Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Treatable Traits in Interstitial Lung Disease (TTRILD) protocol paper: A randomised controlled trial comparing the targeted management of treatable traits versus standard practice

Megan Harrison

megan.harrison@health.wa.gov.au

University of Sydney

Sharon Maxwell

Fiona Stanley Hospital

Vinicius Cavalheri

The University of Notre Dame Australia

Kristin Naragon-Gainey

University of Western Australia

Emily Jeffery

Curtin University

Damien Foo

Curtin University

Caitlin Vicary

Allied Health, South Metropolitan Health Service

Kathryn Watson

Allied Health, South Metropolitan Health Service

Anna Hanran-Smith

University of Western Australia

Olivia Mirams

Sir Charles Gairdner Hospital

Felicity France

Fiona Stanley Hospital

Yet H Khor

Respiratory Research@Alfred

Nicole Goh

Austin Health

John Mackintosh

Prince Charles Hospital

Ingrid Cox
University of Tasmania
Andrew Palmer
University of Tasmania
Jeremy Wrobel
Fiona Stanley Hospital
Joanne L. Dickinson
University of Tasmania
Tamera J. Corte
University of Sydney
Yuben Moodley
Fiona Stanley Hospital

Study protocol

Keywords: Treatable Traits, Precision medicine, Interstitial Lung Disease, Pulmonary fibrosis, Multidisciplinary Care

Posted Date: August 10th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-9017147/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License

Additional Declarations: Competing interest reported. Megan Harrison is supported by an NHMRC postgraduate scholarship. John Mackintosh has honoraria from Boehringer Ingelheim, advisory boards for Boehringer Ingelheim and Gossamer Bio. Jeremy Wrobel receives speaker fees from Boehringer Ingelheim and has previously received conference sponsorship from Boehringer Ingelheim. Nicole Goh receives consulting fees and travel support from Boehringer Ingelheim and Chiesi. She receives payment for honoraria for lectures, presentations or educational events from Boehringer Ingelheim and Astra Zenenca. Nicole participates on a data safety monitoring board for Boehringer Ingelheim, Chiesi, and Gossamer. Yet Khor is supported by an NHMRC investigator grant and has received grants from Austin Medical Research Foundation, Lung Foundation Australia/ Thoracic Society of Australia and New Zealand. She receives consulting fees from Chiesi, Boehringer Ingelheim, and Abbvie. Tamera Corte is supported by an NHRMC investigator grant (L1). She receives grants from Avalyn Pharma, Boehringer Ingleheim, Bristol Myers Squibb, 4D, Phamaxis, Roche, Pliant, Bridge Biotherapeutics, and Avalyn Therapeutics and consulting fees from Qureight, Boehringer Ingleheim, Bristol Myers Squibb, DevPro, Endeavour BioMedicine, Roche, Pliant, Bridge Biotherapeutics, Vicore, Syndax and Avalyn Therapeutics. Honoraria for lectures and support for attending meetings are receives from Bristol Myers and Boehringer Ingelheim. Tamera Corte participates of data safety monitoring boards for Boehringer

Ingelhei, Bristol Myers Squibb, Roche, Ad Alta, Pliant, Bridge Biotherapeutics, Avalyn Therapeutics, DevPro, Endeavour BioMedicine, Vicore, Syndax, and Tianli.

Abstract

Background

Fibrotic interstitial lung diseases (ILDs) are chronic, progressive disorders characterised by marked symptom burden and poor prognosis. The Treatable Traits (TT) precision medicine model has demonstrated improved health outcomes in airway diseases; however, its role in ILD has not previously been studied.

Objective

This randomised controlled trial aims to compare the clinical efficacy and cost-effectiveness of a treatable traits model of care (TTRILD) compared to standard care in people with ILD.

Methods

A total of 110 participants with fibrotic ILD will be recruited from two tertiary ILD centres and randomised 1:1 to either the TTRILD intervention or standard care. Participants in the intervention arm will receive multidimensional assessment and TT-targeted management delivered through a multidisciplinary clinic, with specific interventions provided by allied health professionals. The primary outcome will be change in the King's Brief Interstitial Lung Disease (K-BILD) score at 6 months, reflecting health-related quality of life.

Discussion

This study aims to improve quality of life in people with ILD by assessing the impact of a treatable traits multidisciplinary model of care. Findings are expected to provide key insights into ILD management pathways and inform strategies to reduce symptom burden and optimise patient-centred outcomes.

Trial registration

ClinicalTrials.gov identifier: NCT06626438. Registered on 3 October 2024.

Background

Fibrotic interstitial lung diseases (ILDs) are a group of chronic pulmonary disorders characterised by progressive parenchymal scarring. This scarring leads to disabling breathlessness, intractable cough, impaired quality of life, and premature death[1]. ILD is now the leading indication for lung transplantation worldwide, reflecting the significant morbidity and poor prognosis associated with these conditions. [2]

Current models of care are centred around the identification of ILD subtype at a multidisciplinary meeting, with treatment decisions often based on this diagnosis.[3] Antifibrotics are standard of care for many fibrotic ILDs but have been demonstrated to only slow progression rather than improve quality of.[4,

[5] Patients with ILD consistently identify improving symptom and well-being as a top research priority.[6] This highlights the need for a holistic and symptom-focused approach to ILD care.

The treatable traits (TT) framework represents a precision medicine approach originally developed and validated for the management of obstructive airways diseases wherein specific traits are identified and targeted for treatment. To be a TT, a trait must meet 3 core characteristics: (a) clinically relevant by demonstrating an effect on patient health outcomes, (b) recognisable and identifiable using a validated markers and (c) treatable, ideally with effective therapies already available.[7] In airways disease, TTs span three domains, but in ILD a fourth aetiological domain has been proposed, resulting in an ILD TT model incorporating aetiological, pulmonary, extra-pulmonary, and behavioural traits.

Clinical trial data in severe asthma have demonstrated that TT-based management improves health related quality of life (HRQOL) and asthma control compared to standard care.[8] The benefits of this approach are attributed to addressing the complex, interrelated biological and behavioural factors that contribute to chronic disease burden. These features are even more pronounced in ILD, where overlapping aetiologies, multimorbidity, and disabling symptoms are common. Despite this, the impact of TT-directed management remains unknown.

