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Complete List of Authors:	Holland, Anne E.; Alfred Health, Physiotherapy; Monash University, Allergy, Immunology and Respiratory Medicine Corte, Tamera; Royal Prince Alfred Hospital, Respiratory Medicine; The University of Sydney, Central Clinical School Chambers, Daniel; The University of Queensland, Clinical Medicine; The Prince Charles Hospital, Queensland Lung Transplant Service Palmer, Andrew; University of Tasmania, Menzies Institute for Medical Research; The University of Melbourne, School of Population and Global Health Ekström, Magnus; Lunds Universitet, Glaspole, Ian; Alfred Health, Respiratory and Sleep Medicine; Monash University, Allergy, Immunology and Respiratory Medicine Goh, Nicole; Austin Health, Respiratory and Sleep Medicine; Institute for Breathing and Sleep Hepworth, Graham; The University of Melbourne, Statistical Consulting Centre Khor, Yet; Austin Health, Respiratory and Sleep Medicine; Institute for Breathing and Sleep Hoffman, Mariana; Monash University, Allergy, Immunology and Respiratory Medicine Vlahos, Ross; RMIT University, School of Health and Biomedical Sciences Skold, Magnus; Karolinska Institute, Respiratory Medicine; Karolinska University Hospital, Respiratory Medicine and Allergy Dowman, Leona; Monash University, Allergy, Immunology and Respiratory Medicine; Austin Health, Physiotherapy Troy, Lauren; Royal Prince Alfred Hospital, Respiratory Medicine; The University of Sydney, Central Clinical School Prasad, Jyotika; Alfred Health, Respiratory and Sleep Medicine; Royal Melbourne Hospital, Respiratory Medicine Walsh, James; The Prince Charles Hospital, Physiotherapy McDonald, Christine; Austin Health, Respiratory and Sleep Medicine; Institute for Breathing and Sleep
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Pulmonary Fibrosis ambulatory OXygen (PFOX) trial: protocol for a randomized controlled trial

Anne E Holland[1,2,3,4], Tamera Corte[4,5,6], Daniel C Chambers[4,7,8], Andrew Palmer[4,9,10], Magnus Ekström[11], Ian Glaspole[1,4,12], Nicole SL Goh[3,13,14], Graham Hepworth[15], Yet H Khor[3,12,13,14], Mariana Hoffman[1], Ross Vlahos[16], Magnus Sköld[17,18], Leona Dowman[1,3,19], Lauren K Troy[5,6], Jyotika D Prasad[12,20], James Walsh[21], Christine F McDonald[3,13,14]

[1]Department of Allergy, Immunology and Respiratory Medicine, Monash University, Melbourne, Australia

[2] Department of Physiotherapy, Alfred Health, Melbourne, Australia

[3] Institute for Breathing and Sleep, Melbourne, Australia

[4]NHMRC Centre of Research Excellence in Pulmonary Fibrosis, Australia

[5]The University of Sydney Central Clinical School, Sydney, NSW, Australia

[6]Department of Respiratory Medicine, Royal Prince Alfred Hospital, Sydney, NSW, Australia

[7]School of Clinical Medicine, The University of Queensland, Brisbane, Australia

[8]Queensland Lung Transplant Service, The Prince Charles Hospital, Brisbane, Australia

[9]Health Economics Research Group, Menzies Institute for Medical Research, The University of Tasmania, Hobart, Tasmania, Australia

[10]Centre for Health Policy, School of Population and Global Health, The University of Melbourne, Melbourne, Victoria, Australia

[11]Respiratory Medicine and Allergology, Department of Clinical Sciences, Faculty of Medicine, Lund University, Lund, Sweden

[12]Department of Respiratory and Sleep Medicine, Alfred Health, Melbourne, VIC, Australia

[13]Faculty of Medicine, University of Melbourne, Melbourne, Australia

[14]Department of Respiratory and Sleep Medicine, Austin Health, Melbourne, Australia

[15]Statistical Consulting Centre, University of Melbourne, Melbourne, Australia

[16]School of Health and Biomedical Sciences, RMIT University, Bundoora, Australia

[17]Respiratory Medicine Unit, Department of Medicine Solna and Center for Molecular Medicine, Karolinska Institutet, Stockholm, Sweden

[18]Department of Respiratory Medicine and Allergy, Karolinska University Hospital, Stockholm, Sweden

[19]Department of Physiotherapy, Austin Health, Melbourne, Australia

[20]Department of Respiratory Medicine, Royal Melbourne Hospital, Melbourne, Australia

[21] Physiotherapy Department, The Prince Charles Hospital, Brisbane, Australia

Corresponding author:

Anne E Holland

Central Clinical School, Monash University

99 Commercial Rd Melbourne Victoria Australia 3004

a.holland@alfred.org.au

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Abstract

Introduction: Interstitial lung diseases are characterized by scarring of lung tissue that leads to reduced transfer of oxygen into the blood, decreased exercise capacity and premature death. Ambulatory oxygen therapy may be used to treat exertional oxyhaemoglobin desaturation, but there is little evidence to support its efficacy and there is wide variation in clinical practice. This study aims to compare the clinical efficacy and cost-effectiveness of ambulatory oxygen versus ambulatory air in people with fibrotic interstitial lung disease and exertional desaturation.

Methods and analysis: A randomised, controlled trial with blinding of participants, clinicians and researchers will be conducted at trial sites in Australia and Sweden. Eligible participants will be randomised 1:1 into two groups. Intervention participants will receive ambulatory oxygen therapy using a portable oxygen concentrator (POC) during daily activities and control participants will use an identical POC modified to deliver air. Outcomes will be assessed at baseline, 3 months and 6 months. The primary outcome is change in physical activity measured by number of steps per day using a physical activity monitor (StepWatch). Secondary outcomes are functional capacity (six-minute walk distance), health-related quality of life (St. George Respiratory Questionnaire, EQ-5D-5L and K-BILD), breathlessness (Dyspnoea-12), fatigue (Fatigue Severity Scale), anxiety and depression (HADS), physical activity level (GENEActive), oxygen saturation in daily life, POC usage, and plasma markers of skeletal muscle metabolism, systematic inflammation and oxidative stress. A cost-effectiveness evaluation will also be undertaken.

Ethics and dissemination: Ethical approval has been granted in Australia by Alfred Hospital Human Research Ethics Committee (HREC/18/Alfred/42) with governance approval at all Australian sites, and in Sweden (Lund Dnr: 2019-02963). The results will be published in peer-reviewed scientific journals, presented at conferences, and disseminated to consumers in publications for lay audiences.

Trial registration number clinicaltrials.gov NCT03737409.

Keywords: Interstitial Lung Diseases; Pulmonary Fibrosis; Oxygen Therapy; Physical Activity

Protocol version: 3

Strengths and limitations of this study

- This multi-site randomised controlled trial will recruit participants with fibrotic interstitial lung disease (fILD) from six centres in two countries.
- The control group will receive ambulatory oxygen using a sham portable concentrator, identical to the device used by the intervention group except that it will deliver air rather than oxygen, thus allowing effective blinding of participants, health professionals and researchers.
- The primary outcome is physical activity in daily life, an outcome that is meaningful to people living with fILD, and the study includes a comprehensive economic analysis to inform future funding and policy decisions.
- Participants will be followed for six months, so longer-term outcomes of ambulatory oxygen will not be evaluated.
- It is possible that portable concentrators may not meet the oxygen needs of patients with severe exertional desaturation or rapidly progressive disease, requiring transition to other devices or to long-term oxygen therapy during the trial.

Background

The interstitial lung diseases (ILDs) are a group of over 200 debilitating conditions characterized by scarring of lung tissue. Stiffening of the lungs leads to reduced transfer of oxygen into the blood, decreased exercise capacity and premature death. One of the most common types of ILD is idiopathic pulmonary fibrosis (IPF), which confers a particularly poor prognosis, but there are a range of other chronic fibrosing ILDs (fILD) that are characterised by similar biological and clinical features.[1] Exertional desaturation (low oxygen levels on exertion) is a key feature of fILD, predicting poor outcomes including pulmonary hypertension[2] [3] and increased mortality.[4] Exertional desaturation is also associated with reduced physical activity in daily life.[5] The relationship of exertional desaturation to poor outcomes provides a rationale for correction of oxygen levels during exercise, to improve both daily functioning and long-term prognosis.

