Physical Activity Promotion in Lung Transplant Recipients

Emily Hume

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Emily Hume

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Abstract

Lung transplantation is an established final treatment option for patients with advanced chronic respiratory disease. Despite its success in enhancing pulmonary function and health-related quality of life (HRQoL), limitations in physical and emotional function have been reported to persist in lung transplant recipients. To confirm this notion and to fully understand the level of physical and emotional functioning in these patients, the present thesis compared accelerometry-derived physical activity and HRQoL outcomes between lung transplant recipients and healthy individuals in the UK. Lung transplant recipients displayed significantly lower levels of daily physical activity across a number of parameters, along with significantly lower HRQoL in domains related to physical functioning, highlighting the need for effective interventions to promote physical activity in this population.

Physical inactivity in daily life may contribute to impaired recovery of physical functioning following lung transplantation and diminish long-term outcomes. Given the paucity of research into potential interventions to address physical inactivity in lung transplant recipients, the current thesis includes a systematic review of the evidence supporting the benefits of exercise training for lung transplant candidates and recipients. Whilst exercise training appeared to have a positive impact on exercise capacity and HRQoL, the available evidence is low quality and limited by the lack of randomised controlled trials (RCTs).

The main study of the present thesis investigated the feasibility, acceptability, and safety of a 3-month behavioural modification physical activity tele-coaching (TC) intervention in lung transplant recipients that has been proof-tested previously in COPD patients. The intervention consisted of a validated, commercially available pedometer that was used as a motivational tool to monitor daily activity, and a smartphone app, allowing transmission of pedometer activity data to a cloud-based platform that provided

feedback, activity goals, education, and telephone contact with the researcher when required. The study employed an RCT design to evaluate the potential effect of the intervention, by assessing the short- (3 months) and longer-term (6 months) impact on physical activity, HRQoL, anxiety and depression, compared to usual care (UC).

The results showed that key criteria for progressing to a full-scale RCT study were met. Of the 22 patients eligible, 20 were recruited and randomised to TC or UC and 18 completed (67% male; mean ± SD age; 57 ± 10 years; COPD n=5, ILD n=10, CF n=2, PH n=1): TC (n=10) and UC (n=8). TC was well accepted by patients, with 88% indicating that they enjoyed taking part. Usage of the pedometer was excellent, with 80% of patients wearing it for over 90% of days and rating the pedometer and telephone contact as the most vital aspects. There were no adverse events related to the intervention. After 3 months, both TC and UC displayed clinically important improvements in accelerometer steps/day (by 2945±3056 and 1566±1400 steps/day, respectively) and SF-36 physical component summary (PCS) scores, however TC exceeded UC by clinically important margins (by 1379 steps/day and 5 points, respectively). Only the TC group displayed significant improvement in movement intensity (by 138±148 VMU) and time spent in at least light activity (by 43±28 min/day). At 6 months, the TC group maintained improvements gained in physical activity and HRQoL, however the UC group exhibited clinically important declines in daily steps, SF-36 PCS, and anxiety scores.

In conclusion, physical activity TC is a feasible, safe, and well accepted intervention in lung transplant recipients. Whilst there is a degree of natural recovery in physical activity and HRQoL following lung transplantation, physical activity TC has the potential to optimise these outcomes. Furthermore, the implementation of behavioural modification strategies resulted in better maintenance of health outcomes beyond the initial intervention period. Therefore, this thesis can inform a full-scale RCT to determine the true short- and long-term effect of physical activity TC in lung transplant recipients, compared to UC.

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List of Abbreviations

6MWT	Six-minute walk test
AATD	Alpha-1 Antitrypsin Deficiency
CAT	COPD Assessment Test
CF	Cystic Fibrosis
CO_2	Carbon Dioxide
COPD	Chronic obstructive pulmonary disease
CRQ	Chronic Respiratory Questionnaire
FEV_1	Forced expiratory volume in the first second
GDPR	General Data Protection Regulation
GOLD	Global Initiative for Chronic Lung Disease
HADS	Hospital Anxiety and Depression Scale
HIIT	High intensity interval training
HRA	Health Research Authority
HRQoL	Health-related quality of life
ICC	Intraclass correlation coefficient
ILD	Interstitial Lung Disease
IPF	Idiopathic Pulmonary Fibrosis
LTx	Lung transplantation
MCID	Minimal clinically important difference
MCS	Mental Component Summary
MVV	Maximal voluntary ventilation
O_2	Oxygen
PAH	Pulmonary Arterial Hypertension
PH	Pulmonary Hypertension
PCS	Physical Component Summary
PR	Pulmonary rehabilitation
PWR	Peak work rate
QALY	Quality-adjusted-life-years
R&D	Research and Development
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SF-36	Short-Form 36
SGRQ	St Georges Respiratory Questionnaire
V/Q	Ventilation / perfusion
$\dot{V}E$	Ventilation
$\dot{V}O_{2peak}$	Peak oxygen uptake
WBVT	Whole body vibration training

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DECLARATION

I declare that the work contained in this thesis has not been submitted for any other award and that it is all my own work. I also confirm that this work fully acknowledges opinions, ideas and contributions from the work of others.

Any ethical clearance for the research presented in this thesis has been approved. Approval has been sought and gained by the Faculty of Health and Life Sciences Ethics committee for each study and from the Health Research Authority.

Name: Emily Hume

Signature:

Date: 30th August 2022

Chapter 1: Introduction

1.1 Introduction

A lung transplant is a surgical procedure to remove and replace a diseased lung with a healthy lung from a donor (Thabut & Mal, 2017). Lung transplantation (LTx) is considered for individuals with advanced terminal lung diseases such as Interstitial lung disease (ILD), Chronic Obstructive Pulmonary Disease (COPD), Cystic Fibrosis (CF) and Pulmonary Arterial Hypertension (PAH) whose clinical status has declined despite maximal medical or surgical intervention (Weill, 2018). Although survival rates remain below other organ transplants, lung transplant survival has improved over recent years, with a 5-year survival rate of 55.3% in the UK (NHS Blood and Transplant, 2020). In addition to prolonging survival, enhancing physical functioning and quality of life is an important goal of LTx (Singer & Singer, 2013). Whilst LTx does elicit improvements in general quality of life, compared to pre-transplantation, limitations in physical functioning and health-related quality of life (HRQoL) often persist following LTx (Studer, Levy, McNeil, & Orens, 2004). This is perhaps surprising given that LTx recipients often achieve normal or close to normal pulmonary function and stresses the role of extrapulmonary factors in limiting exercise tolerance following LTx (Mathur, Reid, & Levy, 2004). This could be due to a number of factors such as deconditioning persisting from pre-transplant conditions and extended hospital stay, the side effects of immunosuppressant medications and the psychological stress of undergoing lung transplantation (Langer, 2015).

Evidence investigating the effect of pulmonary rehabilitation (PR) interventions in lung transplant patients demonstrate a beneficial impact on exercise capacity, quality of life and post-operative clinical outcomes (Hume et al., 2020), which is detailed in the systematic review in Chapter 3. However, the evidence is predominantly limited to non-randomised and single cohort studies (Hume et al., 2020). In the UK, physiotherapy support is provided to LTx recipients whilst in hospital to promote early mobilisation,

however referral to a structured PR programme following discharge is not undertaken routinely and will vary depending on the geographical catchment of the patient.

It is evident from previous literature that LTx candidates are significantly inactive in daily life, and this remains the case immediately following LTx (Wickerson, Mathur, Singer, & Brooks, 2015). Whilst there is a degree of improvement in the first 3 months following discharge, physical activity levels remain markedly lower than the general population, with physical inactivity being associated with impaired exercise capacity and HRQoL (Langer et al., 2009; Wickerson et al., 2015). This is also concerning as physical inactivity is associated with an increased risk of mortality in the general population (Lee et al., 2019), as well as in COPD patients (Garcia-Aymerich, Lange, Benet, Schnohr, & Anto, 2006), one of the diseases commonly undergoing LTx. This highlights the importance of promoting physical activity in this population. Studies targeting physical activity promotion in lung transplant recipients is scarce, however trials undertaken in COPD patients as well as non-respiratory chronic diseases highlight the importance of incorporating behavioural modification strategies to optimise participation in daily physical activity (Cavalheri, Straker, Gucciardi, Gardiner, & Hill, 2016; Cradock et al., 2017). These behavioural strategies typically encompass motivational interviewing, individual goal setting, collection of objective physical activity on which to base goals and feedback on, and regular contact with a healthcare professional to enhance motivation, adherence and overcome barriers (Cavalheri et al., 2016). For instance, a systematic review in COPD patients reported that physical activity coaching using objective activity monitoring was deemed a successful intervention for enhancing physical activity, with 11 out of 14 studies demonstrating positive findings (Mantoani, Rubio, McKinstry, MacNee, & Rabinovich, 2016). This was supported more recently in a meta-analysis of 17 studies, which concluded that pedometer based behavioural modification strategies enhanced daily steps in COPD patients when implemented alone of alongside PR (Armstrong et al., 2019).

