# TREATABLE TRAITS IN INTERSTITIAL LUNG DISEASE (TTRILD) STUDY PROTOCOL

## A randomised controlled trial comparing the targeted management of treatable traits versus standard practice: the TRRILD study.

**Protocol Number: 5.020231213**
**Version: 6.2**
**Date: 10th Sep 2025**


**Author/s:**

Dr. Megan Harrison

Prof. Yuben Moodley

Sharon Maxwell

A/ Prof. Vinicius Cavalheri

A/Prof. Kristin Gainey

Dr. Emily Jeffery

Dr. Damien Foo

Caitlin Vicary

A/Prof. Tamera Corte

A/Prof. Yet Khor

A/Prof. Nicole Goh

Dr. John Mackintosh

Dr. Ingrid Cox

**CONFIDENTIAL**



**Statement of Compliance**

This document is a protocol for a research project. This study will be conducted in compliance with all stipulation of this protocol, the conditions of the ethics committee approval, the NHMRC National Statement on ethical Conduct in Human Research (2023) and the Note for Guidance on Good Clinical Practice.

Dr Megan Harrison will be collaborating on the study as a student, to complete a Doctor of Philosophy. Student supervision will be through the University of Sydney conducted by Professor Tamera Corte. Dr Harrison will be the lead author of publications using data from this research. The articles will be published in journals related to Respiratory Medicine and related to the topics noted below. A prospective multi-site analysis to define treatable traits in an Australian ILD population. Treatable Traits model of Care in Interstitial Lung Disease: A randomised controlled trial.

# Table of Contents

## Study Synopsis

| | |
|---|---|
| Title: | A randomised controlled trial comparing the targeted management of treatable traits versus standard practice in people with interstitial lung disease (ILD) |
| Short Title: | TTRILD |
| Study Objectives: | **Aim 1.** To compare the clinical efficacy of a treatable traits model of care (TTRILD) versus standard care in people with ILD.<br>*Hypothesis 1:* People with ILD who are provided with TTRILD MDT care will experience improved health-related quality of life (HRQoL) (primary outcome), symptoms, anxiety, physical activity, and body composition (secondary outcomes).<br><br>**Aim 2.** To compare the cost-effectiveness of TTRILD MDT clinic versus standard care in people with ILD.<br>*Hypothesis 2:* TTRILD MDT care will be a cost-effective intervention compared to standard care, from a societal perspective.<br><br>**Aim 3.** To establish the prevalence of pre-defined treatable traits and determine the association with quality of life and disease severity.<br>*Hypothesis 3:* Increased number of traits will be associated with reduced quality of life and increased disease severity.<br><br>**Aim 4.** To identify cellular, molecular, and genetic TT in ILD for future improved management. |
| Design: | Randomised controlled trial with an embedded economic evaluation |
| Intervention Duration: | 6 months |
| Population: | People with fibrotic ILD |
| Study Site | South Metropolitan Health Service (Fiona Stanley Hospital)<br>North Metropolitan Health Service (Sir Charles Gairdner Hospital) |
| Inclusion Criteria: | Adults ≥ 18 years |

| | |
|---|---|
| | Physician-confirmed diagnosis of fibrotic interstitial lung disease (ILD)<br>Able to provide consent to participate in the study<br>On stable treatment for ILD for 1 month (no changes to ILD medications in the 1 month prior to recruitment) |
| Exclusion Criteria: | Unable to consent due to cognitive impairment or other reason<br>Death or transplant anticipated within the study period<br>An acute exacerbation within one month of recruitment<br>Active suicidality, severe depression, active psychosis or mania, or other severe psychiatric concerns that require more intensive treatment. Any such participants could be referred for individual therapy and/or psychiatric treatment that would be more appropriate for their needs. |
| Intervention group: | Attendance and care as guided by the TTRILD MDT clinic. The MDT team includes respiratory physician, specialist nurse, physiotherapist, dietitian, and psychologist.<br><br>Clinics will occur at initial review, 3 months, and 6 months. Telehealth clinic at 2 weeks will be undertaken with physiotherapy, dietitian, and psychology with an additional 4-week dietitian phone review.<br><br>Initial clinic review will identify presence of treatable traits including those amenable to MDT interventions and will conclude with a meeting attended by the allied health team to produce a comprehensive patient management plan.<br><br>Physiotherapy interventions include 8-week pulmonary rehabilitation, home-based exercise program, pedometer use with goal setting.<br><br>Dietetic intervention includes dietary counselling, education, and oral nutritional supplements.<br><br>Psychological intervention provided will be self-management plan, or referral for individual treatment<br><br>Physician care is provided as per standard of care with targeted recognition and management of treatable traits such as cough, pulmonary inflammation, and reflux. Handheld fans will be provided for those with significant dyspnoea. |

| | |
|---|---|
| Control group: | Standard ILD care from their usual treating health care team.<br>No limitation to MDT referrals including pulmonary rehabilitation, dietitian review and psychology. |
| Outcomes: | **Primary outcome measure**: Change in HRQoL score as measured using the Kings' Brief Interstitial Lung Disease (K-BILD) at 6 months.<br><br>**Secondary outcome measures:**<br>i) HRQoL using the EQ-5D-5L at 3 and 6 months, KB-ILD at 3 months.<br><br>ii) Dyspnoea measured using the Dyspnea-12.<br>iii) Anxiety and depression measured with the Hospital Anxiety and Depression Scale (HADS).<br><br>iv) Physical activity levels: International Physical Activity Questionnaire (IPAQ) will be measures at baseline and 6 months. Physical activity also monitored by 6-monthly 6-minute walk test (6MWT) and 3-monthly 1-minute sit-to-stand (STS).<br><br>v) Muscle mass and body composition assessed using Dual-Energy X-Ray Absorptiometry (DEXA) scan.<br><br>vi) Lung function decline as measured by forced vital capacity (FVC) decline<br><br>vii) Progression free survival: Time to progression, transplant, or death. Progression defined as a relative decline in either FVC of ≥10% or DLCO ≥15%<br><br>viii) All-cause mortality.<br><br>(viii) Economic evaluation: A comparison of per person direct (health system and all patient expenses) and indirect (lost productivity) costs will be performed for the treatable trait program versus standard care. 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.<br><br>(vii) To establish the prevalence of pre-defined treatable traits. This prevalence will be further assessed to understand inter-relationships and patterns of clustering and co-occurrence. The relationship between traits and QOL (defined by K-BILD) and disease severity (defined by FVC) will also be assessed. |
| Number of planned subjects | 110 |
| Safety considerations | The Data Safety and Monitoring Board (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. |
| Trial Governance | A Steering Committee, chaired by CIA Moodley, will include the chief investigators. The steering committee will meet 3-monthly.<br>An independent consumer advocacy group consisting of 2 patients with ILD will review the protocol and progress 6-monthly. |
| Statistical Methods | All data will be analysed using an intention-to-treat approach. Generalised linear models and Cox regression will be performed to illustrate the effects of the primary and secondary outcomes whilst adjusting for relevant covariates, with subgroup analyses by types of ILD, severity of the disease, and types of personalised program (sarcopenia, loss of appetite, anxiety, cough). All statistical analyses will be overseen by an experienced biostatistician. |
| Funding: | MRFF Chronic Respiratory Conditions. |