Ambulatory oxygen therapy, defined as the use of supplemental oxygen during exercise and activities of daily living, has historically been used to optimise oxygen saturation and exercise capacity[6] and is sometimes used to correct exertional desaturation. Access to ambulatory oxygen therapy varies across the world[7-9] and recommendations regarding ambulatory oxygen therapy in international clinical guidelines are contradictory,[6] [10] reflecting a lack of robust science to guide policy and practice. We have previously shown that ambulatory oxygen therapy may improve oxygen delivery to skeletal muscle,[11] providing a potential mechanism by which oxygen therapy could improve exercise capacity and daily physical activity, outcomes that are strongly linked to health-related quality of life (HRQL) and survival.[5] [12] However, our systematic review found no parallel-group randomised controlled trials of ambulatory oxygen therapy for fILD.[13] Recently, a crossover trial with a 2-week treatment period demonstrated that ambulatory oxygen increased quality of life in people with fILD.[14] However, the study was unblinded, and longer-term outcomes beyond two weeks are unknown.

A key issue affecting trials of oxygen therapy is adherence to treatment. Ambulatory oxygen therapy has traditionally been delivered using portable cylinders, which are heavy and awkward to transport. In a randomised controlled trial of ambulatory oxygen therapy conducted in patients with obstructive lung disease[15] the use of cylinder gas averaged just 40 minutes per day in both groups. Portable oxygen concentrators (POCs) have emerged as a potential solution to the problems of finite cylinder life and poor transportability. A concentrator is constantly extracting oxygen from air, so oxygen supply continues as long as the battery is charged. During exercise testing, ambulatory oxygen therapy delivered using a POC had similar effects to a standard portable cylinder and was preferred by patients.[16] The POC provides the opportunity to deliver a robust sham treatment to a control group, as it can be modified to deliver air and thus ensure blinding of participants, health professionals and investigators. However, whether a POC can effectively deliver ambulatory oxygen therapy in daily life for patients with fILD is unknown.

People living with fILD have identified the 'reduction in bureaucratic barriers to oxygen provision' as a major unmet medical need,[17] highlighting the importance of this treatment to patients. However, the burdens of ambulatory oxygen therapy are also well described. Whilst some people with fILD reported that ambulatory oxygen therapy improved their confidence and feeling of control, this was offset by the embarrassment and stigma associated with oxygen use.[18 19] Some reported unmet expectations for symptom relief from ambulatory oxygen therapy, although most felt it helped them to be more active.[19] Oxygen therapy is a key driver of outpatient costs for fILD,[20] but at present there are no data to confirm whether ambulatory oxygen therapy conveys improvements in patient-centred outcomes that outweigh the costs to patients, the health care system and society.

We hypothesise that (1) ambulatory oxygen therapy delivered using a POC will provide clinically significant improvements in physical activity (primary outcome), symptoms and

health-related quality of life; and (2) ambulatory oxygen therapy via POC will be cost-effective compared to ambulatory air.

Methods and analysis

Design: A randomised controlled superiority trial, with blinding of participants, clinicians and researchers, in 260 people with fILD who desaturate during walking. The trial will be conducted in Australia and Sweden, with trial sites detailed on the study registration at clinicaltrials.gov. Participants will be randomised 1:1 into two groups: Group 1: Ambulatory oxygen therapy using a POC (oxygen group), Group 2: Sham therapy using an identical POC (air group). The allocated treatment will be delivered for 6 months. We have previously demonstrated the feasibility of the trial methodology in a pilot study.[21] Figure 1 shows the participant flow through the trial. The overview of the study procedures follows the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist[22] (online supplementary file 1).

Participants: People with fILD who receive their care at the study sites will be invited to participate. Patients will be eligible for inclusion if they are (1) aged 18 years and over; (2) have a physician confirmed diagnosis of fibrosing ILD, such as idiopathic pulmonary fibrosis, connective tissue disease (CTD)-associated ILD, fibrotic hypersensitivity pneumonitis (HP), idiopathic non-specific interstitial pneumonia (iNSIP), unclassifiable idiopathic interstitial pneumonia (IIP), environmental/ occupational lung disease or sarcoidosis, with features of diffuse fibrosing lung disease of >10% extent on high-resolution computed tomography (HRCT), with ILD being the predominant pathologic process;[23] (3) have had stable pharmacotherapy over the last 3 months; and (4) exhibit exertional desaturation, defined as $SpO_2 \leq 88\%$ for at least 10 consecutive seconds during a 6-minute walk test (6MWT) performed on room air. Only fILD will be included as these conditions are often characterised by chronic progressive fibrosis, as opposed to other ILDs with differing pathophysiology (e.g.

inflammatory or granulomatous) where different mechanisms may underlie exertional desaturation.

Participants will be excluded if they: (1) are currently using or eligible for long-term oxygen therapy (LTOT), with eligibility defined as $PaO_2 \leq 55$mmHg at rest on room air, or 56-59mmHg with evidence of right heart failure[10] as it is not ethical to withhold oxygen therapy in this group for whom it is strongly recommended;[24] (2) are current smokers, due to the risk of oxygen use near flames; (3) have predominantly obstructive lung disease, with forced expiratory ratio (FER) less than the lower limit of normal; (4) are pregnant; (5) are cognitively unable to consent; (6) are non-ambulant; (7) have been admitted to an acute care hospital within the last 30 days; or (8) if death or transplant is anticipated within the study period. Participants currently participating in pulmonary rehabilitation will not be enrolled, and participation in pulmonary rehabilitation during the 6-month trial period will be avoided where possible, as this may impact on both primary and secondary outcomes.

Recruitment: Potential participants will be identified by their treating health care team. If the participant is interested in obtaining more detailed information they will be contacted by the trial coordinator or site coordinator, who is not in a dependent relationship with the patient and will provide further information. Patients will be informed that participation in the study is voluntary, their decision about participation will not affect their treatment or relationship with their health care team, their data will be held securely and they will not be identified in any study publications. Only patients who provide written, informed consent will undertake the study procedures outlined in this protocol.

Patient and public involvement: We interviewed patients with fILD and physicians who cared for them, in order to understand experiences and role of oxygen therapy.[7 19] Patients emphasised the need for oxygen devices that were lighter and easier to use. Our subsequent work showed that patients preferred using a POC over traditional oxygen cylinders.[16] In our feasibility trial we interviewed participants about their experiences of trial participation.

Participants expressed positive experiences of the study and stated they would recommend such trial participation to others with ILD.[21] These experiences underpinned the design of the protocol for the current trial.

Randomisation: Participants will be randomly allocated to groups using a computer generated, permuted block randomisation schedule with stratification for (i) desaturation during 6MWT (<80% vs ≥80%) as this is a powerful predictor of physical activity, health-related quality of life and mortality[4 5 25] and (ii) site of recruitment. Sequence generation will be performed by an individual independent of the research team and the allocation sequence will be concealed using a secure online randomisation service. At the conclusion of the trial, participants will be asked two questions to evaluate the success of blinding: (1) Which treatment do you think you were receiving, oxygen or air? and (2) Did you have your own pulse oximeter at home over the last 6 months? If yes, how did you use it?

Interventions: All participants will be informed that the aim of using a POC is to assist them to be more active, with fewer symptoms. They will be encouraged to use the POC at all times when they are moving about, including walking at home or in the community, during exercise or during other activities. The POC should not be used when sitting still or sleeping. Written and verbal education will be provided. Participants will be encouraged to use their allocated POC during physical activity for the 6-month study period. Informed by our pilot study, the Inogen One G3 HF POC will be used at its maximum flow setting of 5 for both groups, as this delivered similar oxygen saturation during walking to a portable cylinder delivering 5L/min of oxygen on continuous flow.[16]

All participants will be contacted monthly by telephone by a blinded investigator to encourage POC use and answer any questions. These calls will also collect adverse events and health care utilisation data for economic analyses and information on concurrent therapies. It is likely that some participants will commence LTOT during the 6-month study period. This will occur if participants meet the usual LTOT eligibility criteria[10] and it is recommended by their treating

physician. Upon commencement of LTOT the participant will cease using the allocated POC. The number of participants in each group who commence LTOT will be recorded, outcome measures will be collected as per the trial protocol and data will be analysed according to allocated treatment group, as per intention to treat principles. Similarly, if a participant deteriorates during the 6-month study period then they may commence new/additional pharmacotherapies at their physician's discretion. The number of participants in each group who commence new pharmacotherapies and their nature will be recorded, outcome measures will be collected as per the trial protocol and data will be analysed according to allocated treatment group, as per intention to treat principles. The hours of usage downloaded from POC flash memory will be evaluated every three months. Reason for cessation of therapy will be recorded where relevant (patient request, commencement of LTOT, other).