While the TT model shares some features with comprehensive care, it is distinguished by two core elements. The first is the use of a structured multidimensional assessment to systematically identify traits. The second is the early and proactive involvement of a multidisciplinary team with input from onset by specialised allied health members including physiotherapy, psychology, and dietetics. This is likely to improve targeting therapy of traits often overlooked, including physical inactivity, malnutrition, fatigue, and sarcopenia. Despite its theoretical advantages, the real-world clinical and economic benefits of a TT model in ILD remain unknown, providing the rationale for this study.

Aims

The aims of this study are to (1) evaluate the clinical efficacy of a Treatable Traits multidisciplinary approach compared to standard care in people with ILD as measured by HRQOL, and (2) assess the cost-effectiveness of the TT multidisciplinary clinic.

Methods

Study Design

This study will be a randomised controlled trial with an embedded economic evaluation among 110 patients with fibrotic ILD. Blinding of participants and personnel is not possible due to the nature of the intervention.

Recruitment of patients will occur from Sir Charles Gairdner Hospital (SCGH) and Fiona Stanley Hospital (FSH) in Western Australia. The intervention clinic will be conducted at Fiona Stanley Hospital and Harry

Perkins Institute in Western Australia. Participants will be randomised 1:1 into two groups. Group 1 will be the intervention group where participants will attend a TTRILD MDT clinic (TT-MDT) where TTs will be identified and targeted with multidisciplinary interventions employed. These interventions will be initiated by (a) a physiotherapist, with pulmonary rehabilitation, goal setting, or home strength training, (b) a dietitian with dietary counselling, oral nutritional supplements, and (c) a psychologist with self-management techniques. Physician-led treatment will prioritise the management of identified traits as specified in Table 1. These will remain at the discretion of the treating respiratory physician for the intervention group. Participants within the intervention group will also undergo detailed family history with screening for genetic variants known to cause inherited forms of ILD. Group 2 will be the control group and will receive the usual standard of care. There will be no limitation in referral for multidisciplinary assessment and management in either group.

Table 1
Summary of treatable traits with their diagnostic tools and intervention.

Treatable Trait	Diagnostic definition	Intervention
Aetiological traits:		
Pulmonary inflammation	MDM consensus of inflammation utilising HRCT pattern, BAL, histopathology	Consider immunosuppression
Connective Tissue Disease	Clinical diagnosis based on clinical features, CTD diagnosis, radiological features, serology [9].	Consider rheumatology/ immunology input. Consider immunosuppression
Drug Exposure	Medication history – exposure of potentially causative drug as defined on pneumotox.com[10]	Withdrawal of causative agent as appropriate Consider glucocorticoids if indicated
Environmental exposures	History of exposure to hypersensitivity-type or occupational exposures.	Antigen avoidance Consider immunosuppression
Genetics	Specialised testing: Telomere length, Whole genome sequencing	Genetic counselling Discussion at national genetics ILD MDT Augmenting of immunosuppression if required Early transplant referral
Pulmonary Traits:		
Progressive Pulmonary Fibrosis	ATS/ERS/JRS/ALAT guidelines, Two or more of: (a) worsening respiratory symptoms (b) physiological deterioration with absolute decline in FVC% predicted ≥ 5% or decline in DLCO% predicted of ≥ 10% or (c) radiological progression over one year with no alternative explanation [1]	Anti-fibrotics as per pharmaceuticals benefit scheme guidelines Australia [11]
Emphysema	HRCT Chest: emphysema ⩾10–15% of total lung volume in the setting of fibrosis[12] +/- Spirometry FEV1/FVC < LLN	Consider bronchodilator if obstructive spirometry

Treatable Trait	Diagnostic definition	Intervention
Pulmonary Hypertension	Transthoracic echocardiogram: TR jet velocity of > 2.8 m/s ≈ mPAP ≥ 35 mmHg [13]	Consider right heart catheter, referral to PH specialist centre and PH-specific therapies
Resting hypoxia	Baseline Sats O2 ≤ 88% and ABG PaO2 < 60 mmHg with PH or < 56mmHg [14]	Long term oxygen therapy as per international guidelines [15]
Exertional Hypoxia	6MWT nadir Sats ≤ 88% [16]	Consider titrated exertional oxygen prescription (titration performed by physiotherapy)
Nocturnal Hypoxia	Overnight oximetry/ polysomnography: Overnight oximetry > 10% of total sleep time with SpO2 < 90% (TST90)[17]	Consider nocturnal oxygen prescription
Obstructive Sleep Apnoea (OSA)	STOP-BANG questionnaire score: 3–4 (intermediate risk), 5–8 (high risk) Polysomnography evidence of OSA	Referral for CPAP/ mandibular splint
Chronic Cough	Clinical history of chronic cough Leicester cough questionnaire score of < 17.68 [18, 19]	Address co-contributing drivers: - GORD: Treat if symptomatic with standard dose PPI - Postnasal drip: intranasal antihistamines/ intranasal steroids - VCD/ ILO: psychological counselling, speech therapy Cough suppression – speech pathology techniques, consider neuromodulators.
Chronic Dyspnoea	History of breathlessness Dyspnea-12 questionnaire with mild + dyspnoea symptoms	Airflow – Handheld fan Pulmonary rehabilitation Consider opioids
Extra-pulmonary traits:		
Peripheral muscle dysfunction	1STST of < 20 repetitions	Physiotherapy: Home based exercise prescription
Exercise Intolerance	6MWT < 350m	Physiotherapy: Pulmonary rehabilitation
Sarcopenia	1STS < 20 repetitions and	Physiotherapy:

Treatable Trait	Diagnostic definition	Intervention
	DEXA demonstrating low muscle mass [20] SARC-F questionnaire [21]	Home based exercise prescription. Dietitian: If borderline intake for high protein diet If poor intake for high protein diet + protein supplementation
Frailty	1STST < 20 repetitions and physician-judged clinical frailty scale (CFS) score of ≥ 4 [22].	Physiotherapy: Pulmonary rehabilitation
Osteoporosis	Clinical history of low trauma fracture DEXA scan: T-score ≤ -2.5	Dietary recommendations Supplements – calcium and vitamin D Consider Anti-resorptive therapy
Poor Appetite and Malnutrition	Poor appetite: Anorexia Cachexia Scale Score ≤ 37 Malnutrition: Patient-Generated Subjective Global Assessment Short Form ≥ 4 and/ or BMI < 18.5	Dietitian: With borderline intake – small, frequent meals and snacks With poor intake – Small frequent meals and snacks, Nourishing drinks/ Oral nutritional supplements
Anxiety and Depression features	Hospital Anxiety and Depression (HADS) score of 7–10 (borderline) HADS ≥ 11 (significant) [23] and/or Perceived Stress Scale (PSS) ≥ 14 [24]. Clinical interview with psychologist.	Psychology: Referral to self-help, or GP referral for individual treatment
Fatigue	Fatigue Severity Scale (FSS) ≥ 36	Physiotherapy: Graded exercise program
Behavioural traits:		
Polypharmacy	Medication list ≥ 5 regular medications	Medication rationalisation
Smoking	History of smoking	Smoking cessation: quitline referral, consider pharmaceutical cessation treatments
Physical Inactivity	International Physical Activity Questionnaire (IPAQ) categories 1 (inactive) or 2 (minimally active)	Physiotherapy: Goal setting with pedometer

Trial status

This study is currently recruiting. The first patient was enrolled in the RCT on the 3rd of September 2025. The planned study completion is 30 December 2026.