# 1. Glossary of Abbreviations and Terms

| 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 |

# 2. Administrative Information

## 2.1 Investigators

| **Chief Investigator** | |
|---|---|
| **Name** | Professor Yuben Moodley |
| **Role** | Chief Investigator |
| **Organisation** | University of Western Australia |
| **Address** | 35 Stirling Hwy, Crawley WA 6009 |

The Chief Investigator will be responsible for supervision and will have authorisation over all activities related to this study including the study design; collection, management, analysis, and interpretation of data; writing the report; and the decision to submit the report for publication.

| **Co-investigators** | Chief Investigators:<br>Dr. Megan Harrison<br>Prof. Tamera Corte<br>Prof. Yet Khor<br>A/Prof Nicole Goh<br>Dr. John Mackintosh<br>A/ Prof. Vinicius Cavalheri<br>Prof. Andrew Palmer<br>Prof. Daniel Chambers<br>Prof. Jo Dickinson<br>Dr. Emily Jeffery<br>Dr. Alan Teoh<br>Dr. Tim Luckett<br>A/Prof. Kristin Gainey | Associate Investigators<br>Dr Ingrid Cox<br>Dr. Jeremy Wrobel<br>Dr. Michael Musk<br>Dr. Vidya Navaratnam<br>Dr. Melissa Simmonds<br>Dr. Adelle Jee<br>Anna Guo<br>Lisa Bateman<br>Dr. Damien Foo |
|---|---|---|

Key partners with which we will engage for the TTRILD study include the clinical trial sites Fiona Stanley Hospital (South Metropolitan Health Service) and Sir Charles Gairdner Hospital (North Metropolitan Health Service). Harry Perkins Institute of Medical Research, and the Centre of Research Excellence in Pulmonary Fibrosis and the Australasian ILD Registry. Other key partners are the NHMRC Clinical Trials Centre, providing clinical trials leadership, statistical expertise and oversight, the Thoracic Society of Australia, and New Zealand (TSANZ), and the patient advocacy organisation, Lung Foundation Australia (LFA).

# 3. Introduction and Background

## Background:

This project will develop a treatable trait-based precision-medicine approach to ILD. ILD encompasses a group of chronic lung disorders that share the hallmark of fibrosis and inflammation of lung tissue [1]. Whilst two anti-fibrotic drugs, nintedanib and pirfenidone, slow the deterioration of progressive fibrotic ILD by approximately 50%, they have minimal impact on common characteristics of ILD such as worsening breathlessness, cough, impaired exercise tolerance, and poor health-related quality of life (HRQoL) [2-4]. Based on the seminal study conducted by the Centre of Research Excellence in collaboration with consumer groups on ILD research priorities, patients emphasized the importance of a good quality of life (QoL). This included addressing key symptoms such as cough and fatigue, as well as answering the fundamental question: "What can make me feel better?"[5].

Currently the cornerstone of ILD diagnosis and ongoing management is the multidisciplinary meeting (MDM). During this meeting, attended by respiratory physicians, radiologists, pathologists +/- immunologists and rheumatologists, clinical cases are discussed, a diagnosis is provided, and management plan is suggested. This diagnosis and subsequent management are centered on the identification of patient underlying aetiology. The utility of this strategy is complex with significant heterogeneity within ILD subtypes, overlapping features and treatment approaches making this challenging. Furthermore, with up to 15% of ILD cases remaining unclassifiable, the potential benefit for a precision model in ILD is apparent [6].

Treatable traits (TT) are a precision medicine approach developed and proposed for the management of obstructive airways diseases, including asthma. It has achieved global support including international guidelines for both Chronic Obstructive Pulmonary Disease (COPD) and severe asthma. Treatable traits are a model of care where a patient undergoes multidimensional assessment to identify clinically important and treatable problems (traits). A specific trait is defined as a 'therapeutic target identified by phenotypes or endotypes through a validated biomarker' [7]. In airways disease these traits fall into three domains: airway, behavioural/risk factor, and comorbidity (ABC). Clinical trials have demonstrated the effectiveness of the TT model in severe asthma and COPD. In a randomised controlled trial (RCT) of 55 patients the TT based intervention resulted in significant improvement in HRQoL (0.86 units, 95% CI 0.49-1.23) and improved asthma control (ACQ reduction of 0.72 (95% CI -1.25- -0.18) compared to standard care [8].

For an ILD TT strategy the addition of a fourth domain has been proposed with the inclusion of aetiological traits. As such a TT model will target TTs across 4 domains: aetiological (e.g. inflammation, connective tissue disease), pulmonary (e.g. exertional hypoxia, cough) extra-pulmonary (e.g. sarcopenia, anxiety/depression), and behavioural (e.g. smoking and physical inactivity) (Figure 1) [9]. ILD represents an ideal candidate for a TT mode of care. While airways

diseases are complex, chronic and have multiple inter-related factors this is even more so in ILD. ILDs have complex overlapping aetiologies, often multiple comorbidities, and significant symptom burden [10].

A TT model of care differs from comprehensive care in several key aspects. The first is the cornerstone of management with the multidimensional assessment. In this process patients undergo intensive assessment to identify and subsequently manage traits in a methodical and detailed manner. The second is the early and intensive involvement of the 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.

# 4. Study Objectives

## 4.1. Hypotheses:

Hypothesis 1: People with ILD who are provided with TTRILD multi-disciplinary team care will experience improved HRQoL (primary outcome), symptoms, anxiety, physical activity, and body composition (secondary outcomes).

Hypothesis 2: TTRILD MDT care will be a cost-effective intervention compared to standard care, from a societal perspective.

## 4.2. Study Aims

**Aim 1. To compare the clinical efficacy of a TTRILD MDT clinic versus standard care in people with ILD.**

**Aim 2. To compare the cost-effectiveness of TTRILD MDT clinic versus standard care in people with ILD.**

**Aim 3. To establish the prevalence of pre-defined treatable traits.**

**Aim 4.** To identify cellular, molecular, and genetic TT in ILD for future improved management.

## 4.3. Outcome measures

**Primary outcome:**
The primary outcome of this trial is the absolute change in HRQoL at 6 months as measured using the King's Brief questionnaire (K-BILD). The K-BILD questionnaire is a brief, validated 15-item, ILD-specific HRQoL questionnaire assessing psychological well-being, breathlessness, activity

limitations, and chest symptoms [11]. It is widely used as an endpoint in international clinical trials.

**Secondary outcomes:**

(i) Further HRQoL assessment.
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 [11]. The KB-ILD will also be measured at 3 months.

(ii) Dyspnoea
Measured using the Dyspnea-12, a simple scale (0-3) validated in fibrotic ILD (fILD) patients, which comprises the physical and affective components of dyspnoea [12].

(iii) Anxiety and depression:
Evaluated using the Hospital Anxiety and Depression Scale (HADS) which is validated to identify psychological distress. It has been shown to demonstrate increased rates of anxiety and depression in patients with ILD [13].