Blinding: Participants, clinicians and researchers will be blinded to group allocation. The Inogen One G3 HF POCs for ambulatory oxygen therapy and air groups will be identical and coded by the distributor, who will not be involved in trial conduct. We successfully used this system to maintain blinding in a previous trial using gas cylinders in COPD.[15] The intervention code will only be available to the randomisation centre. All participants will be advised against measuring oxygen saturation at home during the duration of the trial, as this does not represent usual clinical practice in any of the centres and may unblind the participants.

Outcome measures: Outcome measures will be collected at baseline, 3 and 6-months following randomisation (Table 1), by an assessor who is blinded to group allocation. Three months were selected as this is sufficient to achieve change in the primary outcome[26] and 6 months will provide robust data for economic analyses.

The primary outcome is change in physical activity, measured by the number of steps per day. Steps per day is an objective measure of physical activity in people with fILD that has strong relationships to respiratory function, exercise capacity, exertional desaturation, HRQL and fatigue.[5 12] Physical inactivity, defined as less than 3300 steps per day, is associated with poor

survival (30% vs 70% over 3 years).[5] Steps per day is responsive to changes following non-pharmacological interventions in chronic lung disease[26] and the minimal important difference (MID) has been defined as 599 steps.[27] Steps per day is a direct measure of how a patient functions in daily life and thus fulfils the criteria for meaningful endpoints in fILD clinical trials.[28] Steps per day will be measured using the StepWatch activity monitor (SAM) (Modus Health, Washington DC, USA) which is reliable and valid in chronic lung disease.[29] It accurately detects slow walking speeds and is sensitive to small changes in step rate.[30] The SAM will be worn on the ankle continuously for seven days (except for bathing) following the baseline appointment, and then for 7 days following the 3 month and 6-month assessments. Seven days of monitoring is required for optimum reliability.[29]

Secondary Outcomes are change in functional exercise capacity, HRQL, breathlessness, fatigue, anxiety, depression, time spent in moderate to vigorous physical activity, sedentary time, oxygen saturation in daily life, and plasma markers of skeletal muscle metabolism, systemic inflammation and oxidative stress.

Functional exercise capacity will be measured with the 6-minute walk distance[31] which is responsive to change with acute administration of oxygen[13] and is a strong predictor of survival in fILD.[32] The 6MWT will be performed according to international standards, including performance of 2 tests at each time point to control for the known learning effect, with the best distance recorded.[31] All tests will be performed breathing room air. Health-related quality of life will be measured using three instruments: The St. George's Respiratory Questionnaire (SGRQ), a disease specific HRQL measure that is valid and responsive in fILD;[33] the EQ-5D-5L, a validated generic quality of life measure which is used to derive health utilities for economic analyses; and the K-BILD questionnaire, a validated disease-specific health status questionnaire.[14] The Dyspnoea-12 will be used to capture both the physical and affective components of breathlessness and is a reliable and valid questionnaire in fILD.[34] Fatigue will be measured with the Fatigue Severity Scale (FSS), a valid and sensitive questionnaire in

fILD.[35] Anxiety and depression will be evaluated using the Hospital Anxiety and Depression Scale (HADS), a validated and widely used tool for assessing psychological distress. Anxiety and depression are common in fILD and are increased in users of LTOT.[36] The GeneActiv (GENEActiv, Cambridgeshire, UK) will measure time spent in moderate to vigorous physical activity and sedentary time. This wrist-worn, tri-axial accelerometer has been validated in idiopathic pulmonary fibrosis.[37] Seven days of monitoring are required to accurately capture all activity intensities.[38] Oxygen saturation in daily life will be measured using a Nonin 3150 Wrist Oximeter. The wrist oximeter will be worn during waking hours on two consecutive weekdays. Examination of plasma markers of skeletal muscle metabolism (xanthine, hypoxanthine); systemic inflammation (interleukin-6, tumour necrosis factor-a, c-reactive protein); and oxidative stress (8-isoprostane, thiobarbiuric acid reactive substrates), as previously published [11] will be performed.

Health economic analyses: We will undertake a comparison of per person costs, including direct (health system) and indirect (personal) health care costs, of ambulatory oxygen therapy compared to air. Direct costs will include staff time, consumables, communications and overheads. Intervention costs will include staff inputs by duration, type and resource use (including troubleshooting and support) and equipment (POC and consumables). Personal costs will include transportation, travel time and impact of the intervention on the economic activities of other household members. Health system costs will include visits to the general practitioner, specialist or emergency department; use of chronic disease services; and hospitalisation. We will collect health care utilisation data from hospital records, Medicare Benefits Schedule - MBS and Pharmaceutical Benefits Scheme - PBS data (Australia) and the National Patient Registry of the Swedish Board of Health and Welfare, as well as directly from participants via monthly telephone calls. Sensitivity analyses will use different assumptions about personal healthcare costs across countries.

An incremental cost-effectiveness analysis will be undertaken to compare differences in costs with differences in: (a) Quality-adjusted life years (QALYs): a single preference-based utility score will be derived from the EQ-5D-5L. This will be converted to QALYs on the assumption that the duration of each status is exactly one half of the time between two measurement intervals[39] (b) The number of hospital admissions per enrolled person in the 6-month follow up period. The indicator will be the incremental cost of averting an additional hospitalisation.

Schedule of assessments: Outcomes will be obtained by a blinded assessor at baseline, 3 months and 6 months (Table 1). At the baseline visit, an arterial blood gas will be performed in participants with resting SpO_2<93% to exclude resting hypoxaemia, as this is an indication for LTOT. At each assessment two 6MWTs will be performed according to international standards with continuous pulse oximetry[31] whilst the participant breathes room air. The nadir oxyhaemoglobin from the longest 6MWT will be used to determine eligibility at baseline.[31] Questionnaires will be administered and blood for biomarkers will be obtained. The StepWatch and the GENEActiv activity monitors will be given to participants to wear over the following seven days and the Nonin 3150 Wrist Oximeter will be worn on two consecutive weekdays. The monitors will be returned to the investigators by post. Spirometry is performed every 6 months in usual care, to document disease progression. To minimize patient burden, we will not repeat this test separately for the trial.

Safety and adverse events: Adverse events will be defined according to Good Clinical Practice (GCP) guidelines. Adverse events of specific interest will be defined according to the criteria used in the recent Long-term Oxygen Treatment Trial (LOTT) trial: worsening of fILD (worsening of lung function, development of resting hypoxaemia); exacerbation of fILD; burns (from smoking whilst using a POC, using the POC around an open flame or equipment that sparks); nosebleed or dry nose; musculoskeletal injury from tripping on a POC; hospitalization; or death.[40] Adverse events will be identified during monthly telephone calls and 3-monthly

assessment visits, or by reports from the treating medical team. Participants who experience an adverse event will receive all necessary medical care from their local health care team.

Sample size: A total of 220 participants (110 per group) will provide 80% power to detect, at the two-sided 5% level, a clinically important difference between groups in the primary outcome of 599 steps per day.[27] This assumes a standard deviation (SD) of 1582 steps, based on physical activity data previously collected at our centre in 52 patients with fILD. Our previous trials had less than 10% attrition.[15 41] Previous experience suggests that 5% of participants could start LTOT (and cease POC use) over 6 months. We will therefore randomise 260 participants to ensure that 220 participants complete the study.

Over 1000 patients with fILD are currently managed at our centres, with an additional 300 new patients seen each year. Approximately half of these patients exhibit exertional desaturation and are not using LTOT.[42] Based on the rate of recruitment in our feasibility study[21] we anticipate recruiting the required sample of 260 participants over 3 years.

Analysis: Mean differences for continuous variables will be analysed using linear mixed models, controlling for baseline values as required. Generalized linear mixed models will be used for binary or count outcomes. Estimates will be presented with 95% confidence intervals, and two-sided p-values reported. Results will be displayed graphically where it will illuminate. All data will be analysed by intention to treat, including all randomised participants in the groups to which they were allocated, regardless of adherence.