Participants

Inclusion/ exclusion criteria

Consecutive patients with a new or pre-existing diagnosis of fibrotic ILD who receive care via the Fiona Stanley Hospital (FSH) or Sir Charles Gairdner Hospital (SCGH) ILD service will be invited to participate. All patients must have confirmed fibrotic ILD discussed at an ILD multidisciplinary discussion (MDD). All fibrotic ILD will be eligible for inclusion, except sarcoidosis. Participants will need to be able to provide informed consent and be established on stable ILD treatment for 1 month prior to study initiation.

Participants will be excluded if they have experienced an acute exacerbation 4 weeks prior to starting the study or are expected to experience either a transplant or death during the study period (6 months).

Sample size:

Previous work in ILD has demonstrated a minimum clinically important difference (MCID) of 4.2 (95% CI 3.0 to 5.3) point change in total score of the King's Brief Interstitial Lung Disease health status questionnaire (K-BILD) following the intervention. Based on that data, we anticipate a between-group difference of > 4.2 favouring the intervention group. With an α of 0.05 and 90% power, and accounting for a 15% expected attrition, the target sample size will be 110 participants, with 55 randomised to each group.

Recruitment and Consent

Participants who meet the eligibility criteria will be approached by a member of the research team with the purpose of introducing the study. If the participant expresses interest in joining the study, further discussion with research coordinator will be undertaken via phone. Participants will be able to complete an online consent via a REDCAP link or written consent form.

Randomisation

Participants will be randomised via the REDCAP online randomisation system 1:1 to intervention or control group. Participants will be stratified by i) severity of forced vital capacity (FVC): mild (FVC predicted > 80%), moderate (FVC predicted 50–80%) and severe (FVC predicted < 50%). and ii) subtype of ILD: idiopathic pulmonary fibrosis (IPF) and non-IPF with a limit of 50% of patients with IPF.[25]

Multidimensional assessment

Both groups will undergo an intensive multidimensional assessment as has been established in other chronic lung diseases including asthma.[8, 26] This assessment will identify the traits as outlined in Table 1.

In the intervention group, the results of this assessment will be correlated by the research nurse/ case manager. In the control group, all investigations that are performed as standard of care will be available to the treating clinical team. This will not include questionnaire data which is not standard of care.

Results of the dual energy x-ray (DEXA) scan will be provided to the treating clinician for control group if osteoporosis is identified.

Intervention

Baseline assessment (intervention group)

Patients randomised to the TT intervention will undergo multidisciplinary review by physiotherapist, dietitian, psychologist, research nurse, and respiratory physician. Physiotherapist initial evaluation will involve a clinical assessment and review of pertinent investigations including 6-minute walk test (6MWT), pulmonary function tests (PFTs), 1 minute sit to stand test (1STST), and the international physical activity questionnaire (IPAQ). Key treatable traits for targeting by physiotherapist are exercise intolerance, dyspnoea, physical inactivity, sarcopenia, and frailty. Based on the presence of individual TT patients will be offered a management plan. This may include goal setting with a pedometer, pulmonary rehabilitation, and/or a home exercise program with education.

Dietetic evaluation will involve assessment of dietary intake and review of pertinent investigations including body mass index (BMI), Patient Generated Subjective Global Assessment Short Form (PGSGA-SF), and Dual-Energy X-ray Absorptiometry (DEXA). Treatable traits for dietetic intervention are malnutrition, sarcopenia, osteoporosis, and frailty. When present, patients will be offered a management plan that includes dietary counselling and/or oral nutritional supplements.

The initial evaluation by the team psychologist will involve a psychological interview and review of pertinent investigations including hospital anxiety and depression scale (HADS) and perceived stress scale (PSS). Based on presence of anxiety, depression, or stress, participants will be offered a targeted management plan. Options for this will include an online self-management tool (“This way up”, or referral to GP for individual psychology/psychiatry treatment.[27] During psychologist assessment a risk evaluation will be conducted. Any participant that is identified to be a concern for psychological safety will be referred to the treating physician for consideration of psychiatric discussion and evaluation.

Initial evaluation performed by respiratory physician will involve a clinical assessment and review of pertinent investigations including 6MWT, PFTs, HRCT, and questionnaire data. ILD therapies such as anti-

fibrotic and immunosuppressive therapies will be offered as per standard care. There will be a specific focus on the identification and treatment of the additional TTs, including aetiological traits (pulmonary inflammation, exposures), pulmonary (cough, dyspnoea), extra-pulmonary traits (reflux, anxiety, depression) and behavioural traits (physical inactivity, smoking).

Following the multidisciplinary assessment, a TT multidisciplinary meeting (TT-MDT) will be undertaken. Discussion will include consensus across allied health specialists on presence of traits and the strategy to move forward. It is estimated each participant will require 5-15minutes of discussion. This meeting is led by respiratory physician and each TT and plan documented.

2-week telehealth clinic (Intervention group)

Participants that have been initiated on pedometer-based goal setting, will have a two-week review coordinated by the physiotherapist to review the exercise diary and refine goals as required. Participants receiving dietetic intervention will undergo a dietitian telephone review to assess intervention tolerance and provide feedback or alternative strategies where necessary. For patients undertaking stress management program or considering individual psychology input, team psychologist will contact and check in. Participants not receiving dedicated interventions will be contacted by the research nurse.

3-month and 6-month clinics (Intervention group)

This clinic review will involve a clinical assessment by physiotherapist and review of further investigations including repeat 1STST and IPAQ. An assessment of progress regarding interventions offered will be performed and education provided. This clinic review will also involve a clinical assessment by dietitian and review of further investigations including repeat ACS and PGSGA-SF. An assessment of progress regarding interventions offered will be performed and education provided. Respiratory physician review will include clinical assessment regarding treatments to date, and participant status. Second line therapies of specific traits may be offered or considered. Review of investigations will be performed.