(iv) Physical activity levels:
1. Patient self-reporting of physical activity will be undertaken with the International Physical Activity Questionnaire (IPAQ), a 7-item questionnaire that includes open-ended questions around the participants last 7-day recall of physical activity [13]. This will be assessed at 3- and 6-months and will be compared to baseline.
2. 6-minute walk test (6MWT). Walk distance from 6MWT at 3 and 6 months will be compared to baseline.

(iv) Muscle mass and body composition:
Patients will have their regional and whole-body lean mass and fat mass be assessed using whole-body dual-energy X-ray absorptiometry (DEXA) scans at 6 months compared to baseline. Dual-Energy X-Ray Absorptiometry 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 [14].

(v) Lung function decline and mortality measures:
Forced vital capacity (FVC) decline. A cut-off of 10% reduction in FVC will be recognised as significant FVC decline [15].
Progression free survival: Time to progression, transplant, or death. Progression defined as a relative decline in either FVC of ≥10% or DLCO ≥15% [15]
All-cause hospitalisation and mortality

(vi) Economic evaluation: A comparison of per person direct (health system and all patient expenses) and indirect (lost productivity) costs will be performed for 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. Patient 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, with linkage already approved between these and the Australian ILD Registry, and patient-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.

(vii) To establish the prevalence of pre-defined treatable traits. This will look at overall prevalence of traits at time of recruitment. This prevalence will be further assessed to understand inter-relationships and patterns of clustering and co-occurrence. The relationship between traits and QOL (defined by K-BILD) and disease severity (defined by FVC) will also be assessed.

## 5. Data Collection and Assessments:

Baseline investigations and questionnaires for each participant will be undertaken prior to their initial clinic appointment as part of a multidimensional assessment.

At the time of consent, patients will be enabled to complete their online REDCAP survey which will include information, such as demographics, comorbidities, medications, and exposure history, and the questionnaires. If it is patient preference to not complete these questionnaires virtually, physical questionnaires can be provided in a booked clinic with a research nurse. At this time demographics, comorbidities, medications, and exposure history will be input by the research nurse directly into REDCAP with permission by the patient.

A research nurse will also review electronic medical records and input ILD MDT records and ensure correlation of comorbidities.

Questionnaires to be undertaken at baseline, 3- and 6-months are:

- K-BILD – HRQOL assessment
- Leister Cough questionnaire – assessment of cough
- Stop bang questionnaire – screening tool for OSA
- Dyspnea-12 – evaluation of breathlessness
- Fatigue (FSS) – fatigue screening tool
- Patient-Generated Subjective Global Assessment Short Form (PGSGA-SF) – questionnaire used to determine nutritional status
- Perceived Stress Scale (PSS) – Validated tool to determine patient well-being in response to stress
- Anorexia Cachexia Scale (ACS) – Measures appetite and body perception
- SARC-F – simplified sarcopenia functional assessment tool
- EQ-5D-5L questionnaire – QoL measure to support economic analysis
- International Physical Activity Questionnaire – simple screening tool for inactivity
- HADS – Identifies psychological distress.

An initial cost diary (Appendix 16) will be undertaken as a summary of costs over the last 6 months. Interval cost diary updates will also be performed at 3- and 6-months.

Initial investigations to be performed include baseline blood and sputum samples, pulmonary function testing, 6MWT, 1STST, whole-body DEXA scan, and High-Resolution Computed Topography (HRCT) of the chest. If a HRCT Chest has been undertaken within the last 12 months this will be used as the initial screening HRCT.

Blood tests performed will include FBC, UEC, CRP, LFT, CMP, ANA, ENA, ANCA, ESR, CK, myositis panel, avian, precipitans, and vitamin D. If bloods have been performed within the last 12 months these will not be repeated.

**Table 1 Assessments at each timepoint (Control and Intervention groups)**

| | **Baseline** | **3 month** | **6 months** |
|---|---|---|---|
| **Questionnaires** | + | + | + |
| **Demographics** | + | | |
| **PFTs** | + | + | + |
| **6MWT** | + | | + |
| **1-min STS test** | + | | + |
| **Bloods** | + | | |

| | | | |
|---|---|---|---|
| **Sputum** | + | | |
| **DEXA** | + | | + |
| **HRCT** | + | | |
| **Cost diary** | + | + | + |
| **All-cause hospitalisation / ED visits** | + | + | + |

# 6. Study Design

## 6.1. Study type and 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. Blinding of outcome assessor for the primary outcome is not possible due to the nature of the primary outcome measure (questionnaire completed by the participant who is not blind to group allocation).

The trial will be conducted at Fiona Stanley Hospital in Western Australia with utilisation of research areas in Harry Perkins Institute of Medical Research. Patients will be recruited from ILD clinics in both South and North Metropolitan Health Services. Participants will be randomised 1:1 into two groups. Group 1 will be the intervention group where participants will attend an TTRILD MDT clinic at Fiona Stanley Hospital, where treatable traits will be identified and targeted multidisciplinary interventions will be employed. These interventions will be administered 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 2 in accordance with international treatment guidelines. These will remain at the discretion of the treating respiratory physician for the intervention group. Group 2 will be the control group and will receive the usual standard of care via their ILD clinics. There will be no limitation in referral for multidisciplinary assessment and management.

## 6.2. Eligibility Criteria:

**Inclusion Criteria:** 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. This ILD diagnosis must be made through an ILD MDT.

Included participants will be aged ≥ 18 years with a physician-confirmed diagnosis of fibrotic ILD. Fibrotic ILD is defined as presence of fibrotic changes on CT in the opinion of the investigator. All ILD subtypes, excluding sarcoidosis, will be included. Participants will need to be able to provide consent to participate and be established on stable ILD treatment for 1 month prior to study initiation.

**Exclusion Criteria:** 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. Active suicidality, severe depression, active psychosis or mania, or other severe psychiatric concerns that require more intensive treatment. Any such participants could be referred for individual therapy and/or psychiatric treatment that would be more appropriate for their needs.

## 6.3. 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 and providing a study flyer (Appendix 18). If the participant expresses interest in joining the study further discussion with research coordinator will be undertaken via phone. The names and contact details of potential participants will be documented using a password-protected file stored on a secured network (Microsoft Teams). This will only be accessible to members of the research team and the study coordinator will be advised about new participant added to this list via email.

Participants indicating an interest in participating will be provided with a Participant Consent and Information Form (PCIF) (Appendix 1 with Withdrawal Form 2b) either in person at the study site or via email/mail depending on their preference. Participants will be given at least 24 hours to read the PCIF and an opportunity to ask questions and discuss the study with their healthcare team and/or family before completing the consent form. If they wish to enrol, participants will be able to complete an online consent via the REDCAP link which will then proceed to the questionnaires. If patient prefers to do this in person, they can have this conducted on a written consent form during the screening clinic prior to initiating baseline investigations.

In addition, individuals enrolled in the Australasian ILD Registry may consent to be contacted about future research or clinical trials at the time of enrolment. A cover letter (Appendix 1a) introducing the study and study flyer (Appendix 1) will be sent by mail or email to Australasian ILD Registry participants who are eligible for TTRILD, with instructions on how to contact the relevant site if they are interested in participating.