Data integrity and management: Hardcopy data collection forms will be stored in a locked filing cabinet within a locked office, and electronic data will be stored in a purpose-built on-line database (www.adeptrs.com), with encryption and password protection. The online database will be protected by encryption enabled at up to 256-bits and SSL certificate, and hosted on a dedicated SSL cluster. No identifying information will be stored in the online database or on hardcopy data forms. Electronic data for all sites will be accessible by the principal investigator

and the trial coordinator. Site-specific investigators will only have access to data relating to their individual site. Information will be stored indefinitely, in accordance with Human Research Ethics Committees requirements for interventional studies.

Data monitoring: The Data Safety and Monitoring Committee (DSMB) will meet twice yearly, chaired by a respiratory physician who is independent of the study team and trial sites. The DSMB will include a biostatistician. The DSMB will report its findings to the trial steering committee, consisting of the chief investigators.

Ethics and dissemination

Ethical approval has been granted in Australia by Alfred Hospital Human Research Ethics Committee (HREC/18/Alfred/42) with governance approval at all Australian sites, and in Sweden (Lund Dnr: 2019-02963). The study will be conducted and reported according to the SPIRIT guidelines[22] and the CONSORT statement.[43] Results will be published in peer-reviewed journals and presented at conferences. We will also disseminate our results to people with fILD through lay publications and seminars.

Discussion

This study will recruit people with fILD who desaturate during walking, a group that represents half of all patients with fILD and over 85% of those with severe disease.[42] People with fILD experience distressing breathlessness, cough and fatigue; loss of independence and life roles; financial strain; and unpleasant treatment side effects.[44 45] Many have few treatment options. This multi-centre trial will examine the benefits and costs of ambulatory oxygen, delivered using a POC, in people with fILD and exertional desaturation. Recruitment across 6 sites and 2 countries will enhance external validity. Use of a sham POC allows effective blinding, a feature frequently missing from trials of oxygen therapy, thus substantially reducing the risk of bias. The primary outcome is steps per day, a direct measure of patient function in daily life.

The study also includes a comprehensive economic analysis, to inform future funding and policy decisions.

Recent years have brought a new sense of hope for people with fILD, with the advent of anti-fibrotic therapies that have revolutionised the approach to treatment.[46 47] However, this hope has been tempered by their lack of impact on patient-centred outcomes. Interventions that improve how people with fILD feel and function are urgently needed. Ambulatory oxygen is currently available to some patients with fILD, but patient access is inconsistent across health systems, reflecting the lack of evidence underpinning this treatment. For patients with fILD, ambulatory oxygen has potential benefits but also potential burdens.[19] This clinical trial will provide much-needed evidence to underpin decisions by health professionals and patients regarding prescription and ongoing use of ambulatory oxygen. If successful, the findings of this trial can be rapidly incorporated into clinical guidelines and implemented into clinical practice across the world.

Trial status: Recruitment commenced in July 2019.

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Authors' contributions:

AEH led the study design and funding application and, as chief investigator, has oversight for the trial. AEH and CFM conceived the original idea for the study. AEH and MH wrote the initial draft of the study protocol. TC, DC, AP, ME, IG, NSLG, GH, MS, LB and RV contributed to protocol development and refined the trial design. GH and AEH planned the statistical analyses. YHK, RV, LD, LT, JP and JW collected pilot data and contributed to selection of outcomes. All authors conducted the PFOX trial, critically revised the manuscript and approved the final version for publication.

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Table 1: Assessment schedule

Assessment/ Procedure	Enrolment	Baseline	Allocation	3-month follow-up	6-month follow-up
Informed Consent	x				
Randomization (oxygen or air group)			x		
Resting arterial blood gas (if SpO_2<93%)		x			
StepWatch activity monitor (for 7 days)		x		x	x
Physical activity level (GENEActiv) (for 7 days)		x		x	x
Oxygen saturation in daily life (for 2 days)		x		x	x
6-minute walk test		x		x	x
HRQL- SGRQ, K-BILD, EQ-5D-5L		x		x	x
Dyspnoea-12		x		x	x
Fatigue Severity questionnaire		x		x	x

Anxiety/Depression (HADS)		**x**		**x**	**x**
Biochemical analysis		**x**		**x**	**x**
Portable oxygen concentrator usage (hrs)				**x**	**x**
Patient telephone calls (Monthly)		**x**		**x**	**x**
Adverse events				**x**	**x**
Economic evaluation					**x**

HADS- Hospital Anxiety and Depression Scale; HRQL – health-related quality of life; K-BILD – King's Brief Interstitial Lung Disease questionnaire; SGRQ – St George's Respiratory Questionnaire; SpO_2 – oxyhaemoglobin saturation.

Figure 1. Study flow.

LTOT – long term oxygen therapy; SpO2 – oxyhaemoglobin saturation.

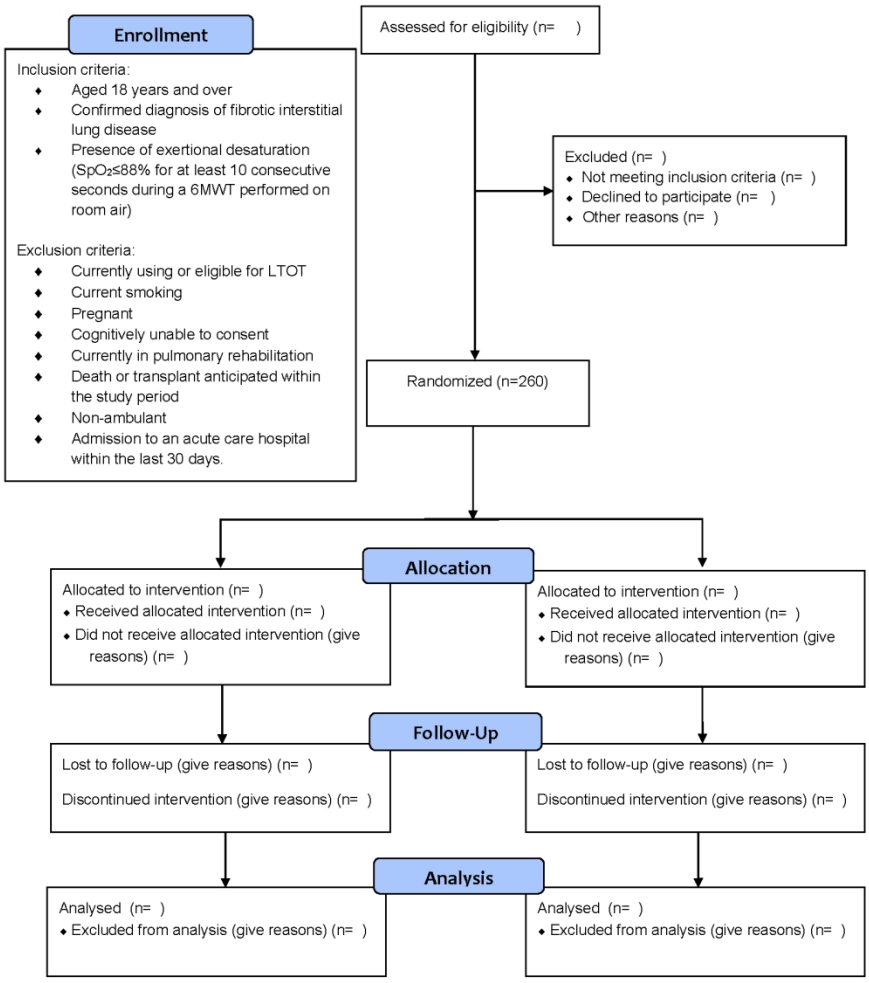

Figure 1. Study Flow.

215x279mm (200 x 200 DPI)

Supplementary file 1

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	3
Protocol version	3	Date and version identifier	3
Funding	4	Sources and types of financial, material, and other support	22
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	22
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	22
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	22
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-6
	6b	Explanation for choice of comparators	7
Objectives	7	Specific objectives or hypotheses	6

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7-8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-10
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	9-10
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	8-9
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9-10
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10-13
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	13
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	13-14
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	14
Methods: Assignment of interventions (for controlled trials)			

Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	9
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	10
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	13
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	14
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	14
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	14
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14

	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	14
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	14
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	14
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	13
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	13
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	13
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	14
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	22

Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	14
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	NA
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons “Attribution-NonCommercial-NoDerivs 3.0 Unported” license.