Specific Interventions

Pulmonary rehabilitation:

For participants with evidence of exercise intolerance and/ or frailty, pulmonary rehabilitation will be offered.[28, 29] This is an 8-week program that involves a twice weekly 1-hour program. This will bean individually tailored exercise program consisting of warmup, endurance exercise, and upper limb strengthening exercises. Each participant program considers their goals and any musculoskeletal limitations they may have. All participants record their exercises on their own exercise log to enable monitoring of progress. Participants receive a written home exercise program once they have an established gym program, usually provided in session 3 or 4.

Home exercise program

For participants with peripheral muscle dysfunction and/ or sarcopenia a home-based exercise program will be offered.[30, 31] This will be in line with the Lung Foundation Australia resource 'Better living with exercise' (Supplementary 1).[32] To enable an individualised plan the following questions will be asked and discussed with the participant (1) What are your exercise options? (2) What is important to you? (3) What is your SMART (specific measurable attractive realistic time-framed) plan? (4) What else needs to be considered?

Fan:

For participants with significant dyspnoea a portable hand-held fan will be provided.[33] Participant education will be undertaken by physiotherapist and include details on how to use the fan (15cm from face and aiming at centre of face), times to use (as often as like, during activities, with other interventions, and ensuring easy access.

Goal setting and pedometer

In participants where physical inactivity is identified as a trait a personal pedometer will be provided.[34] Participants will then be asked to diarise their daily step count during the first week. At the 2-week physiotherapy phone review participant and physiotherapist can set the goals which will be further reviewed and managed at the 3-month clinic appointment.

Dietitian counselling

At time of dietitian review a 24-hour recall and brief dietary analysis will be undertaken. Depending on participant appetite, intake, and presence of frailty, malnutrition and/ or sarcopenia, recommendations regarding meals and diet will be provided by dietitian.[35] Dietary education will be provided using the 'High Protein High Energy Diet' resource (Supplementary 1). During this, participants will be educated on high protein high energy diet, small, frequent meals, meal and snack ideas, food fortification, and management of poor appetite and other nutritional impact syndromes relevant to the participant. The dietitian and participant will collaborate to select food fortification and high energy, high protein meals and snack options consistent with their needs and preferences.

Oral nutritional supplements:

Nutritional supplements will be recommended for those participants recognised to have the nutritional disorders that include frailty, malnutrition and/ or sarcopenia in whom poor dietary intake is identified.[36, 37] Poor dietary intake is defined as less than 50% of estimated nutrition requirements met with dietary strategies alone. For participants identified to have sarcopenia, if adequate protein intake cannot be achieved through dietary intake alone, then a protein powder will be recommended. Participants with frailty and malnutrition in whom adequate calorie and protein intake cannot be achieved through dietary intake alone, will be recommended an oral nutrition supplement. The type of oral nutrition supplement recommended by the dietitian will be individualised to the participant's needs and preferences.

Self-management psychology plan:

Participants who have been identified to have low symptom burden of stress, anxiety, or depression, will be supported through a self-management plan.[38] Specifically, they will be referred to the “Stress Management Program” created by This Way Up (https://thiswayup.org.au/programs/stress-management-program/), an online, on-demand program based on cognitive-behavioural therapy principles.

GP referral for individual mental health treatment:

For participants with moderate-severe psychological symptoms, participants will be offered referral for individual psychology treatment. This will involve liaising with the participant general practitioner (GP) to provide referral to a psychologist with expertise in chronic illness and development of a mental health plan to enable financial reimbursement. Anti-depressant therapy may be advocated for by treating team but require prescription by GP.

Genetics assessment

Genetic predisposition is one of the strongest risk factors for ILD.[39] All participants within the intervention arm will be screened for genetic variants known to contribute to inherited forms of ILD. A detailed family history will be taken, and blood samples will be collected and sent to the Institute of Respiratory Health (IRH) for Flow-FISH (fluorescence in-situ hybridization) to determine telomere length. Defects in genes associated with telomere biology are among the most frequently identified in patients presenting with ILD, particularly those with a family history.[40] Blood/DNA samples will also be sent to the University of Tasmania for whole genome sequencing and analysis to identify rare variants in genes previously associated with ILDs.

Those variants classified as likely pathogenic/pathogenic variants (LP/P) according to the American College of Medical Genetics (ACMG) guidelines will be considered ‘positive’. Variants of ‘unknown’ significance will be noted, and periodically reviewed as the knowledge of genetic predisposition variants is rapidly growing. Participants with a positive pathogenic variant (LP/P) will be referred to local geneticist by the treating physician for National Association of Testing Authorities (NATA) accredited testing and consultation with a clinical geneticist that will include pre- and post-genetic counselling with cascade testing of family members if deemed appropriate.

Participants may elect to not receive their genetic results.

Control:

All participants within the control group will receive baseline assessments as per the intervention group (Table 2). Clinic appointments with their treating ILD team will be at 3 and 6 months (as per Fig. 1).

They will receive phone reviews by research nurse at 2- and 4-week timepoints in lieu of the multidisciplinary check in performed by the intervention group. Physician review will be as per standard of care including treatment of underlying ILD and consideration of comorbidity management.

Participants within the control group will not have limitation to allied health referrals including pulmonary rehabilitation, dietitian assessment, or psychology referral. They will have therapy guided as per their treating respiratory physician.

Table 2
Assessments at each timepoint (Control and Intervention groups)

Questionnaires	Baseline	3 months	6 months
	+	+	+
Demographics	+		
PFTs	+	+	+
6MWT	+		+
1STS test	+		+
Bloods	+		
Sputum	+		
DEXA	+		+
HRCT	+		
Cost diary	+	+	+
All-cause hospitalisation / ED visits	+	+	+

PFTs: pulmonary function tests, 6MWT: 6-minute walk test, 1STS: 1 minute sit-to-stand test, DEXA: dual energy x-ray absorptiometry, HRCT: high resolution computed tomography

Outcome measures:

Primary endpoint

The primary outcome of this trial is the between-group difference in mean change from baseline in King's Brief questionnaire (K-BILD) total score. The K-BILD questionnaire is a brief, validated, 15-item, ILD-specific HRQoL questionnaire assessing psychological well-being, breathlessness, activity limitations, and chest symptoms.[41] It has been widely used internationally as a HRQoL endpoint in interstitial lung disease clinical trials and observational studies. [4]

Secondary endpoints

Secondary outcomes include alternate HRQoL score, with change in European QoL 5-Dimensions 5-Levels questionnaire (EQ-5D-5L) score at 6 months compared to baseline. The EQ-5D-5L questionnaire is a multidimensional patient-reported questionnaire that supports calculation of quality-adjusted life years.[41] Dyspnoea will be measured using the Dyspnea-12, a simple scale validated in ILD patients, which comprises the physical and affective components of dyspnoea.[42] Hospital anxiety and depression

scale (HADs) will be used to identify psychological distress. It has been shown to demonstrate increased rates of anxiety and depression in patients with ILD.[23]

Impact on participant physical activity will be measured with international physical activity questionnaire (IPAQ), a 7-item questionnaire that includes open-ended questions around the participants last 7-day recall of physical activity.[43] This will be assessed at 3- and 6-months and will be compared to baseline. Walk distance from 6MWT at 3 and 6 months will be compared to baseline.