Whilst a degree of natural recovery would be expected following LTx once discharged from hospital, this has not been well investigated, with many intervention studies lacking a usual care arm (Hoffman, Chaves, Ribeiro-Samora, Britto, & Parreira, 2017; Hume et al., 2020; Wickerson, Mathur, & Brooks, 2010). Hence, the final study of this thesis aims to compare a physical activity behavioural modification intervention to usual care. Previous research has emphasised the importance of patient adherence when implementing behavioural modification interventions (Heesch, Mâsse, Dunn, Frankowski, & Mullen, 2003; McLaughlin et al., 2021). With only five lung transplant centres in the UK, LTx recipients often live far away from the transplant hospital (NHS Blood and Transplant, 2020). Thus, digital health technology offers an alternative delivery option to stimulate patients' engagement in daily physical activity and improve patient adherence (Gao & Lee, 2019). Furthermore, at times of infection prevention and control measures due to the COVID-19 pandemic, digital interventions that do not require face-to-face contact may play an increasingly important role in supporting vulnerable patients (Rauschenberg et al., 2021).

Tele-coaching is a digital health intervention that has the potential to enhance physical activity by applying behavioural change techniques such as goal setting, self-monitoring, feedback, and motivational messages, using electronic communication strategies. In COPD patients across Europe, tele-coaching was shown to be a well-accepted and feasible intervention (Loeckx et al., 2018), with results demonstrating improvements in the amount and intensity of daily physical activity undertaken compared to usual care (Demeyer et al., 2017). However, LTx recipients often experience non-linear health trajectories due to episodes of organ rejection, have a high treatment burden and often have other co-morbidities which may impact participation in daily physical activity (Studer et al., 2004). Consequently, it is uncertain whether physical activity tele-coaching will be feasible in these patients and whether patients will engage and adhere to the technology. To date, little is known about the feasibility and acceptability of tele-rehabilitation models,

specifically tele-coaching, in LTx recipients. Therefore, the main study of this thesis will assess the feasibility and acceptability of a physical activity behavioural modification tele-coaching intervention in LTx recipients.

Currently, the research exploring rehabilitation interventions in LTx recipients is limited by the lack of randomised controlled trials (RCT) (Hume et al., 2020). With the absence of a comparator group, it is difficult to determine the true effect of these interventions, particularly as a degree of recovery is expected in the early stages following lung transplant (Langer et al., 2012; Wickerson et al., 2015). Therefore, the main feasibility study of this thesis will employ an RCT design to obtain preliminary data on the effect of tele-coaching in lung transplant recipients and determine whether tele-coaching added to usual care optimises improvements in physical activity and HRQoL outcomes, in comparison to usual care alone. In addition to looking at the acute effects of a tele-coaching intervention, this thesis will examine its longer-term outcomes, to explore whether the intervention group maintains any improvements made in physical activity once tele-coaching is removed, thus determine whether the intervention has embedded behavioural modification towards enhanced daily physical activity. Likewise, it will explore the natural course of recovery in the usual care group by assessing the trajectory of physical activity over the 6 months following hospital discharge.

Before commencing the intervention study of this thesis, a systematic review (Chapter 3) was conducted to examine the existing evidence pertaining to exercise training interventions in lung transplant candidates and recipients. The following experimental chapter then aimed to assess the validity and test re-test reliability of the pedometer that will be used as part of the tele-coaching intervention (Chapter 5). Then, a case control study was undertaken to fully understand the degree of deconditioning and physical inactivity in our specific cohort of LTx recipients in the UK, compared to healthy age matched individuals (Chapter 6). The specific aims of each chapter are as follows:

1.2 Chapter Aims

Chapter 2: To review the existing literature pertaining to chronic respiratory diseases that undergo lung transplantation, the underlying physiology and factors that contribute to exercise intolerance and physical inactivity in these patients and potential interventions to enhance physical activity in chronic respiratory disease.

Chapter 3: To systematically review the existing evidence on the effects of exercise training on exercise capacity, quality of life and clinical outcomes in lung transplant candidates and recipients.

Chapter 4: To provide justification and rationale for the general methods employed throughout this thesis.

Chapter 5: To investigate the criterion validity and test re-test reliability of the pedometer that was employed in the tele-coaching trial in healthy individuals and patients with chronic respiratory disease.

Chapter 6: To evaluate physical activity levels, HRQoL and psychological wellbeing in lung transplant recipients compared to healthy-age matched individuals in the UK.

Chapter 7: To investigate the feasibility and acceptability of a physical activity behavioural modification tele-coaching intervention in lung transplant recipients, as well as the short- and longer-term effect of the intervention to optimise physical activity and HRQoL, compared to usual care.

Chapter 8: To discuss the collective findings of this thesis, with practical implications and directions for future research, including how this preliminary feasibility study can lead to a full multicentre RCT across the UK.

Chapter 2: Literature Review

2.1 Chronic Respiratory Disease

Chronic respiratory disease is a term used to describe diseases of the airways and other structures of the lung. Respiratory disease affects one in five people in England and is the third biggest cause of death (British Lung Foundation, 2022). Each year, lung conditions including lung cancer, are estimated to cost around £9.9 billion each year and remain a major factor in the winter pressures faced by the NHS, with significant increases in hospital admissions over the past seven years (British Lung Foundation, 2017). Common types of chronic respiratory disease include Chronic Obstructive Pulmonary Disease (COPD), Interstitial Lung Disease (ILD), Cystic Fibrosis (CF), Pulmonary Arterial Hypertension (PAH), Bronchiectasis, and Asthma (Burney, Jarvis, & Perez-Padilla, 2015).

2.1.1 Chronic Obstructive Pulmonary Disease

Chronic Obstructive Pulmonary Disease is defined as "a common, preventable, and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases" (Global Initiative for Chronic for Chronic Obstructive Lung Disease, 2022, p. 4). COPD is an umbrella term for two main conditions, emphysema and chronic bronchitis (Devine, 2008). Emphysema is characterised by abnormal permanent enlargement of lung air spaces with the destruction of alveoli walls and lung parenchyma, resulting in a loss of surface area and elasticity (Goldklang & Stockley, 2016). Chronic bronchitis is characterised by long term inflammation of the airways and mucus hyper-secretion (Kim & Criner, 2013).

Statistics from the British Lung Foundation show that COPD affects 4.5% of people in the UK over the age of 40. It is estimated that 3 million people have COPD in the UK, however only 1.2 million have been formally diagnosed. In the UK, COPD is responsible

for nearly 30,000 deaths (5.3% of all deaths) per year, which places it 12th worldwide in terms of deaths per million population a year (British Lung Foundation, 2022). Respiratory disease is a growing concern across the nation, and it has now been prioritised in the NHS long term plan (NHS, 2019). Despite this, there are significant geographic variations in the prevalence of COPD, with higher prevalence present in the North-East, North West and Scotland (Nacul et al., 2011).

2.1.1.1 Aetiology of COPD

It is well established that cigarette smoking is the most important risk factor for the development of COPD, accounting for over 70% of cases in high income countries (Zuo et al., 2014). Literature shows that cigarette smokers with COPD tend to have a higher symptom burden, lung function abnormalities and COPD mortality rate than non-smokers (Tan et al., 2015). Other types of tobacco (e.g. pipe, cigar, marijuana) are also risk factors for COPD. There is also growing evidence that passive exposure to cigarette smoke is associated with an increased risk of COPD, with the risk among non-smokers doubled (OR 1.98), if exposure exceeded 20 h/week (Jordan, Cheng, Miller, & Adab, 2011).

The remaining risk is largely attributed (15-20% of cases) to occupational exposures and air pollution. A Swiss cohort study of working adults concluded that high levels of occupational exposure to biological dusts, mineral dusts and/or gases/fumes were associated with the incidence of moderate COPD, even in non-smokers (Mehta et al., 2012).

2.1.1.2 Pathogenesis and Pathophysiology of COPD

Chronic Obstructive Pulmonary Disease is characterised by poorly reversible airflow obstruction and an abnormal inflammatory response in the lungs (Barnes et al., 2015). Long term exposure to noxious particles and gases leads to an amplified inflammatory

response, that may lead to mucous hypersecretion (chronic bronchitis), tissue destruction (emphysema) and disruption of normal repair and defence mechanisms (bronchiolitis) (MacNee, 2006). In addition to inflammation, an imbalance between proteases and antiproteases and oxidative stress contribute to the pathogenesis of COPD. These mechanisms result in physiological abnormalities including airflow obstruction and hyperinflation, impaired gas exchange, mucous hypersecretion and ciciliary dysfunction, pulmonary hypertension, and systemic effects including cachexia and skeletal muscle wasting, as well as an increased risk of co-morbidities (Fischer, Pavlisko, & Voynow, 2011).