BMJ Open

Ambulatory oxygen for treatment of exertional hypoxaemia in pulmonary fibrosis (PFOX trial): a randomised controlled trial.

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Keywords:	Interstitial lung disease < THORACIC MEDICINE, Thoracic medicine < INTERNAL MEDICINE, Clinical trials < THERAPEUTICS

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Ambulatory oxygen for treatment of exertional hypoxaemia in pulmonary fibrosis (PFOX trial): a randomised controlled trial.

Anne E Holland[1,2,3,4], Tamera Corte[4,5,6], Daniel C Chambers[4,7,8], Andrew Palmer[4,9,10], Magnus Ekström[11], Ian Glaspole[1,4,12], Nicole SL Goh[3,13,14], Graham Hepworth[15], Yet H Khor[3,12,13,14], Mariana Hoffman[1], Ross Vlahos[16], Magnus Sköld[17,18], Leona Dowman[1,3,19], Lauren K Troy[5,6], Jyotika D Prasad[12,20], James Walsh[21], Christine F McDonald[3,13,14]

[1]Department of Allergy, Immunology and Respiratory Medicine, Monash University, Melbourne, Australia

[2] Department of Physiotherapy, Alfred Health, Melbourne, Australia

[3] Institute for Breathing and Sleep, Melbourne, Australia

[4]NHMRC Centre of Research Excellence in Pulmonary Fibrosis, Australia

[5]The University of Sydney Central Clinical School, Sydney, NSW, Australia

[6]Department of Respiratory Medicine, Royal Prince Alfred Hospital, Sydney, NSW, Australia

[7]School of Clinical Medicine, The University of Queensland, Brisbane, Australia

[8]Queensland Lung Transplant Service, The Prince Charles Hospital, Brisbane, Australia

[9]Health Economics Research Group, Menzies Institute for Medical Research, The University of Tasmania, Hobart, Tasmania, Australia

[10]Centre for Health Policy, School of Population and Global Health, The University of Melbourne, Melbourne, Victoria, Australia

[11]Respiratory Medicine and Allergology, Department of Clinical Sciences, Faculty of Medicine, Lund University, Lund, Sweden

[12]Department of Respiratory and Sleep Medicine, Alfred Health, Melbourne, VIC, Australia

[13]Faculty of Medicine, University of Melbourne, Melbourne, Australia

[14]Department of Respiratory and Sleep Medicine, Austin Health, Melbourne, Australia

[15]Statistical Consulting Centre, University of Melbourne, Melbourne, Australia

[16]School of Health and Biomedical Sciences, RMIT University, Bundoora, Australia

[17]Respiratory Medicine Unit, Department of Medicine Solna and Center for Molecular Medicine, Karolinska Institutet, Stockholm, Sweden

[18]Department of Respiratory Medicine and Allergy, Karolinska University Hospital, Stockholm, Sweden

[19]Department of Physiotherapy, Austin Health, Melbourne, Australia

[20]Department of Respiratory Medicine, Royal Melbourne Hospital, Melbourne, Australia

[21] Physiotherapy Department, The Prince Charles Hospital, Brisbane, Australia

Corresponding author:

Anne E Holland

Central Clinical School, Monash University

99 Commercial Rd Melbourne Victoria Australia 3004

a.holland@alfred.org.au

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Abstract

Introduction: Interstitial lung diseases are characterized by scarring of lung tissue that leads to reduced transfer of oxygen into the blood, decreased exercise capacity and premature death. Ambulatory oxygen therapy may be used to treat exertional oxyhaemoglobin desaturation, but there is little evidence to support its efficacy and there is wide variation in clinical practice. This study aims to compare the clinical efficacy and cost-effectiveness of ambulatory oxygen versus ambulatory air in people with fibrotic interstitial lung disease and exertional desaturation.

Methods and analysis: A randomised, controlled trial with blinding of participants, clinicians and researchers will be conducted at trial sites in Australia and Sweden. Eligible participants will be randomised 1:1 into two groups. Intervention participants will receive ambulatory oxygen therapy using a portable oxygen concentrator (POC) during daily activities and control participants will use an identical POC modified to deliver air. Outcomes will be assessed at baseline, 3 months and 6 months. The primary outcome is change in physical activity measured by number of steps per day using a physical activity monitor (StepWatch). Secondary outcomes are functional capacity (six-minute walk distance), health-related quality of life (St. George Respiratory Questionnaire, EQ-5D-5L and K-BILD), breathlessness (Dyspnoea-12), fatigue (Fatigue Severity Scale), anxiety and depression (HADS), physical activity level (GENEActive), oxygen saturation in daily life, POC usage, and plasma markers of skeletal muscle metabolism, systematic inflammation and oxidative stress. A cost-effectiveness evaluation will also be undertaken.

Ethics and dissemination: Ethical approval has been granted in Australia by Alfred Hospital Human Research Ethics Committee (HREC/18/Alfred/42) with governance approval at all Australian sites, and in Sweden (Lund Dnr: 2019-02963). The results will be published in peer-reviewed scientific journals, presented at conferences, and disseminated to consumers in publications for lay audiences.

Trial registration number clinicaltrials.gov NCT03737409.

Keywords: Interstitial Lung Diseases; Pulmonary Fibrosis; Oxygen Therapy; Physical Activity

Protocol version: 3

Strengths and limitations of this study

- This multi-site randomised controlled trial will recruit participants with fibrotic interstitial lung disease (fILD) from six centres in two countries.
- The control group will receive ambulatory oxygen using a sham portable concentrator, identical to the device used by the intervention group except that it will deliver air rather than oxygen, thus allowing effective blinding of participants, health professionals and researchers.
- The primary outcome is physical activity in daily life, an outcome that is meaningful to people living with fILD, and the study includes a comprehensive economic analysis to inform future funding and policy decisions.
- Participants will be followed for six months, so longer-term outcomes of ambulatory oxygen will not be evaluated.
- It is possible that portable concentrators may not meet the oxygen needs of patients with severe exertional desaturation or rapidly progressive disease, requiring transition to other devices or to long-term oxygen therapy during the trial.

Background

The interstitial lung diseases (ILDs) are a group of over 200 debilitating conditions characterized by scarring of lung tissue. Stiffening of the lungs leads to reduced transfer of oxygen into the blood, decreased exercise capacity and premature death. One of the most common types of ILD is idiopathic pulmonary fibrosis (IPF), which confers a particularly poor prognosis, but there are a range of other chronic fibrosing ILDs (fILD) that are characterised by similar biological and clinical features.[1] Exertional desaturation (low oxygen levels on exertion) is a key feature of fILD, predicting poor outcomes including pulmonary hypertension[2] [3] and increased mortality.[4] Exertional desaturation is also associated with reduced physical activity in daily life.[5] The relationship of exertional desaturation to poor outcomes provides a rationale for correction of oxygen levels during exercise, to improve both daily functioning and long-term prognosis.

Ambulatory oxygen therapy, defined as the use of supplemental oxygen during exercise and activities of daily living, has historically been used to optimise oxygen saturation and exercise capacity[6] and is sometimes used to correct exertional desaturation. Access to ambulatory oxygen therapy varies across the world[7-9] and recommendations regarding ambulatory oxygen therapy in international clinical guidelines are contradictory,[6] [10] reflecting a lack of robust science to guide policy and practice. We have previously shown that ambulatory oxygen therapy may improve oxygen delivery to skeletal muscle,[11] providing a potential mechanism by which oxygen therapy could improve exercise capacity and daily physical activity, outcomes that are strongly linked to health-related quality of life (HRQL) and survival.[5] [12] However, our systematic review found no parallel-group randomised controlled trials of ambulatory oxygen therapy for fILD.[13] Recently, a crossover trial with a 2-week treatment period demonstrated that ambulatory oxygen increased quality of life in people with fILD.[14] However, the study was unblinded, and longer-term outcomes beyond two weeks are unknown.