Participants will have their regional and whole-body lean mass and fat mass be assessed using whole-body DEXA scans at 6 months compared to baseline. DEXA is a gold standard measure of body composition providing reliable and accurate measures of body composition. It has been promoted by the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) as a clinical trial secondary endpoint in sarcopenia research to identify increase in muscle mass.[44]

Lung function decline will be measured according to relative decline in forced vital capacity (FVC) or diffusion capacity (DLCO) compared to baseline, with a cut-off of ≥ 10% or ≥ 15% respectively considered significant decline. [45] Additional outcomes will include progression-free survival, and all cause hospitalisation and mortality.

A detailed economic evaluation will be undertaken to develop a comparison of per person direct (health system and all participant expenses) and indirect (lost productivity) costs performed with the TTRILD program versus standard care. Direct costs will include staff time; visits to the GP, specialist, or emergency room; hospitalisation; and use of chronic disease services including pulmonary rehabilitation, nursing, and allied health services. Participant expenses include transportation and parking costs, co-payments for medications and consultations, and costs of equipment and household adaptations. Indirect costs associated with productivity losses include absenteeism and presenteeism (decreased productivity due to working whilst ill) of the participant and household members. Data will be drawn from hospital records, Medicare Benefits Scheme (MBS) and Pharmaceutical Benefits Scheme (PBS) data using data linkage, and participant-completed cost diaries.

Costs will be ascertained at baseline for the 6 months prior to trial entry, then during the trial period at 3- and 6-months for each treatment arm. We will perform an incremental cost-effectiveness analysis to compare differences in total costs in each treatment arm divided by differences in quality-adjusted life years (calculated from EQ-5D-5L utility scores and survival). An additional incremental cost-effectiveness ratio will be calculated based on incremental costs per hospitalisation avoided.

Statistical Analysis:

All data will be analysed using an intention-to-treat approach. Descriptive statistics, such as mean and standard deviation (or median and interquartile range); and frequency and percentage, will be calculated to compare the participant demographic and clinical characteristics between the (i) the intervention group (TTRILD MDT care) vs. (ii) the control group (standard care).

Generalised linear mixed model and Cox regression will be performed to evaluate the efficacy of the intervention on the primary and secondary outcomes, whilst adjusting for relevant covariates. Covariates will include demographics, baseline lung function, and antifibrotic therapy. Subgroup analyses will compare the effects by types of ILD, severity of the disease, and types of personalised program (sarcopenia, loss of appetite, anxiety, cough). One-way repeated measures analysis of variance (ANOVA) will be performed to assess the main effects of group (two levels) and time (three levels), and the interaction effect between group and time. This will provide an overall understanding of whether the TTRILD intervention has met the primary outcome of a 6-month increase in HRQoL (K-BILD). All analyses will be performed using Stata MP/18 (StataCorp, Texas). All statistical analyses will be performed with supervision and oversight by an experienced biostatistician.

Data Safety and Monitoring:

A Trial Steering Committee comprising the chief investigators will oversee study conduct. The Steering Committee will meet regularly to review protocol adherence, recruitment progress, and any adverse events.

An independent consumer advisory group, consisting of two patients with interstitial lung disease, will provide lived-experience input and have reviewed the study protocol and progress on a six-monthly basis.

A Data Safety and Monitoring Board (DSMB) has been convened and will meet twice yearly. The DSMB will be chaired by a respiratory physician independent of the study team and participating trial sites and includes an independent biostatistician.

Discussion

The Treatable Traits (TT) precision medicine model has potential to improve health outcomes in patients with chronic, complex, and difficult-to-manage conditions. ILDs are a heterogeneous group of disorders associated with impaired quality of life and premature mortality. The TT approach offers an opportunity to move beyond the current disease-centred model by targeting clinically meaningful and modifiable traits to guide personalised care. Despite this promise, there is currently no robust evidence evaluating a TT-based model of care in patients with ILD. This study aims to prospectively identify and manage key TTs within a real-world ILD population through the implementation of an embedded multidisciplinary clinic. We anticipate that, analogous to outcomes observed in asthma, implementation of a TT-MDT clinic will be associated with improved quality of life for patients with ILD.

This protocol has several strengths. The prospective randomised controlled design with multicentre recruitment enhances external validity and reflects real-world ILD practice. The undertaking of comprehensive phenotyping using validated patient-reported outcome measures, lung function testing, radiology and biochemical data provides a robust dataset for trait identification. The clinical relevance and feasibility for ILD clinics is maximised by focusing on TTs that are actionable within existing health

systems that are aligned with international guideline recommendations. There is significant value in undertaking an economic evaluation of the MDT clinic. Demonstrating economic viability could meaningfully shift perceptions of the MDT model and support broader access to allied health services within ILD clinics.

The limitations of the study include selection bias, as recruitment through tertiary centre populations potentially limits the generalisability of the study. Furthermore, patients who volunteer for this trial are likely to represent a more motivated subset. To mitigate this, broad inclusion criteria and recruitment across two sites is being used. Loss to follow up may affect longitudinal analyses. To reduce this, we have incorporated digital reminder systems for appointments and questionnaire data with remote data collection options being encouraged when able, including online questionnaires and cost diary. The six-month timeframe represents a potential limitation, as access to some individual components, including sleep studies, may not be achievable within this period. Despite comprehensive data collection there is potential for residual confounders. We will aim to address this using sensitivity analyses. While the TT framework comprises of multiple elements that may each influence patient outcomes, this study was designed to assess the integrated model of care rather than to isolate the effect of individual components.

This study will provide world-first data on a treatable traits model of care in ILD.