2.1.1.3 Symptoms and diagnosis of COPD

The most common symptom of COPD is chronic and progressive breathlessness, which can cause significant disability and have a detrimental impact on quality of life, anxiety and depression and ability to undertake daily activities (Miravitlles & Ribera, 2017). Other symptoms of COPD include a chronic cough, sputum production, wheezing and chest tightness. Those with severe disease may also present with fatigue, weight loss and anorexia (Global Initiative for Chronic Obstructive Pulmonary Disease, 2022).

NICE guidelines recommend that COPD should be suspected in individuals over the age of 35 with a risk factor (smoking or occupational exposure), who have one or more supporting symptom (NICE, 2021). Spirometry is required to make a COPD diagnosis, with a post-bronchodilator $FEV_1/FVC < 0.70$ confirming the presence of persistent airflow limitation (Global Initiative for Chronic Obstructive Pulmonary Disease, 2022). The extent of disease severity can then be characterised using Table 2-1.

Table 2-1: GOLD Classification of airflow limitation severity in COPD (based on post-bronchodilator of FEV1) (Global Initiative for Chronic Obstructive Pulmonary Disease, 2022).

In patients with FEV_1/FVC <0.70:		
Gold 1:	Mild	$FEV_1 \geq 80\%$ predicted
Gold 2:	Moderate	$50\% \leq FEV_1 < 80\%$ predicted
Gold 3:	Severe	$30\% \leq FEV_1 < 50\%$ predicted
Gold 4:	Very Severe	$FEV_1 < 30\%$ predicted

2.1.1.4 Alpha-1 Antitrypsin Deficiency

Alpha-1 Antitrypsin Deficiency (AATD) accounts for 1-2% of all expected COPD cases worldwide (Soriano et al., 2018) and is a genetic condition characterised by low circulating levels of the alpha-1 antitrypsin (AAT) protein that protects lung tissue from damage caused by proteolytic enzymes (Torres-Durán et al., 2018). This deficiency is caused by mutations in the SERPINA1 gene and pre-disposes individuals to a number of conditions, commonly manifesting as emphysema and/or liver disease. A systematic review of European populations reported that 0.12% of COPD patients had AATD PiZZ genotypes, with a prevalence of 1 in 408 people in northern Europe to 1 in 1274 people in Eastern Europe (Blanco et al., 2020). In those with AATD, factors such as smoking and occupational exposures can increase the likelihood of developing COPD (Global Initiative for Chronic Obstructive Pulmonary Disease, 2022). AAT augmentation is the primary treatment for AATD and has been shown to slow the progression of emphysema, however end-stage lung disease remains inevitable in some individuals (Wewers & Crystal, 2013). Although only a small minority of patients (~5%) require transplantation, it constitutes the fourth most common indication for LTx worldwide. Patients undergoing LTx for AATD COPD are on average 10 years younger than non-AATD COPD, with less exposure to tobacco smoke (Giacoboni et al., 2015). Evidence indicates favourable survival rates for AATD COPD compared to non-AATD COPD, however those with AATD are at greater risk for common post-transplant complications (Zamora & Ataya, 2021).

2.1.2 Interstitial Lung Disease

Interstitial lung disease is a collective term for a large group of conditions which result from damage to the cells surrounding the alveoli, causing progressive fibrotic scarring and/or inflammation of the lungs (King, 2005). There are more than 200 ILD's, however most of these are very rare. Idiopathic Pulmonary Fibrosis (IPF) and Sarcoidosis are the most common, accounting for around 50% of all ILD's (Cottin et al., 2018). Lung transplantation is a treatment option for patients with advanced or progressive fibrotic ILD, in particular IPF, which is the most common indication for LTx worldwide, as well as fibrotic hypersensitivity pneumonitis, sarcoidosis and connective tissue disease-associated ILD (Kapnadak & Raghu, 2021).

Idiopathic Pulmonary Fibrosis is an incurable disease, characterised by chronic and progressive scarring of the lungs, with a median survival of two to five years following diagnosis (Günther et al., 2012). It is estimated that around 30,000 people in the UK live with IPF, however due to the limited treatment options, over 5,000 people (1% of all deaths) die from the disease each year (Shaw, Marshall, Morris, & Chaudhuri, 2018). The British Thoracic Society IPF registry from 2021 showed that 79% of those diagnosed were male, with an average age of 74 years old when first seen in hospital (British Thoracic Society, 2021). Additionally, 84% of patients had at least one co-morbidity, with the most common being hypertension, ischaemic heart disease, gastro-oesophageal disease and diabetes (British Thoracic Society, 2021).

2.1.2.1 Pathogenesis and Pathophysiology of IPF

Historically, IPF was considered a chronic inflammatory disorder, however it is now considered to be caused by the interaction of multiple genetic and environmental risk factors, with sustained alveolar epithelial micro-injury playing a key role (Richeldi, Collard, & Jones, 2017). A history of cigarette smoking is associated with IPF

development, as well as other environmental exposures, including metal and wood dusts, silica dust, viruses and agriculture and farming (Sgalla et al., 2018). Growing evidence suggests that genetic susceptibility plays a role in the development of IPF, with studies identifying common genetic variants, which account for approximately a third of the disease development risk (Fingerlin et al., 2013). Idiopathic Pulmonary Fibrosis manifests as structural scar tissue, collapse of the alveolar walls, parenchymal damage and interstitial fibrosis. At rest, IPF patients exhibit restrictive pulmonary physiology of reduced total lung capacity and forced vital capacity, in addition to severely impaired gas exchange (Vainshelboim, 2016).

2.1.2.2 Symptoms and Diagnosis of IPF

The symptom burden experienced by patients with IPF is high, with breathlessness, chronic cough, fatigue, and clubbing presenting as the most common symptoms (Barratt, Creamer, Hayton, & Chaudhuri, 2018). The most recent BTS report highlights that significant delays from symptom onset to diagnosis remain, with 63.5% of patients experiencing chest symptoms for more than 12 months before their first hospital visit (British Thoracic Society, 2021). Diagnosing IPF can be challenging and requires a multidisciplinary approach involving pulmonologists, radiologists, and pathologists. The diagnostic approach commonly involves evaluation of clinical presentation, medical history, smoking status, lung function, serological test results, imaging and, if required, lung biopsy (Cottin et al., 2018). The primary diagnostic tool is high-resolution computed tomography (HRCT). Once known causes of ILD (e.g. connective tissue disease or environmental exposures) are excluded, a usual interstitial pneumonia pattern on HRCT is sufficient to diagnose IPF; however, for patients with indeterminate patterns on HRCT, lung biopsy and/or bronchoalveolar lavage may be considered (Raghu et al., 2018). Lung function tests have little diagnostic value as a restrictive lung pattern is common to all

ILDs with fibrosis, however they may help to determine progression and prognosis (Zappala et al., 2010).

2.1.3 Cystic Fibrosis

Cystic Fibrosis (CF) is a genetic disorder that causes sticky mucus to build up in the lungs and digestive system, which can lead to lung infections and breathing problems. In the UK, approximately 10,600 people are diagnosed with CF, with around 200-300 new diagnoses annually (Taylor-Robinson et al., 2018). Recent data from the newborn screening programs for CF does show that the incidence in Europe appears lower than in previous years, decreasing from 1 in 2,500 births to between 1 in 3,000 and 1 in 6,000 births (Scotet, L'Hostis, & Férec, 2020).

Although there have been significant improvements in life expectancy over subsequent decades, median life expectancy remains at approximately 50 years (Scotet et al., 2020). The disease has more hospital admissions and bed days per patient than most lung diseases, accounting for 9,500 hospital admissions and over 100,000 hospital bed days a year (British Lung Foundation, 2022). In patients with severe CF disease, LTx remains the only therapeutic option for restoring patients in the direction of normal respiratory health. A retrospective study in the UK reported that LTx provided significant early survival and functional benefits for patients with CF, and whilst long term benefits were promising, transplant associated co-morbidities and rates of graft dysfunction increased over time (Meachery et al., 2008).

2.1.3.1 Symptoms and Diagnosis of CF

There are three main types of screening for CF: carrier testing, newborn screening, and antenatal testing. Since newborn screening was introduced across the UK in 2007, CF is often diagnosed through this heel prick test (specifically immunoreactive trypsin test)

shortly after birth (Schlüter, Southern, Dryden, Diggle, & Taylor-Robinson, 2020). If this test is positive, then it will be followed up with sweat and gene tests for confirmation (NICE, 2017). If there is a family history of CF then carrier testing can be undertaken using a mouthwash or blood test, to determine whether an individual is a carrier of the faulty gene. If both parents carry the faulty gene, but don't have CF, there is a 1 in 4 chance of being born with CF (Brown, White, & Tobin, 2017). Once diagnosed, extensive follow up is required and disease progression is often monitored with chest radiographs, pulmonary function tests and arterial blood gas analysis (Bayfield et al., 2021).