## 6.4. Randomisation and Stratification:

Participants will be randomised via an online randomisation system in a 1:1 fashion to intervention or control group. Participants will be stratified by i) severity of FVC: mild (FVC predicted >80%), moderate (FVC predicted 50-80%) and severe (FVC predicted <50%). and ii) type of ILD: IPF and non-IPF with a limit of 50% IPF.

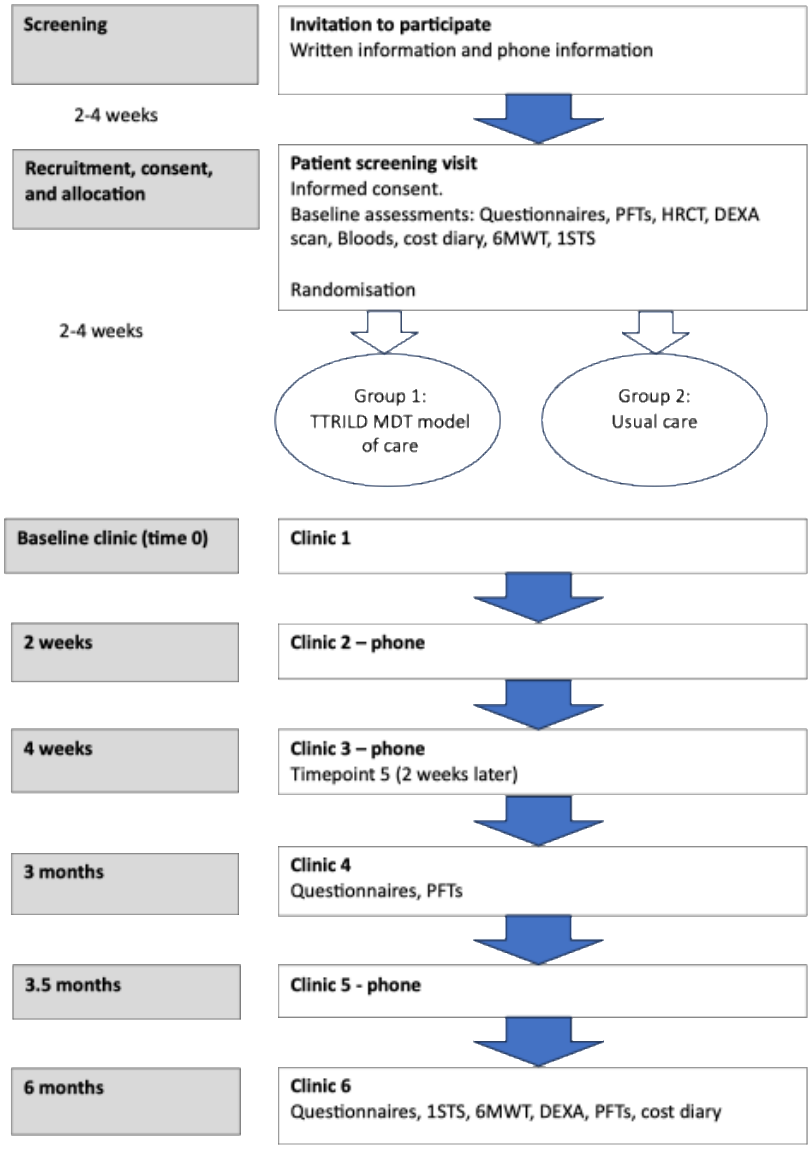



**Figure 1. Recruitment flow chart and assessment/ procedure timeline**

# 7. Interventions

This trial will aim to highlight that the targeted multidisciplinary treatment of TTs will improve patient outcomes, particularly quality of life.

## 7.1. Multidimensional assessment

Both groups will undergo an intensive multidimensional assessment as has been established in other chronic lung diseases including asthma [8,16]

This assessment will aim to identify the following traits as outlined in Table 2 with the following identification markers.

The results of this assessment will be correlated by the research nurse/ case manager and for the interventional team be provided within the TT patient management plan (Appendix 2). All investigations that are performed as standard of care will be provided to the standard of care treating clinical team. This includes HRCT Chest, lung function, 6MWT, 1-min STS test and bloods.

Results of the DEXA scan will be provided to the treating clinician for control group if evidence of osteoporosis is identified. Patients that have an increased STOP-BANG and HADS scores will also be highlighted to treating physician.

**Table 2. Summary of treatable traits with their diagnostic tools and intervention. *Appendix 2* provides further details.**

| 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 [17]. | Consider rheumatology/ immunology input.<br>Consider immunosuppression |
| Drug Exposure | Medication history – exposure of potentially causative drug as defined on pneumotox.com[18] | Withdrawal of causative agent as appropriate<br>Consider glucocorticoids if indicated |
| Environmental exposures | History of exposure to hypersensitivity-type or occupational exposures. | Antigen avoidance<br>Consider immunosuppression |

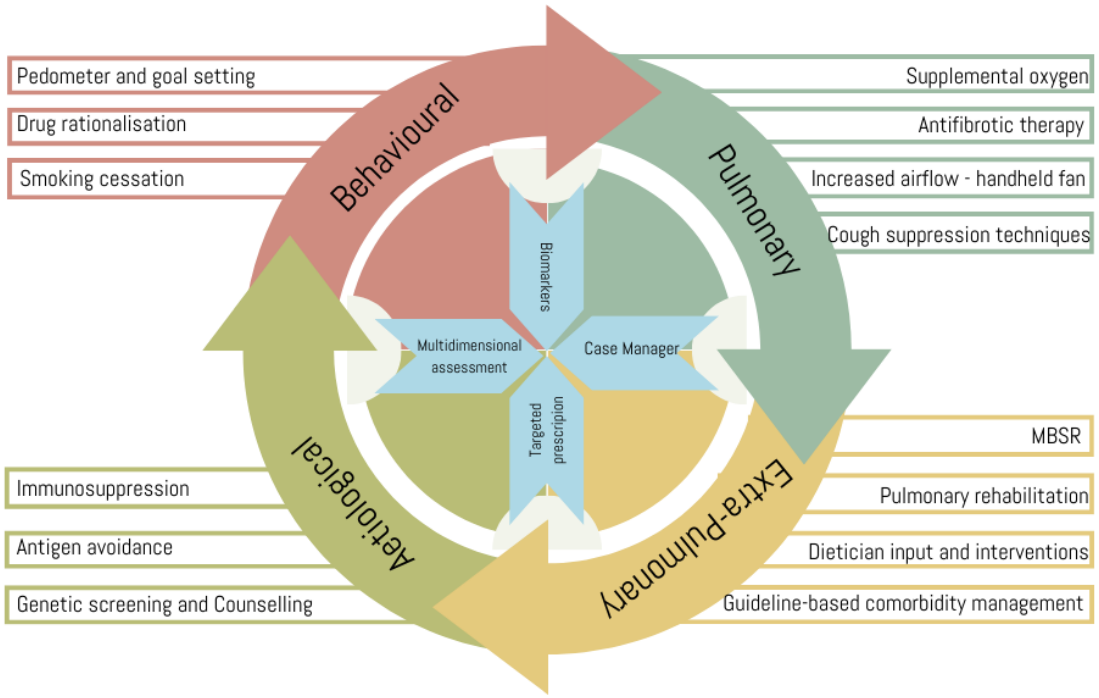
| | | |
|---|---|---|
| Genetics | Specialised testing: Telomere length, Whole genome sequencing | Genetic counselling<br>Discussion at national genetics ILD MDT<br>Augmenting of immunosuppression if required<br>Early transplant referral |
| *Pulmonary Traits:* | | |
| Progressive Pulmonary Fibrosis | ATS/ERS/JRS/ALAT guidelines,<br>Two or more of:<br>(a) worsening respiratory symptoms<br>(b) physiological deterioration with absolute decline in FVC% predicted ≥5% or decline in DLCO% predicted of ≥10% or<br>(c) radiological progression over one year with no alternative explanation [19] | Anti-fibrotics as per pharmaceuticals benefit scheme guidelines Australia [20] |
| Emphysema | HRCT Chest: emphysema ⩾10-15% of total lung volume in the setting of fibrosis[21]<br>+/- Spirometry FEV1/FVC < LLN | Consider bronchodilator if obstructive spirometry |
| Pulmonary Hypertension | Transthoracic echocardiogram: TR jet velocity of >2.8 m/s ≈ mPAP ≥35 mmHg [22] | 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 [23] | Long term oxygen therapy as per international guidelines [24] |
| Exertional Hypoxia | 6MWT nadir Sats ≤ 88% [25] | 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)[26] | Consider nocturnal oxygen prescription |
| Obstructive Sleep Apnoea (OSA) | STOP-BANG questionnaire score: 3-4 (intermediate risk), 5-8 (high risk)<br>Polysomnography evidence of OSA | Referral for CPAP/ mandibular splint |