Findings may support early risk stratification, identify subgroups most likely to benefit from targeted interventions, and inform development of TT-based clinical pathways.

The study adheres to the principles of the Declaration of Helsinki and Good Clinical Practice. Ethics approval has been obtained from the Western Australia Central Human Research Ethics Committee, Reference number (PRN): RGS00000006668. This trial is registered with clinicaltrials.gov (registration NCT06626438). Risks to participants are minimal and primarily related to routine clinical assessments. Informed consent processes are standardised to ensure participant autonomy and comprehension. Data management complies with privacy regulations and secure storage protocols. Results will be disseminated through peer-reviewed journals, national and international respiratory conferences, and presentations to patient advocacy groups. A summary of findings will be shared with participants where possible.

Overall, the findings of this study are expected to determine the efficacy of a TT model of care in ILD and work towards improving holistic care for ILD patients.

Abbreviations

Abbreviation/ Term	Description (using lay language)
1STST	1 minute sit to stand. A quick assessment tool that is validated to measure peripheral muscle function and functional sarcopenia
6MWT	6-minute walk test
ACS	Anorexia Cachexia Scale. Measures appetite and body perception
DEXA	Dual-Energy X-Ray Absorptiometry
DSMB	Data Safety and Management Board
Dyspnea-12	Tool to determine patient breathlessness
EQ-5D-5L	European Quality of Life 5-Dimensions 5-Levels questionnaire. A multidimensional patient-reported questionnaire that supports calculation of quality-adjusted life years
fILD	Fibrotic interstitial lung disease
FSS	Fatigue Severity Scale. Measure of fatigue
FSH	Fiona Stanley Hospital
FVC	Forced vital capacity
HADS	Hospital Anxiety and Depression Scale. Identifies psychological distress.
HRCT	High-resolution computed tomography
HRQoL	Health-related quality of life
ILD	Interstitial lung disease
IPAQ	International Physical Activity Questionnaire
K-BILD questionnaire	King's Brief Interstitial Lung Disease. Assessment of health-related quality of life
LCQ	Leister Cough questionnaire. Assesses cough
MBSR	Mindfulness-Based Stress Reduction
MDT	Multi-disciplinary team
OSA	Obstructive sleep apnoea
PGSGA-SF	Patient-Generated Subjective Global Assessment Short Form. Determines participant nutritional status
PSS	Perceived Stress Scale. Validated tool to determine patient well-being in response to stress
QoL	Quality of life

STOP-BANG	Stop bang questionnaire. Effective screening tool for obstructive sleep apnoea
TT	Treatable trait
TTRILD	Treatable traits in interstitial lung disease

Declarations

Ethics approval and consent to participate:

Ethics approval has been obtained from the Western Australia Central Human Research Ethics Committee, Reference number (PRN): RGS00000006668. Written informed consent will be obtained from all participants prior to enrolment.

Consent for publication

Not applicable

Availability of data and materials

Data generated from this study will be available from the corresponding author on reasonable request, subject to ethics approval and data governance requirements.

Competing interests

Megan Harrison is supported by an NHMRC postgraduate scholarship.

John Mackintosh has honoraria from Boehringer Ingelheim, advisory boards for Boehringer Ingelheim and Gossamer Bio.

Jeremy Wrobel receives speaker fees from Boehringer Ingelheim and has previously received conference sponsorship from Boehringer Ingelheim.

Nicole Goh receives consulting fees and travel support from Boehringer Ingelheim and Chiesi. She receives payment for honoraria for lectures, presentations or educational events from Boehringer Ingelheim and Astra Zenenca. Nicole participates on a data safety monitoring board for Boehringer Ingelheim, Chiesi, and Gossamer.

Yet Khor is supported by an NHMRC investigator grant and has received grants from Austin Medical Research Foundation, Lung Foundation Australia/ Thoracic Society of Australia and New Zealand. She receives consulting fees from Chiesi, Boehringer Ingelheim, and Abbvie.

Tamera Corte is supported by an NHRMC investigator grant (L1). She receives grants from Avalyn Pharma, Boehringer Ingleheim, Bristol Myers Squibb, 4D, Phamaxis, Roche, Pliant, Bridge Biotherapeutics, and Avalyn Therapeutics and consulting fees from Qureight, Boehringer Ingleheim, Bristol Myers Squibb,

DevPro, Endeavour BioMedicine, Roche, Pliant, Bridge Biotherapeutics, Vicore, Syndax and Avalyn Therapeutics. Honoraria for lectures and support for attending meetings are receives from Bristol Myers and Boehringer Ingelheim. Tamera Corte participates of data safety monitoring boards for Boehringer Ingelhei, Bristol Myers Squibb, Roche, Ad Alta, Pliant, Bridge Biotherapeutics, Avalyn Therapeutics, DevPro, Endeavour BioMedicine, Vicore, Syndax, and Tianli.

Funding

This study is supported by the Medical Research Future Fund (grant number 2022914). The funder had no role in the study design; data collection, analysis, or interpretation; or manuscript preparation.

Authors' contributions

YM conceived the study. MH and YM led protocol development. MH, VC, KG, EJ, NG, YHK, JM, IC, JW, and TC contributed to the study design. MH drafted the manuscript. All authors reviewed, edited, and approved the final manuscript.

Acknowledgements

The authors acknowledge the contribution of patients and clinicians involved in study development, and the support of the MRFF.

References

1. Raghu G, Remy-Jardin M, Richeldi L, et al. Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults: An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. Am J Respir Crit Care Med. 2022;205:e18–47. 10.1164/rccm.202202-0399ST.
2. Leong SW, Bos S, Lordan JL, et al. Lung transplantation for interstitial lung disease: evolution over three decades. BMJ Open Respir Res. 2023;10. 10.1136/bmjresp-2022-001387.
3. Ryerson CJ, Adegunsoye A, Piciucchi S, et al. Update of the International Multidisciplinary Classification of the Interstitial Pneumonias: An ERS/ATS Statement. Eur Respir J. 2025;20250828. 10.1183/13993003.00158-2025.
4. Wells AU, Flaherty KR, Brown KK, et al. Nintedanib in patients with progressive fibrosing interstitial lung diseases-subgroup analyses by interstitial lung disease diagnosis in the INBUILD trial: a randomised, double-blind, placebo-controlled, parallel-group trial. Lancet Respir Med. 2020;8:453–60. 10.1016/S2213-2600(20)30036-9.
5. Richeldi L, du Bois RM, Raghu G, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med. 2014;370:2071–82. 10.1056/NEJMoa1402584.
6. Tikellis G, Corte TJ, Hey-Cunningham AJ et al. Top 10 research priorities for pulmonary fibrosis in Australia: an update. *Thorax* 2025 20251008. 10.1136/thorax-2025-223844