Due to the requirement of newborn screening, diagnosis is usually made before the presentation of symptoms. The most common signs and symptoms of CF in the respiratory system include chronic cough, recurrent wheezing or pneumonia, dyspnoea on exertion, haemoptysis and bronchiolitis (Brown et al., 2017). In addition to respiratory symptoms, many patients have pancreatic insufficiency leading to steatorrhea, diarrhoea, and abdominal distension (Davies, Alton, & Bush, 2007). Additionally, CF can cause a number of complications such as CF related diabetes (>30% of adults with CF), CF related liver disease, osteoporosis, osteopenia, arthritis and fertility problems (Ronan, Elborn, & Plant, 2017).

2.1.3.2 Pathogenesis and Pathophysiology of CF

CF is caused by a mutation in the CF transmembrane conductance regulator (CFTR) gene. This mutation causes absence or dysfunction of the CFTR protein, which regulates the movement of chloride and sodium ions across epithelial cell membranes (Brown et al., 2017). In the lung, this results in airway surface liquid depletion which leads to impaired mucus clearance, resulting in a build-up of thick mucus (Donaldson & Boucher, 2006). Decreased mucociliary clearance in combination with defective ion transport

results in a vicious cycle of phlegm retention, chronic infection and inflammation, leading to progressive and permanent airway destruction (Donaldson & Boucher, 2006).

2.1.4 Pulmonary Hypertension

Pulmonary hypertension (PH) is a progressive disease, characterised by elevated pulmonary artery pressure, which is diagnosed when mean pulmonary artery pressure >25mmHg at rest, assessed by right heart catheterization. Pulmonary hypertension can be classified into five groups based on the underlying aetiology, these include: 1) Pulmonary Arterial Hypertension (PAH), 2) PH due to left heart disease, 3) PH due to lung disease, 4) PH due to chronic blood clots in the lungs and 5) PH due to unknown causes (Connolly & Kovacs, 2012). From national databases, the global prevalence of all forms of PH is estimated to be 1% of the population, increasing to 10% in individuals over 65 years old (Hoeper et al., 2016). In the UK, incidence and prevalence rates have been reported as 1.1 to 2.4 and 6.6 to 15 cases per million per year, respectively (Lan, Massam, Kulkarni, & Lang, 2018). Despite advances in medical therapy, PAH remains a fatal disease, due to progressive right ventricular dysfunction. In the UK National Audit of PAH, 5-year survival rate was 28% in those with co-morbidities and 56% in those without morbidities. Mean annual healthcare utilisation rates ranged from 2.9 to 3.2 for hospital admissions, 9.4 to 10.3 for outpatient visits and 0.8 to 0.9 for emergency department visits (Exposto et al., 2021).

Lung transplantation is an important treatment option for patients with PAH who show an inadequate treatment response to medical therapy. Previous data shows that patients with PAH have the greatest short-term risk and 3 month mortality after transplant compared to other disease indications, often due to left ventricular dysfunction or primary graft dysfunction, however for patients who survive the early post-transplant period, long-term outcomes usually exceed other diseases (George, Champion, & Pilewski, 2011).

Following LTx, patients with PAH often demonstrate an immediate reversal in right ventricular failure and striking reductions in pulmonary artery pressures, leading to amelioration of symptoms (Bartolome, Hoeper, & Klepetko, 2017).

2.1.4.1 Symptoms and Diagnosis of PAH

The diagnosis of PAH can be challenging, as symptoms may be confused for other respiratory or cardiovascular diseases that cause a lack of oxygen in the blood. These symptoms include breathlessness, excessive fatigue, cough, weakness, chest pain, dizziness or syncope, cardiac arrhythmias, oedema of the ankles and legs or heart failure (Montani et al., 2013). Screening for PAH is usually conducted using transthoracic echocardiography and confirmed using the gold standard of right heart catheterisation, which is usually performed at a specialist national PH centre (McLaughlin & McGoon, 2006).

2.1.4.2 Pathophysiology of PAH

Pulmonary arterial hypertension may be idiopathic or secondary to other conditions such as congenital heart disease, HIV infection or systemic sclerosis, however patients tend to display similar pathological changes which include endothelial dysfunction, increased pulmonary arteriole contractility and remodelling and proliferation of endothelial and smooth muscle cells (Thenappan, Ormiston, Ryan, & Archer, 2018). Physiologically, this results in occlusion of small pulmonary arteries, leading to increased pulmonary vascular resistance, right ventricular failure, and ultimately death if untreated (Lan et al., 2018).

2.2 Lung transplantation

When the above-mentioned chronic respiratory diseases progress to advanced stages, LTx may be a final treatment option to extend life expectancy and enhance quality of life. Lung transplantation is a surgical procedure in which a diseased lung is removed from an individual and replaced with a healthy lung from a donor (Yeung & Keshavjee, 2014).

The first human lung transplant was performed by James Hardy in 1963 (Hardy, Webb, Dalton, & Walker, 1963), following years of experimentation in animal models. The procedure started to become clinically viable in the mid 1980's, following a number of surgical and pharmacological advances. The field of LTx has continued to develop, due to improvements in surgical techniques, immunosuppression, post-transplant treatment regimens and the processes of recipient and donor selection (van der Mark, Hoek, & Hellemons, 2020). Over the past decade, median survival has increased from 4.3 years (1990-1998) to 6.2 years (2009-2016) worldwide (Khush et al., 2018).

Despite the favourable trends in LTx outcomes, morbidity and mortality remains higher than other organ transplants (Studer et al., 2004). This is largely due to short- and long-term complications related to primary graft dysfunction and chronic lung allograft dysfunction (Gauthier, Hachem, & Kreisel, 2016). The 2020 annual NHS report on cardiothoracic organ transplantation showed that for LTx the UK 90-day survival rate was 90.9%, 1-year survival rate was 82.6% and 5 year survival rate was 55.3% (NHS Blood and Transplant, 2020). One- and five-year survival rates for other transplants in the UK were 83.2% and 69.9% for heart transplants (NHS Blood and Transplant, 2020), 97% and 88% for kidney transplants (NHS Blood and Transplant, 2020), 94% and 84% for liver transplants (NHS Blood and Transplant, 2020) and 96% and 88% for pancreas transplants (NHS Blood and Transplant, 2020), respectively. When looking at specific disease groups for LTx, there were no statistically significant differences in survival rates

across disease groups at 1 year (CF and Bronchiectasis: 85.8%, COPD: 79.7%, Fibrosing Lung Disease: 77.6% and Other: 81.1%). At 5 years, there was some evidence of lower survival rates in patients categorised as “other” (Other: 47.4%, CF and Bronchiectasis: 61.9%, COPD: 59.4% and Fibrosing Lung Disease: 51.1%).

A major issue in LTx is the scarcity of available donor lungs and low lung donor utilization rates, which ultimately leads to wait-list mortality (Kourliouros et al., 2019). Outcomes for patients registered on UK lung transplant waiting lists between April 2016 and March 2017, show that at 3 years 47% had been transplanted and 21% had died whilst waiting (NHS Blood and Transplant, 2020). In the UK, reports show a median waiting time of 422 days for LTx, with a bilateral lung offer decline rate of 66% (NHS Blood and Transplant, 2020). Data obtained from the UK transplant registry showed that at 3 years post-registration, those with pulmonary fibrosis had the highest waitlist mortality (37%) compared to other disease categories. Height and blood group were also reported to have a high impact on the chance of transplantation, with taller patients and those with blood group A having a greater chance of transplant (Kourliouros et al., 2019).

To increase the number of organ donations in England, a new opt out law was introduced in May 2020. This law works on the understanding that all adults agree to become organ donors when they die, unless they have made it known that they do not wish to donate (van der Mark et al., 2020). Additionally, in recent years, donor criteria have been extended to address the donor shortage. Examples of these criteria include older donor age (>55 years), increased smoking history, more medical co-morbidities and known drug abuse (Chaney, Suzuki, Cantu, & van Berkel, 2014). Furthermore, new technologies such as ex vivo lung perfusion (EVLP) allow for an extended evaluation of the lungs outside of the donor, by placing them on a device that ventilates and perfuses the lungs with an electrolyte and protein solution (Divithotawela et al., 2019). This is now

being used in centres worldwide and has shown to enhance lung utilization by 30% (Machuca & Cypel, 2014).

When considering a recipient for LTx the following general criteria should be met: 1) High (>50%) risk of death within 2 years if transplant is not performed; 2) High (>80%) likelihood of surviving at least 90 days after LTx and 3) High (>80%) likelihood of 5-year post transplant survival from a general medical perspective, provided there is adequate graft function (Weill, 2018). Due to the complexity of LTx, it is imperative to consider all clinical characteristics of candidates, to lower the risk of perioperative morbidity and mortality (Leard et al., 2021). Therefore, a thorough multidisciplinary patient assessment is required to evaluate lung disease severity, anatomy, degree of frailty, presence and severity of comorbidities, psychosocial circumstances, nutritional status, and health-related behaviours that impact recovery and long-term survival (Leard et al., 2021).