A key issue affecting trials of oxygen therapy is adherence to treatment. Ambulatory oxygen therapy has traditionally been delivered using portable cylinders, which are heavy and awkward to transport. In a randomised controlled trial of ambulatory oxygen therapy conducted in patients with obstructive lung disease[15] the use of cylinder gas averaged just 40 minutes per day in both groups. Portable oxygen concentrators (POCs) have emerged as a potential solution to the problems of finite cylinder life and poor transportability. A concentrator is constantly extracting oxygen from air, so oxygen supply continues as long as the battery is charged. During exercise testing, ambulatory oxygen therapy delivered using a POC had similar effects to a standard portable cylinder and was preferred by patients.[16] The POC provides the opportunity to deliver a robust sham treatment to a control group, as it can be modified to deliver air and thus ensure blinding of participants, health professionals and investigators. However, whether a POC can effectively deliver ambulatory oxygen therapy in daily life for patients with fILD is unknown.

People living with fILD have identified the 'reduction in bureaucratic barriers to oxygen provision' as a major unmet medical need,[17] highlighting the importance of this treatment to patients. However, the burdens of ambulatory oxygen therapy are also well described. Whilst some people with fILD reported that ambulatory oxygen therapy improved their confidence and feeling of control, this was offset by the embarrassment and stigma associated with oxygen use.[18 19] Some reported unmet expectations for symptom relief from ambulatory oxygen therapy, although most felt it helped them to be more active.[19] Oxygen therapy is a key driver of outpatient costs for fILD,[20] but at present there are no data to confirm whether ambulatory oxygen therapy conveys improvements in patient-centred outcomes that outweigh the costs to patients, the health care system and society.

We hypothesise that (1) ambulatory oxygen therapy delivered using a POC will provide clinically significant improvements in physical activity (primary outcome), symptoms and

health-related quality of life; and (2) ambulatory oxygen therapy via POC will be cost-effective compared to ambulatory air.

Methods and analysis

Design: A randomised controlled superiority trial, with blinding of participants, clinicians and researchers, in 260 people with fILD who desaturate during walking. The trial will be conducted in Australia and Sweden, with trial sites detailed on the study registration at clinicaltrials.gov. Participants will be randomised 1:1 into two groups: Group 1: Ambulatory oxygen therapy using a POC (oxygen group), Group 2: Sham therapy using an identical POC (air group). The allocated treatment will be delivered for 6 months. We have previously demonstrated the feasibility of the trial methodology in a pilot study.[21] Figure 1 shows the participant flow through the trial. The overview of the study procedures follows the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist[22] (online supplementary file 1).

Participants: People with fILD who receive their care at the study sites will be invited to participate. Patients will be eligible for inclusion if they are (1) aged 18 years and over; (2) have a physician confirmed diagnosis of fibrosing ILD, such as idiopathic pulmonary fibrosis, connective tissue disease (CTD)-associated ILD, fibrotic hypersensitivity pneumonitis (HP), idiopathic non-specific interstitial pneumonia (iNSIP), unclassifiable idiopathic interstitial pneumonia (IIP), environmental/ occupational lung disease or sarcoidosis, with features of diffuse fibrosing lung disease of >10% extent on high-resolution computed tomography (HRCT), with ILD being the predominant pathologic process;[23] (3) have had stable pharmacotherapy over the last 3 months; and (4) exhibit exertional desaturation, defined as $SpO_2 \leq 88\%$ for at least 10 consecutive seconds during a 6-minute walk test (6MWT) performed on room air. Only fILD will be included as these conditions are often characterised by chronic progressive fibrosis, as opposed to other ILDs with differing pathophysiology (e.g.

inflammatory or granulomatous) where different mechanisms may underlie exertional desaturation.

Participants will be excluded if they: (1) are currently using or eligible for long-term oxygen therapy (LTOT), with eligibility defined as $PaO_2 \leq 55$mmHg at rest on room air, or 56-59mmHg with evidence of right heart failure[10] as it is not ethical to withhold oxygen therapy in this group for whom it is strongly recommended;[24] (2) are current smokers, due to the risk of oxygen use near flames; (3) have predominantly obstructive lung disease, with forced expiratory ratio (FER) less than the lower limit of normal; (4) are pregnant; (5) are cognitively unable to consent; (6) are non-ambulant; (7) have been admitted to an acute care hospital within the last 30 days; or (8) if death or transplant is anticipated within the study period. Participants currently participating in pulmonary rehabilitation will not be enrolled, and participation in pulmonary rehabilitation during the 6-month trial period will be avoided where possible, as this may impact on both primary and secondary outcomes.

Recruitment: Potential participants will be identified by their treating health care team. If the participant is interested in obtaining more detailed information they will be contacted by the trial coordinator or site coordinator, who is not in a dependent relationship with the patient and will provide further information. Patients will be informed that participation in the study is voluntary, their decision about participation will not affect their treatment or relationship with their health care team, their data will be held securely and they will not be identified in any study publications. Only patients who provide written, informed consent will undertake the study procedures outlined in this protocol.

Patient and public involvement: We interviewed patients with fILD and physicians who cared for them, in order to understand experiences and role of oxygen therapy.[7 19] Patients emphasised the need for oxygen devices that were lighter and easier to use. Our subsequent work showed that patients preferred using a POC over traditional oxygen cylinders.[16] In our feasibility trial we interviewed participants about their experiences of trial participation.

Participants expressed positive experiences of the study and stated they would recommend such trial participation to others with ILD.[21] These experiences underpinned the design of the protocol for the current trial.

Randomisation: Randomisation will occur following completion of the baseline assessment, including measures of physical activity. Participants will be randomly allocated to groups using a computer generated, permuted block randomisation schedule with stratification for (i) desaturation during 6MWT (<80% vs ≥80%) as this is a powerful predictor of physical activity, health-related quality of life and mortality[4 5 25] and (ii) site of recruitment. Sequence generation will be performed by an individual independent of the research team and the allocation sequence will be concealed using a secure online randomisation service.

Interventions: All participants will be informed that the aim of using a POC is to assist them to be more active, with fewer symptoms. They will be encouraged to use the POC at all times when they are moving about, including walking at home or in the community, during exercise or during other activities. The POC should not be used when sitting still or sleeping. Written and verbal education will be provided. Participants will be encouraged to use their allocated POC during physical activity for the 6-month study period. Participants will be provided with a standard POC carry bag, worn over one shoulder, but will have the option to use a backpack if required. The method by which each participant chooses to carry their POC will be recorded. Informed by our pilot study, the Inogen One G3 HF POC will be used at its maximum pulse flow setting of 5 for both groups, as this delivered similar oxygen saturation during walking to a portable cylinder delivering 5L/min of oxygen on continuous flow.[16] No titration of flow rates will be performed, in order to maintain blinding of clinicians, researchers and participants.

All participants will be contacted monthly by telephone by a blinded investigator to encourage POC use and answer any questions. These calls will also collect adverse events, health care utilisation data for economic analyses and information on concurrent therapies, including changes to medications. It is likely that some participants will commence LTOT during the 6-

month study period. This will occur if participants meet the usual LTOT eligibility criteria[10] and it is recommended by their treating physician. Upon commencement of LTOT the participant will cease using the allocated POC. The number of participants in each group who commence LTOT will be recorded, outcome measures will be collected as per the trial protocol and data will be analysed according to allocated treatment group, as per intention to treat principles. Similarly, if a participant deteriorates during the 6-month study period then they may commence new/additional pharmacotherapies at their physician's discretion. The number of participants in each group who commence new pharmacotherapies and their nature will be recorded, outcome measures will be collected as per the trial protocol and data will be analysed according to allocated treatment group, as per intention to treat principles. The hours of usage downloaded from POC flash memory will be evaluated every three months. Reason for cessation of therapy will be recorded where relevant (patient request, commencement of LTOT, other).

Blinding: Participants, clinicians and researchers will be blinded to group allocation. The Inogen One G3 HF POCs for ambulatory oxygen therapy and air groups will be identical in appearance, display, weight and operation, with the only difference being the gas delivered. The POCs will be coded by the distributor, who will not be involved in trial conduct. We successfully used this system to maintain blinding in a previous trial using gas cylinders in COPD[15] and our feasibility trial did not identify any safety issues in randomising participants with fILD and exertional desaturation to POCs delivering air.[21] The intervention code will only be available to the randomisation centre. All participants will be advised against measuring oxygen saturation at home during the duration of the trial, as this does not represent usual clinical practice in any of the centres and may unblind the participants. At the conclusion of the trial, participants will be asked two questions to evaluate the success of blinding: (i) Which treatment do you think you were receiving, oxygen or air?; and (ii) Did you have a pulse oximeter at home over the last 6 months? If yes, how did you use it?