| | | |
|---|---|---|
| Chronic Cough | Clinical history of chronic cough<br>Leicester cough questionnaire score of <17.68 [27,28] | <u>Address co-contributing drivers:</u><br>- GORD: Treat if symptomatic with standard dose PPI<br>- Postnasal drip: intranasal antihistamines/ intranasal steroids<br>- VCD/ ILO: psychological counselling, speech therapy<br>Cough suppression – speech pathology techniques, consider neuromodulators. |
| Chronic Dyspnoea | History of breathlessness<br>Dyspnea-12 questionnaire with mild + dyspnoea symptoms | Airflow – Handheld fan<br>Pulmonary rehabilitation<br>Consider opioids |
| *Extra-pulmonary traits:* | | |
| Peripheral muscle dysfunction | 1STST of < 20 repetitions | <u>Physiotherapy:</u><br>Home based exercise prescription |
| Exercise Intolerance | 6MWT <350m | <u>Physiotherapy:</u><br>Pulmonary rehabilitation |
| Sarcopenia | 1STS < 20 repetitions and<br>DEXA demonstrating low muscle mass [29]<br>SARC-F questionnaire [30] | <u>Physiotherapy:</u><br>Home based exercise prescription.<br><u>Dietitian:</u><br>If borderline intake for high protein diet<br>If poor intake for high protein diet + protein supplementation |
| Frailty | 1STST < 20 repetitions and physician-judged clinical frailty scale (CFS) score of ≥ 4 [31]. | <u>Physiotherapy:</u><br>Pulmonary rehabilitation |
| Osteoporosis | Clinical history of low trauma fracture<br>DEXA scan: T-score ≤ -2.5 | Dietary recommendations<br>Supplements – calcium and vitamin D<br>Consider Anti-resorptive therapy |
| Poor Appetite and Malnutrition | <u>Poor appetite:</u><br>Anorexia Cachexia Scale Score ≤ 37<br><u>Malnutrition:</u> | <u>Dietitian:</u><br>With borderline intake – small, frequent meals and snacks<br><br>With poor intake – Small frequent meals and snacks, |

| | | |
|---|---|---|
| | Patient-Generated Subjective Global Assessment Short Form ≥ 4 and/ or<br>BMI < 18.5 | Nourishing drinks/ Oral nutritional supplements |
| Anxiety and Depression features | Hospital Anxiety and Depression (HADS) score of 7-10 (borderline)<br>HADS ≥ 11 (significant) [13]<br>and/or<br>Perceived Stress Scale (PSS) ≥ 14 [32]. | <u>Psychology:</u><br>Referral to self-help, treatment in Mindfulness-Based Stress Reduction, or GP referral for individual treatment |
| Fatigue | Fatigue Severity Scale (FSS) ≥ 36 | <u>Physiotherapy:</u><br>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) | <u>Physiotherapy:</u><br>Goal setting with pedometer |

## 7.2 Intervention group:

**Figure 2. Core aspects of the MDT intervention**




**Baseline clinic visit**

*Physiotherapist:*
This initial evaluation will involve a clinical assessment and review of pertinent investigations including 6MWT, PFTs, 1STST, and IPAQ. Based on clinical assessment and presence of treatable traits identified, including exercise intolerance, physical inactivity, sarcopenia, and frailty, patients will be offered a management plan that may include goal setting with a pedometer, pulmonary rehabilitation, and/or a home exercise program (see below for further details). Education will be provided at this time.

*Dietitian:*
This initial evaluation will involve a clinical assessment including discussion regarding patient diet and review of pertinent investigations including BMI, PGSGA-SF, and ACS. Based on clinical

assessment and presence of treatable traits identified, including malnutrition, sarcopenia, and frailty, patients will be offered a management plan that may include a dietary plan and/or oral nutritional supplements (see below for further details). Dietary counselling will be provided at this time.

*Psychologist:*
This initial evaluation will involve a psychological interview and review of pertinent investigations including HADS and PSS. Based on clinical assessment and presence of treatable traits identified (specifically anxiety and depression traits), participants will be offered a targeted management plan. Options for this will include patient self-management resources, MBSR administered via the study, or referral to GP for individual psychology/psychiatry treatment. At this assessment a risk assessment will be performed. Any patient that is identified to be a concern for psychological safety will be referred on to the treating physician for consideration of psychiatric discussion and evaluation.

*Physician:*
This initial evaluation will involve a clinical assessment and review of pertinent investigations including 6MWT, PFTs, HRCT, and questionnaire data. Based on clinical assessment and presence of treatable traits that will be documented on patient management plan, the treating physician will offer therapies as per standard of care and international guidelines. Standard ILD therapies that include anti-fibrotics and immunosuppression will be offered as per standard care. There will be a specific focus on the identification and treatment of the additional TTs that include aetiological traits (drugs, exposures), pulmonary (cough, dyspnoea, exercise intolerance), extra-pulmonary traits (reflux and anxiety/depression) and behavioural traits (physical inactivity, smoking).

**The post clinic-MDT**
Immediately post the initial clinic review an MDT meeting will be undertaken for approx. 60 minutes. This will involve discussion of all patients seen in the initial clinic. Documentation will be via the patient management document and discussion will include ensuring agreement across MDT on presence of traits and the strategy to move forward. It is estimated each patient will require 15-20 minutes of discussion.

**2-week telehealth clinic**

*Physiotherapist:*
For those patients undertaking goal setting with pedometer a 2-week review will be coordinated to review exercise diary and provide goal setting.