2.2.1 Characteristics of UK lung transplant recipients

Of the 87 lung transplants performed in the UK from 2020 to 2021, 64% of recipients were male and the median age was 53 years (IQR: 47 to 60). In terms of the primary disease of lung transplant recipients, 14% had CF or bronchiectasis, 31% Fibrosing Lung Disease, 37% COPD and Emphysema, 5% Pulmonary Hypertension and 14% other. The majority of lung transplants were categorised as non-urgent (78%), with 22% categorised as urgent. In Newcastle upon Tyne specifically, 76% of recipients were male and the median age was 57 (IQR: 50 to 61). Most lung transplants were performed for Fibrosing Lung Disease (57%), followed by COPD (19%), CF and bronchiectasis (14%), PH (5%) and other (5%) (NHS Blood and Transplant, 2021).

2.2.2 The impact of the COVID-19 Pandemic on Lung Transplantation

The COVID-19 pandemic has had a profound impact on solid organ transplantation worldwide, affecting potential donors, candidates and recipients (Danziger-Isakov, Blumberg, Manuel, & Sester, 2021). In the year preceding the pandemic (April 2019 to March 2020), 156 lung transplants were performed in the UK, with 30 of these undertaken at Freeman Hospital, Newcastle upon Tyne (NHS Blood and Transplant, 2020). This was significantly reduced during the first year of the pandemic (April 2020 to March 2021), with 87 lung transplants conducted across all UK centres and 21 performed in Newcastle upon Tyne (NHS Blood and Transplant, 2021). Indeed, Hardman et al. (2021) reported a 77% decrease in the number of lung transplants performed in the early stages of the pandemic in the UK, predominantly due to a 48% fall in organ donors (Figure 2-1).

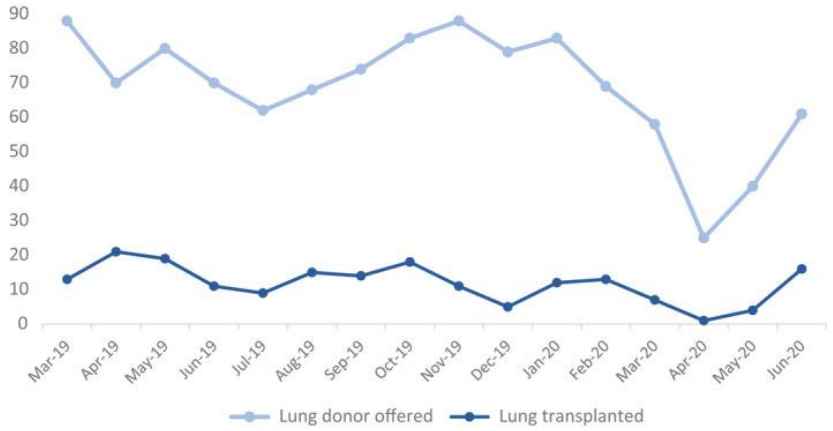


Figure 2-1: Number of deceased donors offered for lung transplantation and lung transplants performed from March 2019 to June 2020 from (Hardman et al., 2021)

At these early stages, COVID-19 was a novel disease, thus the initial evidence to inform clinical practice was limited (Hardman et al., 2021). Alterations to clinical practice were driven by concerns regarding the safety of donors, hospital-acquired infection in recipients and the resource requirement of COVID-19 patients at local sites (Hardman et al., 2021). Previous research shows the extent of immunosuppression tends to

correlate with the severity of infectious diseases (Duncan & Wilkes, 2005), thus it is predicted that organ recipients may be more susceptible to severe COVID-19. Evidence from cohort studies support a worse prognosis and higher mortality following COVID-19 infection in LTx recipients compared to the general population, with a case fatality rate of 10 to 46% (Kamp, Hinrichs, Fuge, Ewen, & Gottlieb, 2021), however it is unclear whether immunosuppression intensity is a predictor of mortality (Kates et al., 2021). In line with findings in the general population (Docherty et al., 2020), increasing age and underlying co-morbidities are associated with mortality in solid organ recipients following COVID-19 infection (Kamp et al., 2021; Kates et al., 2021; Ravanan et al., 2020).

The higher risk of severe COVID-19 in lung transplant recipients presented challenges with balancing the safety of transplantation versus remaining on the waiting list. A national cohort study in England showed that the overall risk of infection was higher in waitlisted patients, with a higher proportion of patients testing positive for COVID-19 compared to solid organ transplant recipients (3.8% vs 1.3%). However, there was higher all-cause mortality in recipients compared to waitlisted patients (25.8% vs 10.2%) (Ravanan et al., 2020).

2.3 Exercise limitation in lung transplant candidates

Functional exercise capacity before LTx has been shown to be a strong predictor of survival across all lung disease categories (Martinu et al., 2008), as well as post-transplant health outcomes such as time spent on mechanical ventilation, length of hospital and ICU stay (Li, Mathur, Chowdhury, Helm, & Singer, 2013). Patients with advanced lung disease are medically complex and commonly present with severe dyspnoea and activity limitation, as well as diminished psychological wellbeing and comorbidities (Lahaije, van Helvoort, Dekhuijzen, & Heijdra, 2010). Additionally, these patients often require multi-drug medication regimes, supplemental oxygen and/or use

non-invasive assisted ventilation during activities of daily living (Rochester, 2008). In patients with chronic lung disease, exercise limitation is often multifactorial comprising ventilatory, gas exchange, cardiovascular and peripheral muscle abnormalities (Vogiatzis & Zakynthinos, 2012). However, at advanced stages of disease, ventilatory factors often constitute the major limitation to exercise capacity (Bartels et al., 2011; Donnell et al., 2016; Hulzebos, Werkman, Bongers, Arets, & Takken, 2015). Cardiopulmonary exercise testing in LTx candidates showed severe exercise intolerance ($\dot{V}O_2$peak: 34% predicted), with markedly impaired cardiopulmonary parameters in all underlying diseases (Schwaiblmair et al., 1999). In the majority of patients with chronic lung disease, there is a mismatch between ventilatory capacity and ventilatory demand during exercise. Ventilatory capacity is limited by abnormal respiratory system mechanics and/or reduced lung compliance, which increase the work of breathing (Vogiatzis & Zakynthinos, 2012). However, the underlying mechanisms limiting physical activity in lung transplant candidates differ depending on the underlying primary disease diagnosis, but ultimately depend on the magnitude of dysfunction in each physiological system (Vogiatzis & Zakynthinos, 2012).

2.3.1 Factors limiting exercise capacity in COPD

In COPD patients' physical activity levels and exercise capacity are significantly lower than in healthy individuals (Pitta et al., 2005; Vorrink, Kort, Troosters, & Lammers, 2011). The mechanisms of exercise limitation are complex, involving the interaction of symptoms, gas exchange limitations, impaired ventilatory and respiratory mechanics, haemodynamic and peripheral muscle abnormalities (Vogiatzis & Zakynthinos, 2012). Limitations in activities of daily living are common in COPD patients, often resulting from intolerable symptoms of dyspnoea and leg discomfort/fatigue. The locus of exercise limitation can vary between individuals, however previous research suggests that patients with more advanced disease such as those who are candidates for LTx, tend to

experience more intense symptoms of dyspnoea than leg fatigue, whereas this may be reversed in milder disease (Killian et al., 1992). Dyspnoea in COPD patients is caused by structural lung abnormalities which lead to reduced ventilatory capacity, predominantly caused by expiratory limitation and subsequent lung hyperinflation, a key pathophysiological defect in COPD (Bourdin et al., 2009). This is worsened when ventilatory demand and breathing frequency increases, such as during physical activities, further exacerbating expiratory flow limitation (dynamic hyperinflation) (O'Donnell, Revill, & Webb, 2001) (Figure 2-2). This has dire implications on pulmonary mechanics and the oxygen cost of breathing, imposing restrictive mechanics on the respiratory system, which may lead to carbon dioxide (CO_2) retention and arterial oxygen desaturation in patients with ventilation-perfusion abnormalities (O'Donnell, D'Arsigny, Fitzpatrick, & Webb, 2002). Furthermore, dynamic hyperinflation increases the work and oxygen cost of breathing through abrupt increases in the elastic and threshold loads placed on the inspiratory muscles (Laveneziana, Parker, & O'Donnell, 2007).

