Saturation at rest on room air <94%)
- Patients with significant communication or other locomotor difficulties, and/or severe co-morbidities
- Patients with musculoskeletal/joint involvement/symptoms
- Current smokers
- Pregnant women
- Recent history of symptomatic ischaemic cardiac disease (exertion-induced chest pain)
- Anaemia, Hb < 9g/dl
- Unable to provide informed written consent

Supplementary Table 1. Oxygen Companies

Oxygen company	Light cylinder weight	Number of patients
Air Liquide (North and South London, North and South West England, East Midlands)	2.23kg	44
Baywater (Yorkshire and Humberside, West Midlands and Wales)	2.1 kg	3
BOC (Eastern England and North East)	1.8 kg	4
Dolby Vivisol (South Central England and South East Coast)	2.2 kg	25