*Dietitian:*
A review to assess intervention tolerance and provide feedback/alternatives as required.

*Psychologist:*

After discussion between the psychology team and at MDT, a decision will be made regarding offered therapies, including MBSR. This phone review will be an update to confirm intervention offered and answer any questions or concerns from patients.

**4-week telehealth clinic:**
*Dietitian:*
A review to assess intervention tolerance and provide feedback/alternatives as required.

**3-month and 6-month clinics:**

*Physiotherapist:*
This clinic review will involve a clinical assessment and review of further investigations including repeat 1STST and IPAQ. An assessment of progress regarding interventions offered will be performed and education provided.

*Dietitian:*
This clinic review will involve a clinical assessment and review of further investigations including repeat ACS and PGSGA-SF. An assessment of progress regarding interventions offered will be performed and education provided.

*Physician:*
This review will include clinical assessment regarding treatments to date, and patient status. Second line therapies of specific traits may be offered or considered. Review of investigations will be performed.

## 7.3. Specific interventions:

**Pulmonary rehabilitation:**
For patients with evidence of exercise intolerance and/ or frailty pulmonary rehabilitation will be offered. This is an 8-week program that involves twice weekly 1 hour program. This will be an individually tailored exercise program, which may consist of warmups exercises, stretches, endurance exercises such corridor walking, incline walking on a treadmill, cycling, functional strengthening exercises such as sit to stands, step ups or calf raises. Upper limb endurance and strengthening exercises are incorporated with patient specific weights. Each patient program considers their goals and any musculoskeletal limitations they may have. All patients record their exercises on their own exercise log to enable monitoring of progress. Patients receive a written home exercise program once they have an established gym program, usually given out in session 3 or 4. See appendix 16 for further details.

**Home exercise program:**
This will be planned between the participant and the treating physiotherapist. This will be in line with the lung foundation resource 'Better living with exercise' (Appendix 17). 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?

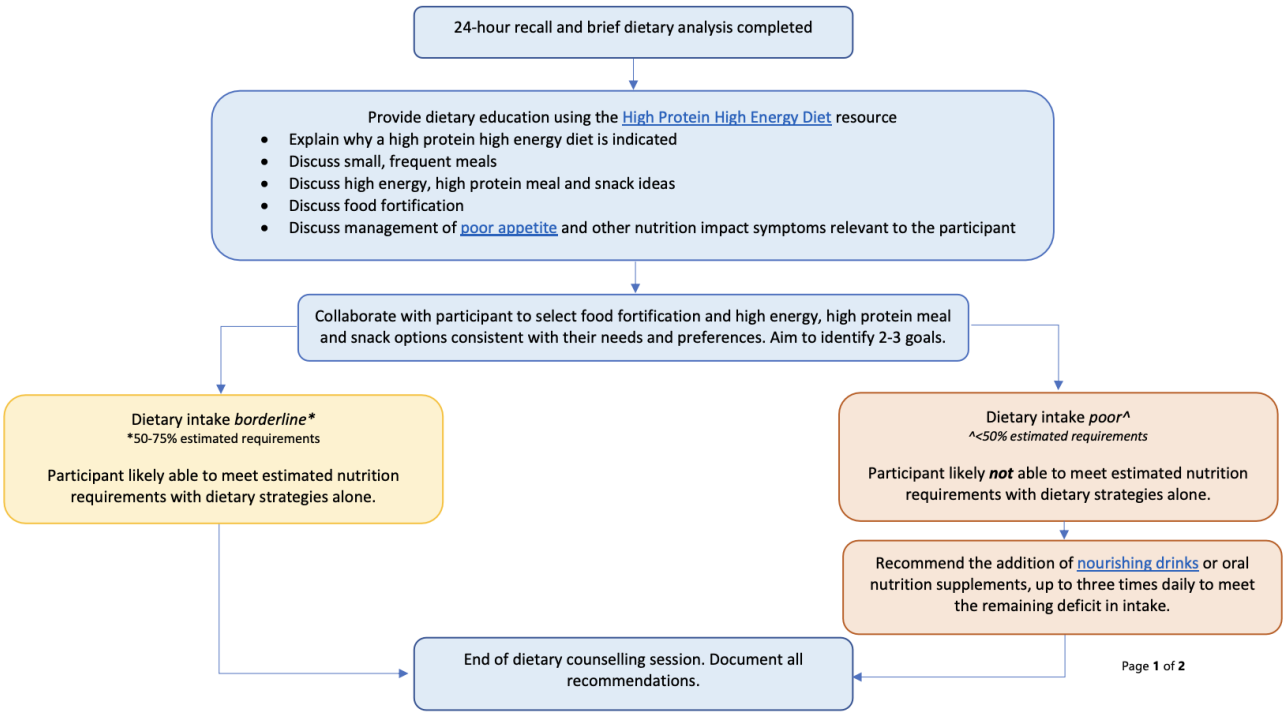
**Goal setting and pedometer:**

In patients where physical inactivity is identified as a trait a personal pedometer will be provided. 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.

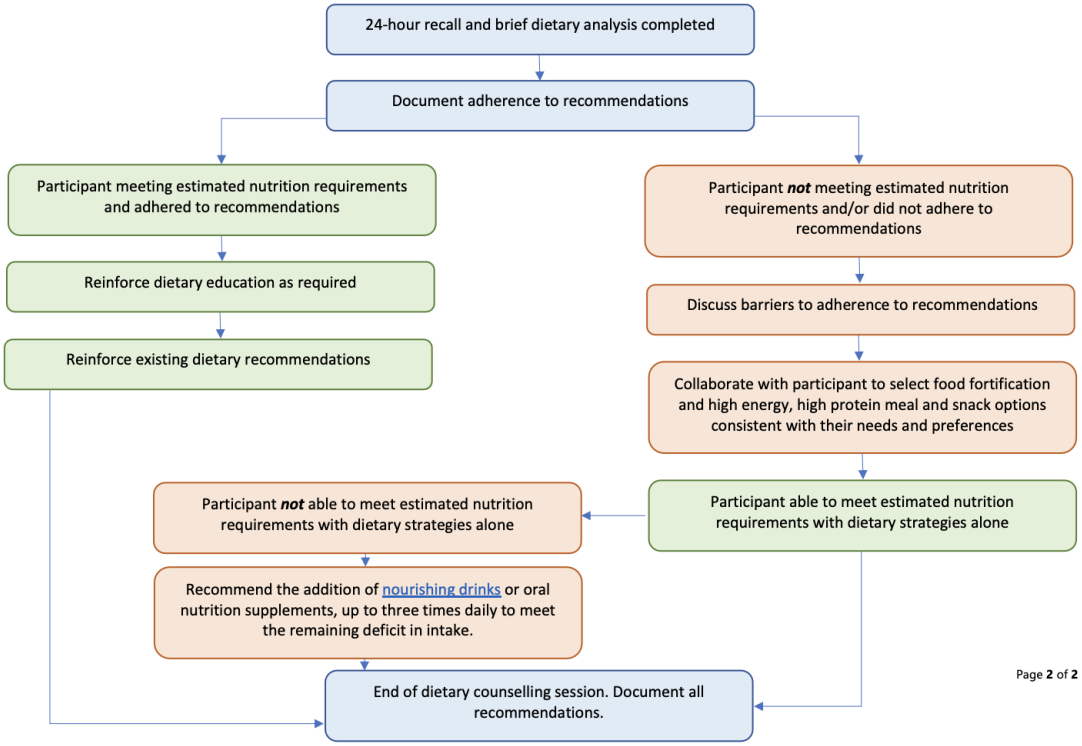
**Dietitian counselling and education:**
Depending on patient appetite, intake, and presence of sarcopenia guidelines regarding meals and diet will be provided by dietitian as per table 4.