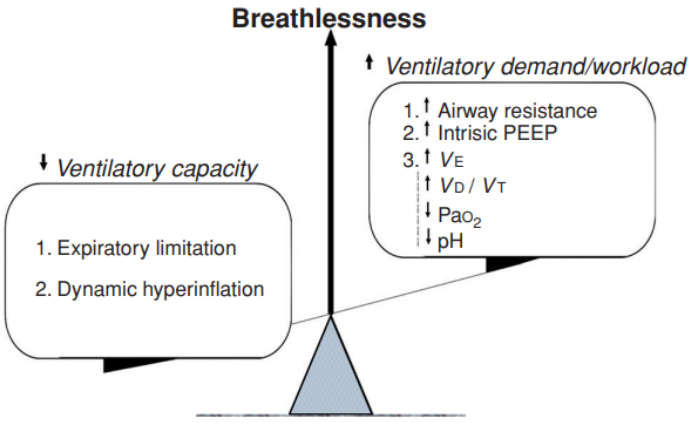


Figure 2-2: Diagram depicting the factors contributing to ventilatory limitation in COPD patients from (Vogiatzis & Zakynthinos, 2012)

Dynamic hyperinflation has also been associated with an impaired cardiovascular response to exercise, as a result of heart compression, intrathoracic hypovolemia and increased pulmonary vascular resistance, which compromise the normal increase in

cardiac output during exercise (Agustí et al., 1990) (Figure 2-3). Consequently, this leads to insufficient oxygen supply to the working respiratory and locomotor muscles, intensifying symptoms of leg discomfort and dyspnoea (Vogiatzis & Zakynthinos, 2012).

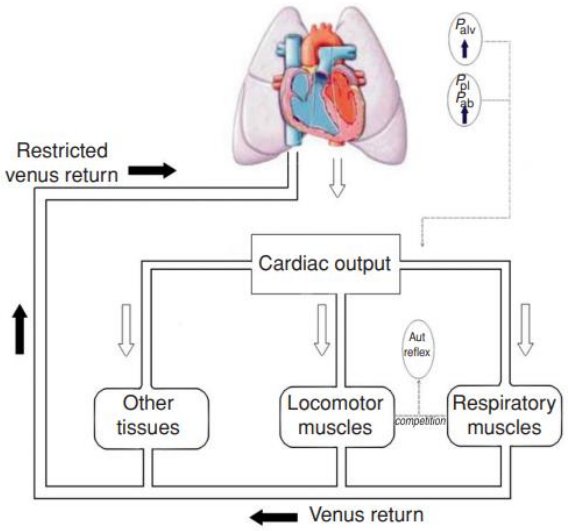


Figure 2-3: Diagram depicting cardiovascular limitation to exercise in patients with COPD from Vogiatzis and Zakynthinos (2012).

The final mechanism that may limit exercise capacity in COPD patients is peripheral muscle dysfunction (Figure 2-4). Muscle dysfunction in COPD can be attributed to several factors including physical inactivity and deconditioning, with patients commonly exhibiting a shift from type I oxidative fibres to type II muscle fibres (Gosker, Zeegers, Wouters, & Schols, 2007). Other factors include increased systemic inflammation, nutritional depletion, and the side effects of medications (Vogiatzis & Zakynthinos, 2012). Overall, COPD patients tend to exhibit atrophied, weak, fatigable, and metabolically inefficient muscle characteristics, which play an important role in limiting exercise tolerance (Mador & Bozkanat, 2001).

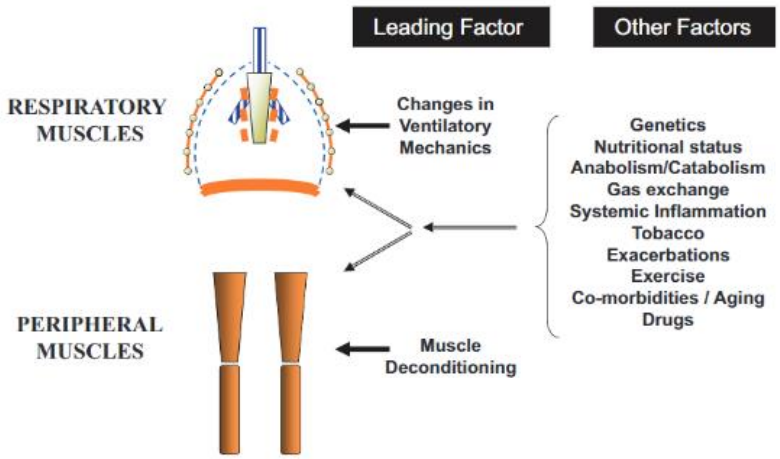


Figure 2-4: Factors contributing to respiratory and peripheral muscle dysfunction in patients with COPD from (Gea, Agustí, & Roca, 2013)

2.3.2 Factors limiting exercise tolerance in ILD

Exercise limitation accompanied by dyspnoea is a common characteristic of ILDs, often limiting activities of daily living (Mendes et al., 2021). In patients with ILD, measurements of aerobic capacity have been shown as strong predictors of disease prognosis (Fell et al., 2009; Kawut et al., 2005). In LTx candidates with IPF, reduced functional exercise capacity has been associated with an increased mortality rate, with patients achieving a six minute walk test (6MWT) distance <207m having a fourfold greater risk of mortality, despite adjustments for demographics, forced vital capacity (FVC), PH and medical co-morbidities (Lederer et al., 2006).

In patients with IPF, peak oxygen consumption ($\dot{V}O_2$peak) and peak work rate are often reduced, along with sub-maximal exercise endurance (lower anaerobic threshold) (Lama & Martinez, 2004). There are a number of pathophysiological responses that are observed in ILD patients during exercise, including ventilatory, diffusional cardiovascular and musculoskeletal dysfunctions (Molgat-Seon, Schaeffer, Ryerson, & Guenette, 2019). The persistent inflammatory process and formation of fibrotic tissue lead to structural and mechanical pulmonary system irregularities (Mendes et al., 2021).

Abnormal lung mechanics limit the ventilatory adaptation to exercise, leading to a rapid, shallow, and less efficient breathing pattern (Bonini & Fiorenzano, 2017). Ventilatory inefficiency is primarily due to a high volume of dead space, but also arterial hypoxemia and premature metabolic acidosis. Indeed, significant exercise-induced arterial hypoxemia during exercise is common in individuals with IPF, which occurs as a result of gas exchange abnormalities and ventilation/perfusion mismatch, caused by thickening of the alveolar capillary membrane (Agustí et al., 1991). Additionally, markers of desaturation during a 6MWT such as a threshold oxygen saturation (SpO_2) < 88% or $\Delta SpO_2 \geq 10\%$ have been associated with an increased risk of mortality in patients with ILD (Holland, 2010).

Cardiovascular abnormalities also play a pertinent role in limiting exercise tolerance in ILDs, occurring as a result of capillary destruction and hypoxic pulmonary vasoconstriction (Panagiotou, Church, Johnson, & Peacock, 2017). Severe capillary destruction limits venous return to the left side of the heart, subsequently causing reduced cardiac output and inadequate systemic oxygen (O_2) delivery to the working muscles during exercise (Hansen & Wasserman, 1996). The increase in pulmonary vascular resistance also contributes to the development of PH in patients with ILD (Magro et al., 2003).

Finally, limitations in peripheral muscle function have been reported as a factor contributing to exercise intolerance in ILD patients. Studies have shown that quadriceps muscle force is significantly reduced in patients with IPF (65% predicted) and Sarcoidosis (67% predicted) and represents an independent predictor of $\dot{V}O_2$peak (Nishiyama et al., 2005; Spruit et al., 2005). The degree of peripheral muscle dysfunction has also been strongly associated with the severity of ILD, which could be due to increasing inactivity and muscle deconditioning, but also other factors such as systemic inflammation, hypoxemia and malnutrition (Guler, Hur, Lear, Camp, & Ryerson, 2019).

2.3.3 Factors limiting exercise capacity in CF

Deficits in exercise capacity in CF are due to a host of factors, including ventilatory dysfunction, peripheral muscle abnormalities, cardiac constraint, changes in nutritional status and deconditioning (Hulzebos et al., 2015). In those with mild-to-moderate disease, non-pulmonary factors tend to predominate exercise limitation (Moorcroft, Dodd, Morris, & Webb, 2005). A wealth of evidence reports reduced peripheral muscle strength in patients with CF (Gruet, Troosters, & Verges, 2017). Troosters et al. (2009) reported significantly lower quadricep force compared to healthy controls, with 56% of patients demonstrating quadriceps muscle weakness. Analysis of patient physical activity demonstrated no differences in the amount of mild intensity activity (>3 METs) and daily steps undertaken, compared to healthy controls. However, time spent in moderate intensity activities (>4.8 METs) was significantly reduced in CF patients and this was a modest contributor to impaired $\dot{V}O_2$peak and quadriceps force in these patients, suggesting that other factors also play a role. In addition to muscle weakness, mitochondrial dysfunction and altered muscle metabolism may also limit exercise tolerance in CF patients (Hulzebos et al., 2015). Skeletal muscle abnormalities may result from inflammation, hypoxemia, oxidative stress, exacerbations, and use of corticosteroids (Gruet et al., 2017).