7. Agusti A, Bel E, Thomas M, et al. Treatable traits: toward precision medicine of chronic airway diseases. Eur Respir J. 2016;47:410–9. 10.1183/13993003.01359-2015.
8. McDonald VM, Clark VL, Cordova-Rivera L, et al. Targeting treatable traits in severe asthma: a randomised controlled trial. Eur Respir J. 2020;55:20200305. 10.1183/13993003.01509-2019.
9. Jee AS, Sheehy R, Hopkins P, et al. Diagnosis and management of connective tissue disease-associated interstitial lung disease in Australia and New Zealand: A position statement from the Thoracic Society of Australia and New Zealand. Respirology. 2021;26(20201124):23–51. 10.1111/resp.13977.
10. Camus PPM, Camus P. The drug-induced respiratory disease website., http://www.pneumotox.com/drug/index (2024).
11. care Ag-dohaa. The pharmaceuticals benefits scheme https://www.pbs.gov.au/pbs/home (2025).
12. Cottin V, Selman M, Inoue Y, et al. Syndrome of Combined Pulmonary Fibrosis and Emphysema: An Official ATS/ERS/JRS/ALAT Research Statement. Am J Respir Crit Care Med. 2022;206:e7–41. 10.1164/rccm.202206-1041ST.
13. Humbert M, Kovacs G, Hoeper MM, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Respir J. 2023;61:20230106. 10.1183/13993003.00879-2022.
14. Khor YH, Gutman L, Abu Hussein N, et al. Incidence and Prognostic Significance of Hypoxemia in Fibrotic Interstitial Lung Disease: An International Cohort Study. Chest. 2021;160:994–100520210424. 10.1016/j.chest.2021.04.037.
15. Jacobs SS, Krishnan JA, Lederer DJ, et al. Home Oxygen Therapy for Adults with Chronic Lung Disease. An Official American Thoracic Society Clinical Practice Guideline. Am J Respir Crit Care Med. 2020;202:e121–41. 10.1164/rccm.202009-3608ST.
16. Alfieri V, Crisafulli E, Visca D, et al. Physiological predictors of exertional oxygen desaturation in patients with fibrotic interstitial lung disease. Eur Respir J. 2020;55:20200220. 10.1183/13993003.01681-2019.
17. Khor YH, Ng Y, Sweeney D, et al. Nocturnal hypoxaemia in interstitial lung disease: a systematic review. Thorax. 2021;76(20210429):1200–8. 10.1136/thoraxjnl-2020-216749.
18. Birring SS, Prudon B, Carr AJ, et al. Development of a symptom specific health status measure for patients with chronic cough: Leicester Cough Questionnaire (LCQ). Thorax. 2003;58:339–43. 10.1136/thorax.58.4.339.
19. Reynolds JE, Jette ME, Wright ML, et al. Normative Values for the Leicester Cough Questionnaire in Healthy Individuals. Ann Otol Rhinol Laryngol. 2023;132:705–8. 10.1177/00034894221112517.
20. Cruz-Jentoft AJ, Bahat G, Bauer J, et al. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing. 2019;48:601. 10.1093/ageing/afz046.
21. Malmstrom TK, Morley JE. SARC-F: a simple questionnaire to rapidly diagnose sarcopenia. J Am Med Dir Assoc. 2013;14:531–53220130625. 10.1016/j.jamda.2013.05.018.

22. Guler SA, Marinescu DC, Cox G et al. The Clinical Frailty Scale for Risk Stratification in Patients With Fibrotic Interstitial Lung Disease. *Chest* 2024 20240227. 10.1016/j.chest.2024.02.043
23. Holland AE, Fiore JF Jr., Bell EC, et al. Dyspnoea and comorbidity contribute to anxiety and depression in interstitial lung disease. Respirology. 2014;19:1215–21. 10.1111/resp.12360.
24. Ezzati A, Jiang J, Katz MJ, et al. Validation of the Perceived Stress Scale in a community sample of older adults. Int J Geriatr Psychiatry. 2014;29:645–52. 10.1002/gps.4049.
25. Jo HE, Troy LK, Keir G, et al. Treatment of idiopathic pulmonary fibrosis in Australia and New Zealand: A position statement from the Thoracic Society of Australia and New Zealand and the Lung Foundation Australia. Respirology. 2017;22(20170827):1436–58. 10.1111/resp.13146.
26. McDonald VM, Higgins I, Wood LG, et al. Multidimensional assessment and tailored interventions for COPD: respiratory utopia or common sense? Thorax. 2013;68(20130316):691–4. 10.1136/thoraxjnl-2012-202646.
27. Murphy MJ, Newby JM, Butow P, et al. Randomised controlled trial of internet-delivered cognitive behaviour therapy for clinical depression and/or anxiety in cancer survivors (iCanADAPT Early). Psychooncology. 2020;29:76–85. 10.1002/pon.5267.
28. Dowman L, Hill CJ, May A, et al. Pulmonary rehabilitation for interstitial lung disease. Cochrane Database Syst Rev. 2021;2:CD006322. 10.1002/14651858.CD006322.pub4.
29. Dowman L, Hill CJ, Holland AE. Pulmonary rehabilitation for interstitial lung disease. Cochrane Database Syst Rev 2014: CD006322. 20141006. 10.1002/14651858.CD006322.pub3
30. Saha R, Singh VP, Samuel SR, et al. Effect of Home-Based Pulmonary Rehabilitation on Pulmonary Fibrosis. Multidiscip Respir Med. 2024;19(20240605). 10.5826/mrm.2024.950.
31. Ozalevli S, Karaali HK, Ilgin D, et al. Effect of home-based pulmonary rehabilitation in patients with idiopathic pulmonary fibrosis. Multidiscip Respir Med. 2010;5(20100228):31–7. 10.1186/2049-6958-5-1-31.
32. Australia LF. *Better Living With Exercise* 2026. https://lungfoundation.com.au/support-resources/resource-hub/better-living-with-exercise-booklet/
33. Khor YH, Saravanan K, Holland AE, et al. A mixed-methods pilot study of handheld fan for breathlessness in interstitial lung disease. Sci Rep. 2021;11:6874. 10.1038/s41598-021-86326-8.
34. Han X, Li P, Yang Y, et al. An Exploration of the Application of Step Counter-Based Physical Activity Promotion Programs in Patients With Chronic Obstructive Pulmonary Disease: A Systematic Review. Front Public Health. 2021;9:691554. 10.3389/fpubh.2021.691554.
35. Ferreira IM, Brooks D, White J, et al. Nutritional supplementation for stable chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2012;12:CD000998. 10.1002/14651858.CD000998.pub3.
36. Collins PF, Stratton RJ, Elia M. Nutritional support in chronic obstructive pulmonary disease: a systematic review and meta-analysis. Am J Clin Nutr. 2012;95:1385–139520120418. 10.3945/ajcn.111.023499.