| TREATABLE TRAIT | INTERVENTION |
|---|---|
| **Poor appetite** (ACS score ≤37) | |
| + borderline intake | • Small frequent meals and snacks |
| + poor intake | • Small frequent meals and snacks + nourishing drinks/oral nutrition supplements |
| **Malnutrition** (PG-SGA score ≥4) | |
| + borderline intake | • Small frequent meals and snacks |
| + poor intake | • Small frequent meals and snacks + nourishing drinks/oral nutrition supplements |
| **Sarcopenia** | |
| + borderline intake | • High protein diet |
| + poor intake | • High protein diet + protein powder |

## Initial Dietary Counselling Session – Poor Appetite and Malnutrition




## Follow up Dietary Counselling Session – Poor Appetite and Malnutrition



**Oral nutritional supplements:**
Nutritional supplements will be recommended for those patients recognised to have the nutritional disorders that include frailty, sarcopenia, and malnutrition.

For patients identified to have sarcopenia, treatment will focus on achieving adequate protein intake through dietary counselling. If adequate protein intake cannot be achieved through dietary intake alone, then a protein powder will be recommended. A whey protein isolate product, such as Bulk Nutrients WPI, is recommended in the first instance. A plant-based protein powder, such as Bulk Nutrients Earth Protein, can be recommended if the patient does not consume milk or animal products.

Patients with frailty and malnutrition will have treatment to prioritise adequate calories and protein through dietary counselling. If adequate calorie and protein intake cannot be achieved through dietary intake alone, then an oral nutrition supplement will be recommended. A nutritionally complete and balanced powdered nutritional supplement, such as Sustagen Hospital Formula or Ensure Powder, is recommended in the first instance, and can be recommended one to three times daily to meet the deficit in calorie and protein intake. A plant-based protein powder, such as Bulk Nutrients Earth Protein, can be recommended if the patient does not consume milk or animal products. Patients with severe malnutrition or very poor oral intake (i.e., meeting <25% energy requirements with food) may require a nutritional supplement with higher calorie density, such as Resource 2.0, Fresubin 2.0 or Fortisip Compact Protein.

**Self-management psychology plan:**

Patients who have been identified to have low symptom burden will be supported through a self-management plan. Specifically, they will be referred to the "Stress Management Program" created by This Way Up (https://thiswayup.org.au/programs/stress-management-program/), which is a freely available, online, on-demand program based on cognitive-behavioural therapy principles.

**GP referral for individual mental health treatment:**

For patients with moderate-severe psychological symptoms and/or at high risk for self-harm or suicide not identified at time of screening, we will contact their attending doctor to liaise with their GP to discuss a mental health treatment plan that includes psychology and/or psychiatry treatment as needed.

**Genetics assessment**

All patients within the intervention arm will be screened for genetic abnormalities variants known to contribute to inherited forms of ILD. This will include a detailed family history. Blood samples

will be sent to the Institute of Respiratory Health (IRH) for Flow-FISH (fluorescence in-situ hybridization) to determine telomere length. Blood/DNA samples will also be sent to Prof. Jo Dickinson at 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. 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. Patients may elect to not receive their genetic results.

**Circulatory Biomarkers**

We will use circulatory biomarkers with methods including proteomics, metabolomics, transcriptomics, EV analysis and scRNA sequence. These biomarkers will be used to try an identify the presence of biomarker signatures that can predict response to treatment that would help is predict a patient 'fingerprint' that would help us select treatment options.

**Telomeres**

FISH flow will be done on all blood samples from the intervention group to determine if shorter telomeres influence the outcomes in all ILD patients. Mechanisms of shortening to endotype patients will be done.

**Microbiome**

Prog. Phil Hansbro will undertake microbiome analysis of available sputum samples to better phenotype the microbiome of ILD and t determine if intervention in dysbiosis will improve outcomes for ILD patients.

**Personalised Treatment:**

We will analyse scRNAseq to determine if we can identify treatment targets for individual patients using bioinformatic clustering.

## 7.4. Control group:

All participants within the control group will receive baseline assessments as per the intervention group. This includes a 1STS test performed by a research nurse at baseline and at 3- and 6-month clinic appointments. Physician review will be as per standard of care including treatment of underlying ILD and consideration of comorbidity management.

# 8. Feasibility

There are currently over 500 patients with fibrotic ILD receiving care at Fiona Stanley Hospital with an estimated 200 new patients to the ILD service per year. If 30% of these provide consent, which is in line with prior clinical experience in this service, a recruitment goal of 20 participants per quarter is achievable, resulting in the completion of recruitment within 18 months.

If inadequate recruitment is achieved by the first quarter of 20, recruitment will be expanded to ILD patients receiving care at Sir Charles Gairdner Hospital.

# 9. Participant Safety and Withdrawal

## 9.1. Risk management and safety

Data privacy and confidentiality considerations are protected by the University of Western Australia Information and Communications Technology procedures. A Data Safety and Management Board (DSMB), consisting of external experts in the field and consumer representatives, will meet quarterly to review study progress and patient data safety to ensure protection. This DSMB will be include Prof. Vanessa McDonald, Prof Haydn Walters and Prof. Geoff Stewart. A consumer advocacy group made of 3 independent ILD patients will review trial protocol and best practice document and provide feedback. They will also meet with researchers at 6 months to discuss progress.

## 9.2. Handling of withdrawals

If a patient withdraws from the study, a member of the research team will discuss any concerns or issues linked to withdrawing. No further personal information will be collected from the participant from this time. Personal information already collected will be retained to ensure the results of the project can be measured properly. Participants will be informed that data collected up to the time of withdrawal will form part of the study results. If the participant is unhappy with this, the research team will be advised immediately.

## 9.3. Replacements

No withdrawn participants will be replaced in the study. If a participant agrees, they can undertake the remaining assessments to reduce the impact of study analysis and meet the intention-to-treat requirements.

# 10. Statistical methods

## 10.1. Sample size calculation

Previous work in pulmonary rehabilitation and interstitial lung disease 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 K-BILD following the intervention. Based on that data, we anticipate a between-group difference of 4.2 points favouring the experimental group, which will receive multidisciplinary management of their treatable traits. With an α of 0.05 and 90% power, and accounting for a 15% expected attrition, the target sample size will be 110 participants.

## 10.2. Statistical Methods

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 patient 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. 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). All analyses will be performed using Stata MP/18 (StataCorp, Texas). All statistics analysis will be performed with supervision and oversight by an experienced biostatistician.

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).