In more severe disease states, ventilatory constraints are a major contributor to exercise tolerance (McKone, Barry, FitzGerald, & Gallagher, 2005). Airway obstruction is prevalent in CF patients due to mucus within the airways, resulting in an increased requirement of inspiratory airflow to maintain gas exchange during exercise, leading to increased work of breathing and metabolic demand (Urquhart & Vendrusculo, 2017). Pastré et al. (2014) showed $\dot{V}$O2peak for all patients was 25 ± 9 mL/kg/min (65 ± 21% predicted). In patients with severe disease, forced expiratory volume in the first second (FEV_1) was the strongest predictor of $\dot{V}$O2peak, whereas excessive hyperventilation

accounted for the alteration in $\dot{V}O_2$peak in those with mild-to-moderate disease (Pastré et al., 2014). CF patients have increased lung dead space compared to healthy individuals, limiting the ability to increase alveolar ventilation (Godfrey & Mearns, 1971). During exercise, CF patients often have greater ventilation ($\dot{V}_E$) for a given $\dot{V}O_2$, with maximal exercise $\dot{V}_E$ often reaching or exceeding predicted maximal voluntary ventilation (MVV) (Urquhart & Vendrusculo, 2017).

2.3.4 Factors limiting exercise capacity in PAH

Exercise intolerance in PAH is multifactorial and stems from increased mean arterial pressure, resulting in greater pulmonary vascular resistance. In a cohort of PAH patients undergoing cardiopulmonary exercise testing, average $\dot{V}O_2$peak was reported as 44% predicted, with reductions in anaerobic threshold, peak O_2 pulse, rate of increase in $\dot{V}O_2$ and ventilatory efficiency being consistent findings (Sun, Hansen, Oudiz, & Wasserman, 2001). The predominant symptoms limiting exercise were leg fatigue (49%), dyspnoea (43%), palpitations (4%) and light headedness (2%). The key common anomalies during exercise in PAH patients is ventilation/perfusion (V/Q) inequalities, abnormal pulmonary gas exchange and increased right ventricle afterload and accompanying reduced left ventricle filling. V/Q inequalities result from increased ventilation of poorly perfused alveoli, leading to increased dead space ventilation and hypoxemia (Laveneziana & Weatherald, 2020). Additionally, significant oxygen desaturation occurs when right arterial pressure exceeds left arterial pressure, causing a right-to-left shunt through a patent foramen ovale. The hypoxemic blood entering the circulation, further stimulates excessive and inefficient ventilation (Weatherald, Farina, Bruno, & Laveneziana, 2017).

Diminished cardiac function occurring as a consequence of increased right ventricle afterload and associated reduction of left ventricular filling (Oudiz et al., 2010), along with peripheral muscle abnormalities and deconditioning result in impaired cardiac output and

systemic oxygen delivery to the working muscles (Mainguy et al., 2010). Reduced oxygen delivery to locomotor muscles results in reduced aerobic capacity and a consequential reduction in the anaerobic threshold. Furthermore, mechanical abnormalities to tidal volume expansion and dynamic lung hyperinflation can contribute to exertional dyspnoea and exercise intolerance in PAH patients (Laveneziana et al., 2013; Richter et al., 2012).

2.4 Exercise limitation in lung transplant recipients

Following LTx there are significant improvements in pulmonary function, however, increases in exercise capacity parameters are dyssynchronous and remain limited to 40 to 60% of predicted values (Mathur et al., 2004). This is concerning as diminished exercise capacity parameters have been independently associated with greater post-transplant mortality (Armstrong, Garber, & Bartels, 2012). Reduced $\dot{V}O_2$peak is also evident in other solid-organ recipients such as renal and liver recipients (65-80% predicted values) and heart recipients (50-60% predicted values), but to a lesser extent when compared to predicted values (Williams & McKenna, 2012). In single and double lung recipients, low work rates and $\dot{V}O_2$ max have been reported at 3 months post-transplant, with no significant improvements shown when retested 1 to 2 years following transplant (Williams, Patterson, McClean, Zamel, & Maurer, 1992). The impairment in exercise capacity is likely not due to respiratory function, with Bartels et al. (2011) showing markedly improved pulmonary function following lung LTx, with a 67% and 136% increase in FVC and FEV_1 values, respectively. Peak work rate increased significantly (by 78%), however, there was only a 19% increase in $\dot{V}O_2$peak, with values remaining at only 52% of predicted. When comparing the reason for exercise termination, most patients (91%) reported leg fatigue as the limiting factor post-transplant, compared to only 30% of patient's pre-transplant, where dyspnoea was the predominant limiting factor.

2.4.1 Post-transplant skeletal muscle dysfunction

Evidence points increasingly to the role of skeletal muscle dysfunction as the major factor limiting exercise capacity following LTx, as a result of chronic deconditioning and immunosuppressive regimes (Mathur et al., 2004). The majority of studies implementing cardiopulmonary exercise testing in LTx recipients, describe leg fatigue as the dominant reason for terminating exercise (Braccioni et al., 2020; Dudley & El-Chemaly, 2012; Studer et al., 2004). Furthermore, delayed recovery of exercise capacity following LTx appears to occur secondary to delayed recovery of quadriceps muscle strength, rather than lung function parameters (Walsh et al., 2013).

Similarly, to deconditioned individuals, LTx recipients often demonstrate early onset of the lactate threshold during incremental exercise, which has been largely attributed to abnormalities in skeletal muscle oxidative capacity (Evans et al., 1997; Wang et al., 1999). Evans et al. (1997) showed that in the quadriceps muscle of LTx recipients, intracellular pH was more acidic at rest, with greater lactate concentrations present during incremental exercise, compared to healthy controls. The early reduction in pH, was also strongly correlated with $\dot{V}O_2$peak and endurance time. This indicates that a greater reliance on anaerobic metabolism, due to impaired oxygen uptake or utilisation by the muscle, may be an important contributor to limited exercise capacity in LTx recipients. Similarly, muscle biopsies have revealed a lower proportion of type I muscle fibres and significantly impaired mitochondrial oxidative capacity in LTx recipients compared to healthy controls (Wang et al., 1999). Whereas only a mild obstructive/restrictive ventilatory deficiency was evident during incremental exercise testing (Wang et al., 1999). The reduction in the percentage of type I oxidative fibres is also evident in lung transplant candidates with severe lung diseases, showing little change at 3 months following LTx (Morton et al., 1999). This suggests that abnormalities post LTx, can be at least partly attributed to the chronic deconditioning of skeletal muscle

whilst waiting for LTx. In a study comparing LTx recipients to COPD patients, changes in muscle mass and strength were similar, however endurance of the quadriceps muscle tended to be lower in LTx recipients (Mathur, Levy, & Reid, 2008). In a study exploring symptom onset during cardiopulmonary exercise tests, higher symptoms of muscle pain were reported by LTx recipients with poorer $\dot{V}O_2$peak (<15 ml/kg/min) or those requiring a higher cost of ventilation for exercise ($\dot{V}_E/\dot{V}CO_2$ slope (≥ 32)) (Braccioni et al., 2020). This suggests that LTx recipients with poorer aerobic capacity are more prone to muscle pain at peak exercise, or those requiring a greater energy cost of ventilation to compensate for metabolic acidosis. On the other hand, dyspnoea was the limiting symptom only in LTx recipients who reached high work rates and greater minute ventilation (>53 L/min) (Braccioni et al., 2020).

A key factor that contributes to muscle dysfunction in LTx recipients is the chronic intake of immunosuppressive medications such as corticosteroids and cyclosporine, which are essential to avoid organ rejection. The impact of chronic corticosteroid use on skeletal muscle myopathy is well known, with long-term use associated with limb muscle weakness and type II fibre atrophy (Decramer, de Bock, & Dom, 1996). Furthermore, an acute course, as used for acute rejection, has been shown to result in generalised muscle weakness compared to pre-treatment in 45% patients, with a recovery time of ~2 months in most patients (Nava et al., 2002). Cyclosporine, a calcium inhibitor, has been shown to impair mitochondrial function and the oxidative capacity of skeletal muscle in animal models (Hokanson, Mercier, & Brooks, 1995; Mercier, Hokanson, & Brooks, 1995). In addition to immunosuppressive medications, LTx recipients are subjected to a prolonged period of bed rest and reduced muscle activity in the early stages following transplant surgery. In healthy older adults, muscle wasting has been shown to occur within 10 days of bed rest (Kortebein et al., 2008). Thus, reduced ICU length of stay in LTx recipients has been associated with increased quadriceps muscle strength at

hospital discharge (Maury et al., 2008). Whereas, a prolonged stay in ICU can have significant and long term health consequences (Herridge, 2009).