Outcome measures: Outcome measures will be collected at baseline (two visits, one week apart), 3 and 6-months following randomisation (Table 1), by an assessor who is blinded to group allocation. Three months were selected as this is sufficient to achieve change in the primary outcome[26] and 6 months will provide robust data for economic analyses.

The primary outcome is change in physical activity, measured by the number of steps per day. Steps per day is an objective measure of physical activity in people with fILD that has strong relationships to respiratory function, exercise capacity, exertional desaturation, HRQL and fatigue.[5 12] Physical inactivity, defined as less than 3300 steps per day, is associated with poor survival (30% vs 70% over 3 years).[5] Steps per day is responsive to changes following non-pharmacological interventions in chronic lung disease[26] and the minimal important difference (MID) has been defined as 599 steps.[27] Steps per day is a direct measure of how a patient functions in daily life and thus fulfils the criteria for meaningful endpoints in fILD clinical trials.[28] Steps per day will be measured using the StepWatch activity monitor (SAM) (Modus Health, Washington DC, USA) which is reliable and valid in chronic lung disease.[29] It accurately detects slow walking speeds and is sensitive to small changes in step rate.[30] The SAM will be worn on the ankle continuously for seven days (except for bathing) between the first and second baseline visits, and then for 7 days following the 3 month and 6-month assessments. Seven days of monitoring is required for optimum reliability.[29]

Secondary Outcomes are change in functional exercise capacity, HRQL, breathlessness, fatigue, anxiety, depression, time spent in moderate to vigorous physical activity, sedentary time, oxygen saturation in daily life, and plasma markers of skeletal muscle metabolism, systemic inflammation and oxidative stress.

Functional exercise capacity will be measured with the 6-minute walk distance[31] which is responsive to change with acute administration of oxygen[13] and is a strong predictor of survival in fILD.[32] The 6MWT will be performed according to international standards, including performance of 2 tests at each time point to control for the known learning effect, with the best

distance recorded.[31] All tests will be performed breathing room air so that a valid comparison can be made across time points,[31] and to maintain blinding. Health-related quality of life will be measured using three instruments: The St. George's Respiratory Questionnaire (SGRQ), a disease specific HRQL measure that is valid and responsive in fILD;[33] the EQ-5D-5L, a validated generic quality of life measure which is used to derive health utilities for economic analyses; and the K-BILD questionnaire, a validated disease-specific health status questionnaire.[14] The Dyspnoea-12 will be used to capture both the physical and affective components of breathlessness and is a reliable and valid questionnaire in fILD.[34] Fatigue will be measured with the Fatigue Severity Scale (FSS), a valid and sensitive questionnaire in fILD.[35] Anxiety and depression will be evaluated using the Hospital Anxiety and Depression Scale (HADS), a validated and widely used tool for assessing psychological distress. Anxiety and depression are common in fILD and are increased in users of LTOT.[36] The GeneActiv (GENEActiv, Cambridgeshire, UK) will measure time spent in moderate to vigorous physical activity and sedentary time. This wrist-worn, tri-axial accelerometer has been validated in idiopathic pulmonary fibrosis.[37] Seven days of monitoring are required to accurately capture all activity intensities.[38] Oxygen saturation in daily life will be measured using a Nonin 3150 Wrist Oximeter. The wrist oximeter will be worn during waking hours on two consecutive weekdays, with the display turned off so that participants remain blinded to their oxygen saturation during POC use. Examination of plasma markers of skeletal muscle metabolism (xanthine, hypoxanthine); systemic inflammation (interleukin-6, tumour necrosis factor-a, c-reactive protein); and oxidative stress (8-isoprostane, thiobarbiuric acid reactive substrates), as previously published [11] will be performed.

Health economic analyses: We will undertake a comparison of per person costs, including direct (health system) and indirect (personal) health care costs, of ambulatory oxygen therapy compared to air. Direct costs will include staff time, consumables, communications and overheads. Intervention costs will include staff inputs by duration, type and resource use (including troubleshooting and support) and equipment (POC and consumables). Personal

costs will include transportation, travel time and impact of the intervention on the economic activities of other household members. Health system costs will include visits to the general practitioner, specialist or emergency department, including any telemedicine visits; use of chronic disease services; and hospitalisation. We will collect health care utilisation data from hospital records, Medicare Benefits Schedule - MBS and Pharmaceutical Benefits Scheme - PBS data (Australia) and the National Patient Registry of the Swedish Board of Health and Welfare, as well as directly from participants via monthly telephone calls. Sensitivity analyses will use different assumptions about personal healthcare costs across countries.

An incremental cost-effectiveness analysis will be undertaken to compare differences in costs with differences in: (a) Quality-adjusted life years (QALYs): a single preference-based utility score will be derived from the EQ-5D-5L. This will be converted to QALYs on the assumption that the duration of each status is exactly one half of the time between two measurement intervals[39] (b) The number of hospital admissions per enrolled person in the 6-month follow up period. The indicator will be the incremental cost of averting an additional hospitalisation.

Schedule of assessments: Outcomes will be obtained by a blinded assessor at baseline, 3 months and 6 months (Table 1). At the baseline visit, an arterial blood gas will be performed in participants with resting SpO_2<93% to exclude resting hypoxaemia, as this is an indication for LTOT. At each assessment two 6MWTs will be performed according to international standards with continuous pulse oximetry[31] whilst the participant breathes room air. The nadir oxyhaemoglobin from the longest 6MWT will be used to determine eligibility at baseline.[31] Questionnaires will be administered and blood for biomarkers will be obtained. The StepWatch and the GENEActiv activity monitors will be given to participants to wear over the following seven days and the Nonin 3150 Wrist Oximeter will be worn on two consecutive weekdays. The monitors will be returned to the investigators by post. Spirometry is performed every 6 months in usual care, to document disease progression. To minimize patient burden, we will not repeat this test separately for the trial.

Safety and adverse events: Adverse events will be defined according to Good Clinical Practice (GCP) guidelines. Adverse events of specific interest will be defined according to the criteria used in the recent Long-term Oxygen Treatment Trial (LOTT) trial: worsening of fILD (worsening of lung function, development of resting hypoxaemia); exacerbation of fILD; burns (from smoking whilst using a POC, using the POC around an open flame or equipment that sparks); nosebleed or dry nose; musculoskeletal injury from tripping on a POC; hospitalization; or death.[40] Adverse events will be identified during monthly telephone calls and 3-monthly assessment visits, or by reports from the treating medical team. Participants who experience an adverse event will receive all necessary medical care from their local health care team.

Sample size: A total of 220 participants (110 per group) will provide 80% power to detect, at the two-sided 5% level, a clinically important difference between groups in the primary outcome of 599 steps per day.[27] This assumes a standard deviation (SD) of 1582 steps, based on physical activity data previously collected at our centre in 52 patients with fILD. Our previous trials had less than 10% attrition.[15 41] Previous experience suggests that 5% of participants could start LTOT (and cease POC use) over 6 months. We will therefore randomise 260 participants to ensure that 220 participants complete the study.

Over 1000 patients with fILD are currently managed at our centres, with an additional 300 new patients seen each year. Approximately half of these patients exhibit exertional desaturation and are not using LTOT.[42] Based on the rate of recruitment in our feasibility study[21] we anticipate recruiting the required sample of 260 participants over 3 years.

Analysis: Mean differences for continuous variables will be analysed using linear mixed models, controlling for baseline values as required. Generalized linear mixed models will be used for binary or count outcomes. Estimates will be presented with 95% confidence intervals, and two-sided p-values reported. Results will be displayed graphically where it will illuminate. All data will be analysed by intention to treat, including all randomised participants in the groups to which they were allocated, regardless of adherence.

Data integrity and management: Hardcopy data collection forms will be stored in a locked filing cabinet within a locked office, and electronic data will be stored in a purpose-built on-line database (www.adeptrs.com), with encryption and password protection. The online database will be protected by encryption enabled at up to 256-bits and SSL certificate, and hosted on a dedicated SSL cluster. No identifying information will be stored in the online database or on hardcopy data forms. Electronic data for all sites will be accessible by the principal investigator and the trial coordinator. Site-specific investigators will only have access to data relating to their individual site. Information will be stored indefinitely, in accordance with Human Research Ethics Committees requirements for interventional studies.