The prevalence of each TT will be defined including number of TTs per participant with median and interquartile range (IQRR). Cluster analysis with k-mean clustering will be used to identify patterns of TTs within cohort and assess which traits tend to co-occur. To assess relationship between treatable traits and FVC (as a surrogate for ILD severity) we will use univariable regression analysis for each TT and multivariable logistic regression analysis with FVC as outcome. To assess relationship between treatable traits and QOL (using KB-ILD) will use univariable and multivariable logistic regression analysis with KB-ILD score as outcome.

# 11. STORAGE OF BLOOD AND TISSUE SAMPLING

Blood samples will initially be stored securely at Harry Perkins Level2 University of Western Australia (UWA) Freezer (adjacent to Fiona Stanley Hospital). The nurse will take the samples, they will be de-identified, processed in the lab, and then stored before being transported via courier to the laboratory of the Institute of Respiratory Health, UWA for analysis. Coded DNA samples will be sent to Professor Jo Dickinson's laboratory for whole genome sequencing. Data will be entered into a secure online database against the patient unique code. No identifiable information will be entered into the secure online database. Information obtained for this research project will be treated as confidential and securely stored with the option for future use. If a patient does not consent for future use, samples will be destroyed after a period of 10 years.

## 12. DATA STORAGE AND HANDLING

Written information including patient management documents, paper questionnaires, and printed results will be stored in a locked filing cabinet within a locked office at Happy Perkins Institute. Only the named researchers will have access to the information.

All other data will be input directly to the secure UWA REDCAP database. Trial data will be stored securely on the UWA Redcap data base and archived for a period of 15 years as per SMHS data management policy. Access to participant data will be password protected and available only to the trial researchers. If at some stage in the future, the ethics committee deems storage is no longer required, then data will be deleted.

## 13. List of Appendices

| **Document name** | **Page of Supplementary document** |
|---|---|
| 1. Patient Consent and Information Document with withdrawal form | 1 - 13 |
| 2. Patient management document | 14 - 50 |
| 4. Kings Brief Interstitial Lung Disease Questionnaire | 51 - 53 |
| 5. Leister Cough questionnaire | 54 |
| 6. STOP BANG questionnaire | 55, 56 |
| 7. Dyspnea-12 questionnaire | 57 |
| 8. Fatigue Severity Scale | 58 |

| | |
|---|---|
| 9. Patient-Generated Subjective Global Assessment Short Form (PGSGA-SF) | 59, 60 |
| 10. Anorexia Cachexia Scale (ACS) | 61 - 63 |
| 11. Perceived Stress Scale (PSS) | 65, 66 |
| 12. EQ-5D-5L questionnaire | 67, 68 |
| 13. International Physical Activity Questionnaire (IPAQ) | 69, 70 |
| 14. Hospital Anxiety and Depression Scale (HADS) | 71 |
| 15. SARC-F questionnaire | 72 |
| 16. Trial Cost Diary | 73 - 127 |
| 17. Pulmonary rehabilitation material | 128 - 129 |
| 18. Living Better with Exercise | 130 - 166 |

## 14. References


[1] Travis WD, Costabel U, Hansell DM, et al. An official American Thoracic Society/European Respiratory Society statement: Update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med. 2013 Sep 15;188(6):733-48.

[2] Richeldi L, du Bois RM, Raghu G, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med. 2014 May 29;370(22):2071-82.

[3] 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 May;8(5):453-460.

[4] Behr J, Prasse A, Kreuter M, et al. Pirfenidone in patients with progressive fibrotic interstitial lung diseases other than idiopathic pulmonary fibrosis (RELIEF): a double-

blind, randomised, placebo-controlled, phase 2b trial. Lancet Respir Med. 2021 May;9(5):476-486.
[5] Tikellis G, Tong A, Lee JYT, et al. Top 10 research priorities for people living with pulmonary fibrosis, their caregivers, healthcare professionals and researchers. Thorax. 2021 Jun;76(6):575-581.
[6] Ryerson CJ, Urbania TH, Richeldi L, et al. Prevalence and prognosis of unclassifiable interstitial lung disease. Eur Respir J. 2013 Sep;42(3):750-7.
[7] Agusti A. The path to personalised medicine in COPD. Thorax. 2014 Sep;69(9):857-64.
[8] McDonald VM, Clark VL, Cordova-Rivera L, et al. Targeting treatable traits in severe asthma: a randomised controlled trial. Eur Respir J. 2020 Mar;55(3).
[9] Khor YH, Cottin V, Holland AE, et al. Treatable traits: a comprehensive precision medicine approach in interstitial lung disease. Eur Respir J. 2023 Jul;62(1).
[10] Amati F, Spagnolo P, Oldham JM, et al. Treatable traits in interstitial lung diseases: a call to action. Lancet Respir Med. 2023 Feb;11(2):125-128.
[11] 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 Dec 31;29(158).
[12] 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 Jan;139(1):159-64.
[13] Holland AE, Fiore JF, Jr., Bell EC, et al. Dyspnoea and comorbidity contribute to anxiety and depression in interstitial lung disease. Respirology. 2014 Nov;19(8):1215-21.
[14] 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 Jan;33(1):3-17.
[15] 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 Feb;161(2 Pt 1):646-64.
[16] McDonald VM, Higgins I, Wood LG, et al. Multidimensional assessment and tailored interventions for COPD: respiratory utopia or common sense? Thorax. 2013 Jul;68(7):691-4.
[17] 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 Jan;26(1):23-51.
[18] Camus P PM, Camus P. The drug-induced respiratory disease website. Immunol Allergy Clin North Am [Internet]2024. Available from: http://www.pneumotox.com/drug/index
[19] 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 May 1;205(9):e18-e47.
[20] care Ag-dohaa. The pharmaceuticals benefits scheme 2025. Available from: https://www.pbs.gov.au/pbs/home
[21] 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 Aug 15;206(4):e7-e41.

[22] Humbert M, Kovacs G, Hoeper MM, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Respir J. 2023 Jan;61(1).
[23] 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 Sep;160(3):994-1005.
[24] 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 Nov 15;202(10):e121-e141.
[25] 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 Feb;55(2).
[26] Khor YH, Ng Y, Sweeney D, et al. Nocturnal hypoxaemia in interstitial lung disease: a systematic review. Thorax. 2021 Dec;76(12):1200-1208.
[27] 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 Apr;58(4):339-43.
[28] Reynolds JE, Jette ME, Wright ML, et al. Normative Values for the Leicester Cough Questionnaire in Healthy Individuals. Ann Otol Rhinol Laryngol. 2023 Jun;132(6):705-708.
[29] Cruz-Jentoft AJ, Bahat G, Bauer J, et al. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing. 2019 Jul 1;48(4):601.
[30] Malmstrom TK, Morley JE. SARC-F: a simple questionnaire to rapidly diagnose sarcopenia. J Am Med Dir Assoc. 2013 Aug;14(8):531-2.
[31] Guler SA, Marinescu DC, Cox G, et al. The Clinical Frailty Scale for Risk Stratification in Patients With Fibrotic Interstitial Lung Disease. Chest. 2024 Feb 27.
[32] 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 Jun;29(6):645-52.