37. Collins PF, Elia M, Stratton RJ. Nutritional support and functional capacity in chronic obstructive pulmonary disease: a systematic review and meta-analysis. Respirology. 2013;18:616–29. 10.1111/resp.12070.
38. Sgalla GCS, Ferrari R. Mindfulness-based stress reduction in patients with interstitial lung diseases: a pilot, single-centre observational study on safety and efficacy. BMJ Open Respir Res. 2015;2. 10.1136/bmjresp-2014-000065.
39. Kropski JA. Familial Interstitial Lung Disease. Semin Respir Crit Care Med. 2020;41:229–37. 10.1055/s-0040-1708054.
40. Southern BD, Gadre SK. Telomeropathies in Interstitial Lung Disease and Lung Transplant Recipients. J Clin Med. 2025;14(20250224). 10.3390/jcm14051496.
41. Cox IA, Borchers Arriagada N, de Graaff B, et al. Health-related quality of life of patients with idiopathic pulmonary fibrosis: a systematic review and meta-analysis. Eur Respir Rev. 2020;29:20201105. 10.1183/16000617.0154-2020.
42. Yorke J, Swigris J, Russell AM, et al. Dyspnea-12 is a valid and reliable measure of breathlessness in patients with interstitial lung disease. Chest. 2011;139:159–16420100701. 10.1378/chest.10-0693.
43. Lee PH, Macfarlane DJ, Lam TH, et al. Validity of the International Physical Activity Questionnaire Short Form (IPAQ-SF): a systematic review. Int J Behav Nutr Phys Act. 2011;8:115. 10.1186/1479-5868-8-115.
44. Reginster JY, Beaudart C, Al-Daghri N, et al. Update on the ESCEO recommendation for the conduct of clinical trials for drugs aiming at the treatment of sarcopenia in older adults. Aging Clin Exp Res. 2021;33:3–17. 10.1007/s40520-020-01663-4.
45. American Thoracic Society. Idiopathic pulmonary fibrosis: diagnosis and treatment. International consensus statement. American Thoracic Society (ATS), and the European Respiratory Society (ERS). Am J Respir Crit Care Med. 2000;161:646–64. 10.1164/ajrccm.161.2.ats3-00.

Figures

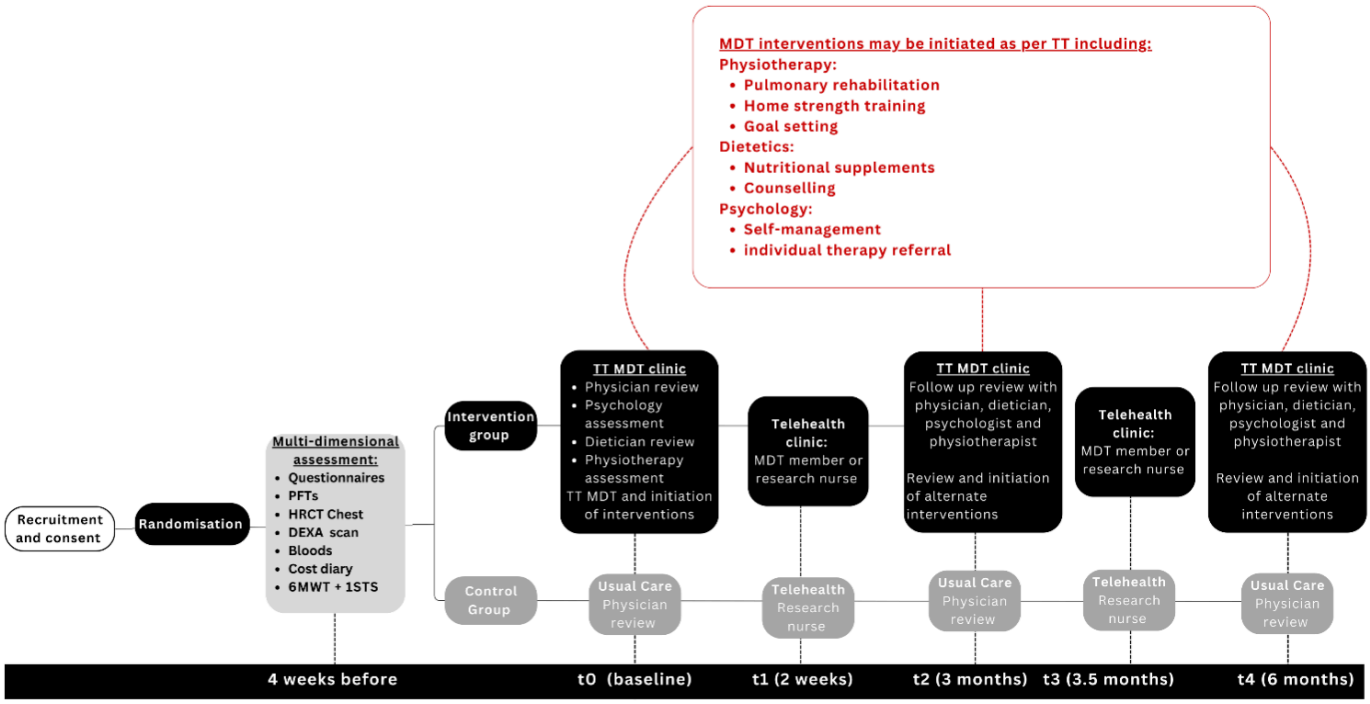


Figure 1

Flow diagram depicting participant journey from recruitment and randomisation to clinic assessments over the 6-month trial period. Abbreviations: PFTs, pulmonary function tests; HRCT, high resolution computed tomography; DEXA, dual energy x-ray absorptiometry; 6MWT, 6-minute walk test; 1STS, 1 minute sit to stand test; TT, treatable traits; MDT, multidisciplinary; t, timepoint

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementarymaterial.pdf