Data monitoring: The Data Safety and Monitoring Committee (DSMB) will meet twice yearly, chaired by a respiratory physician who is independent of the study team and trial sites. The DSMB will include a biostatistician. The DSMB will report its findings to the trial steering committee, consisting of the chief investigators.

Ethics and dissemination

Ethical approval has been granted in Australia by Alfred Hospital Human Research Ethics Committee (HREC/18/Alfred/42) with governance approval at all Australian sites, and in Sweden (Lund Dnr: 2019-02963). The study will be conducted and reported according to the SPIRIT guidelines[22] and the CONSORT statement.[43] Results will be published in peer-reviewed journals and presented at conferences. We will also disseminate our results to people with fILD through lay publications and seminars.

Discussion

This study will recruit people with fILD who desaturate during walking, a group that represents half of all patients with fILD and over 85% of those with severe disease.[42] People with fILD experience distressing breathlessness, cough and fatigue; loss of independence and life roles; financial strain; and unpleasant treatment side effects.[44 45] Many have few treatment options.

This multi-centre trial will examine the benefits and costs of ambulatory oxygen, delivered using a POC, in people with fILD and exertional desaturation. Recruitment across 6 sites and 2 countries will enhance external validity. Use of a sham POC allows effective blinding, a feature frequently missing from trials of oxygen therapy, thus substantially reducing the risk of bias. The primary outcome is steps per day, a direct measure of patient function in daily life. The study also includes a comprehensive economic analysis, to inform future funding and policy decisions.

Limitations of our trial include a follow up period of six months, so longer-term outcomes of ambulatory oxygen will not be evaluated. A diagnosis of fILD by a multidisciplinary team (MDT) is not required for inclusion, which may reduce certainty regarding the fILD subtypes included, however it is common practice in our centres that diagnosis is made by an MDT. Patients who have previously used ambulatory oxygen therapy are not excluded, which could affect participant expectations and response to treatment with the POC; however we have previously shown that less than 30% of eligible patients with fILD are currently using ambulatory oxygen,[42] so we anticipate that the majority will be naïve to this treatment.

Recent years have brought a new sense of hope for people with fILD, with the advent of anti-fibrotic therapies that slow the progression of disease and have revolutionised the approach to treatment.[46 47] However, this hope has been tempered by their lack of impact on patient-centred outcomes, including HRQL. Interventions that improve how people with fILD feel and function are urgently needed. Ambulatory oxygen is currently available to some patients with fILD, but patient access is inconsistent across health systems, reflecting the lack of evidence underpinning this treatment. For patients with fILD, ambulatory oxygen has potential benefits but also potential burdens.[19] This clinical trial will provide much-needed evidence to underpin decisions by health professionals and patients regarding prescription and ongoing use of ambulatory oxygen. If successful, the findings of this trial can be rapidly incorporated into clinical guidelines and implemented into clinical practice across the world.

Trial status: Recruitment commenced in July 2019.

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Authors' contributions:

AEH led the study design and funding application and, as chief investigator, has oversight for the trial. AEH and CFM conceived the original idea for the study. AEH and MH wrote the initial draft of the study protocol. TC, DC, AP, ME, IG, NSLG, GH, MS, LB and RV contributed to protocol development and refined the trial design. GH and AEH planned the statistical analyses. YHK, RV, LD, LT, JP and JW collected pilot data and contributed to selection of outcomes. All authors conducted the PFOX trial, critically revised the manuscript and approved the final version for publication.

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Figure 1. Study flow.

Table 1: Assessment schedule

Assessment/ Procedure	Enrolment	Baseline	Allocation	3-month follow-up	6-month follow-up
Informed Consent	x				
Randomization (oxygen or air group)			x		
Resting arterial blood gas (if SpO_2<93%)		x			
StepWatch activity monitor (for 7 days)		x		x	x
Physical activity level (GENEActiv) (for 7 days)		x		x	x
Oxygen saturation in daily life (for 2 days)		x		x	x
6-minute walk test		x		x	x
HRQL- SGRQ, K-BILD, EQ-5D-5L		x		x	x
Dyspnoea-12		x		x	x
Fatigue Severity questionnaire		x		x	x

Anxiety/Depression (HADS)		**x**		**x**	**x**
Biochemical analysis		**x**		**x**	**x**
Portable oxygen concentrator usage (hrs)				**x**	**x**
Patient telephone calls (Monthly)		**x**		**x**	**x**
Adverse events				**x**	**x**
Economic evaluation					**x**

HADS- Hospital Anxiety and Depression Scale; HRQL – health-related quality of life; K-BILD – King's Brief Interstitial Lung Disease questionnaire; SGRQ – St George's Respiratory Questionnaire; SpO_2 – oxyhaemoglobin saturation.

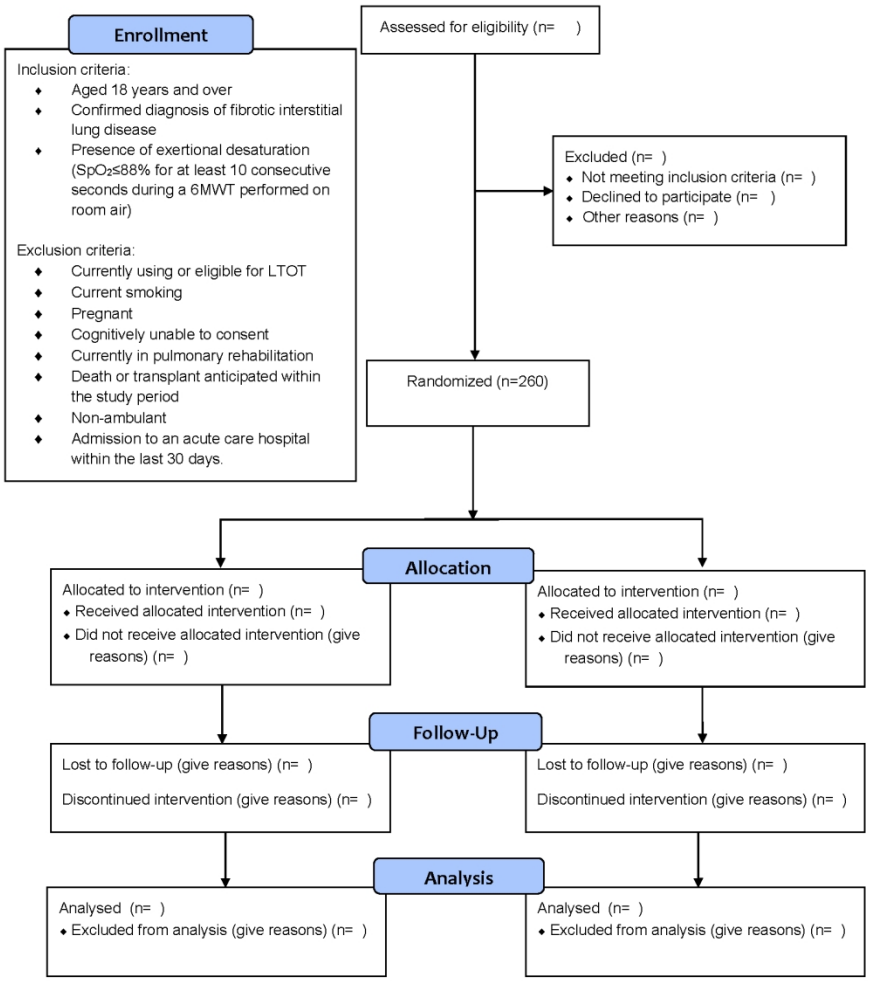

Figure 1. Study Flow.

215x279mm (200 x 200 DPI)

Supplementary file 1

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	3
Protocol version	3	Date and version identifier	3
Funding	4	Sources and types of financial, material, and other support	22
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	22
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	22
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	22
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-6
	6b	Explanation for choice of comparators	7
Objectives	7	Specific objectives or hypotheses	6

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7-8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-10
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	9-10
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	8-9
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9-10
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10-13
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	13
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	13-14
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	14
Methods: Assignment of interventions (for controlled trials)			

Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	9
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	10
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	13
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	14
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	14
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	14
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14

	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	14
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	14
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	14
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	13
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	13
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	13
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	14
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	22

Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	14
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	NA
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons “Attribution-NonCommercial-NoDerivs 3.0 Unported” license.