2.4.2 Post-transplant ventilatory limitation

Most studies in LTx recipients indicate that ventilatory factors do not play a significant role in exercise limitation. Cardiopulmonary exercise tests in LTx recipients revealed that at peak exercise, minute $\dot{V}_E$ reached 47% of MVV, with oxygen saturation maintained close to resting values (Miyoshi et al., 1990). Similar findings were reported by Levy et al, with peak ventilation reaching ~54% of MVV in double LTx recipients (Levy et al., 1993). In contrast, Ulvestad et al. (2020) showed that deconditioning limited $\dot{V}O_2$ peak in 41% of patients, however ventilatory limitation and abnormal gas exchange were observed in 26% of patients and 37% displayed more than one finding, suggesting both deconditioning and cardiopulmonary factors contributed to low exercise capacity. However, in most cases ventilatory limitation to exercise was due to respiratory pathology, such as chronic lung allograft dysfunction or post-operative complications. Additionally, a number of patients both with and without post-operative complications displayed an elevated $\dot{V}_E/\dot{V}CO_2$ slope, demonstrating excessive ventilation to metabolic demand, commonly caused by ventilation-perfusion mismatch. This has also been reported previously by (Schwaiblmair et al., 1999), suggesting transplanted lungs may have mild abnormalities which could be due denervation of the lungs, episodes of acute rejection or medications.

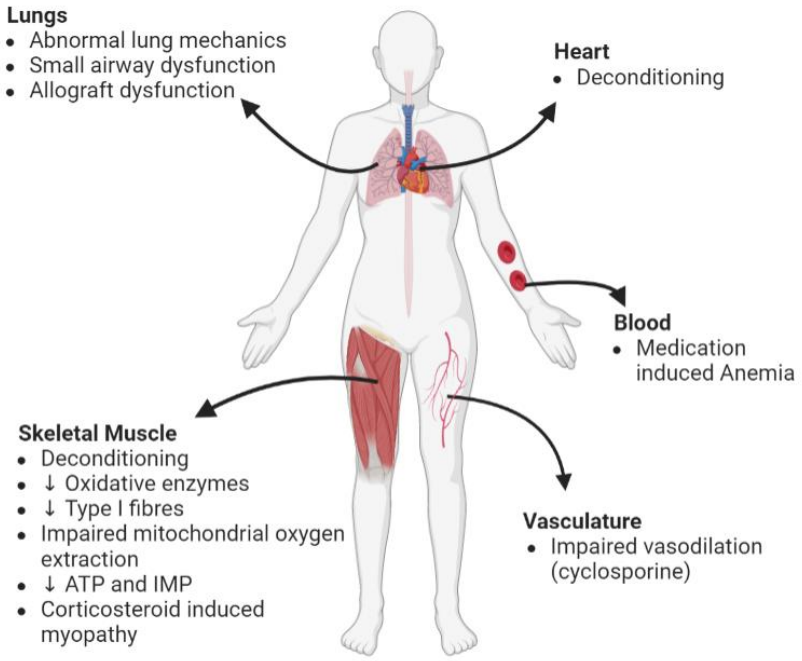


Figure 2-5: Factors limiting exercise capacity following lung transplantation, adapted from Mathur, Reid, and Levy (2004)

2.5 Physical activity

Whilst exercise capacity and physical activity are both closely related to clinical outcomes in chronic respiratory diseases, it is important that these two terms are distinguished from one another. Physical activity can be defined as 'any bodily movement produced by the skeletal muscles that requires energy expenditure' (Caspersen, Powell, & Christenson, 1985). Therefore, physical activity reflects the overall amount of activity that an individual engages in, in everyday life. It can take many forms, occur in many settings and serve many purposes (e.g. working, house-hold tasks, travelling and recreational activity). On the other hand, exercise capacity refers to what a person is actually capable of doing (Troosters et al., 2013).

Whilst an individual's physical activity is constrained by the limits of exercise capacity, there are a host of additional factors that may influence physical activity levels including sociodemographic factors (e.g. age, sex, education levels and working status), lifestyle and environmental factors (e.g. smoking, alcohol consumption and weather) and clinical

factors (e.g. BMI, co-morbidities, symptoms) (Gimeno-Santos et al., 2014). A broader framework acknowledges that personal, environmental, social and policy may all influence physical activity (Bauman et al., 2012). A review exploring physical activity correlates in adults, reported self-efficacy and health status as the clearest correlates with physical activity. Other correlates included age (inversely), male sex and social support (Bauman et al., 2012). In terms of environmental factors, physical activity has been correlated with access to recreation facilities, transportation environment (e.g. pavement and safety of crossings) and aesthetics (e.g. greenness), however findings between studies have been inconsistent (Bauman et al., 2012).

In COPD patients, Alahmari et al. (2015) has demonstrated variability in physical activity related to weather and climate, with significantly lower daily step counts undertaken on days that were cold, wet and overcast. Similar to that in healthy individuals, evidence in patients with severe COPD has shown that women and older subjects exhibited lower levels of physical activity (Cla, 2018; Garcia-Aymerich et al., 2004). Although the literature highlights potential mediators of physical activity, a major limitation is the cross-sectional nature of studies, thus limiting the quality of evidence to establish clear determinants of physical activity (Bauman et al., 2012; Gimeno-Santos et al., 2014). Hence, more longitudinal research into what predicts changes in physical activity is needed to definitively understand why people are active or not (Bauman et al., 2012).

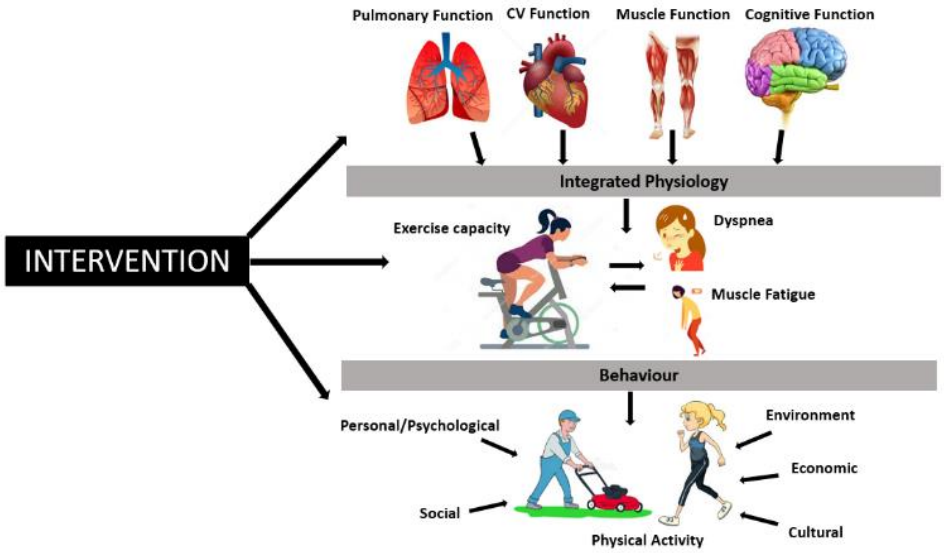


Figure 2-6: Factors determining physical activity in Chronic Respiratory Disease adapted from (Demeyer et al., 2021)

2.5.1 Health related quality of life and its link to physical activity

Optimising health related quality of life (HRQoL) is an important goal of LTx. Health related quality of life is multi-dimensional and encompasses domains related to physical, mental and social functioning, that can be affected by disease as well as medical treatment (Yin, Njai, Barker, Siegel, & Liao, 2016), and is a key indicator of health status across the spectrum of health and disease (Machón, Larrañaga, Dorronsoro, Vrotsou, & Vergara, 2017). Numerous studies have demonstrated improvements in HRQoL following LTx, regardless of the measurement instrument used (Singer & Singer, 2013). However, impairments in HRQoL remain in comparison to normative population values. (Singer et al., 2013). Evidence in LTx recipients shows that measures of HRQoL are significantly related to levels of daily physical activity, particularly HRQoL domains related to physical functioning (Langer et al., 2009). Thus, physical rehabilitation may enhance improvements in HRQoL in the early stages of recovery (Singer & Singer, 2013), while the development of complications such as chronic lung allograft dysfunction and/or Bronchiolitis Obliterans Syndrome have been associated with diminished HRQoL (van Den et al., 2000). In patient's developing Bronchiolitis Obliterans Syndrome,

detriments in HRQoL were attributed to significant limitations in energy levels and physical mobility (van Den et al., 2000). Therefore, interventions aiming to improve HRQoL should primarily target functional status, but also consider physiological factors, symptoms and perceptions of general health, in line with the Wilson and Clearly (1995) model of HRQoL (Ojelabi, Graham, Haighton, & Ling, 2017).

2.5.2 Physical activity in lung transplant candidates

Evidence shows that LTx candidates have significantly reduced levels of physical activity compared to the general population (Langer et al., 2012; Wickerson, Mathur, Helm, Singer, & Brooks, 2013; Wickerson et al., 2015). In LTx candidates with a range of diseases, very low levels of physical activity have been demonstrated with an average of 2856 steps/day undertaken and only 7.2 minutes of moderate intensity activity per day (Wickerson et al., 2015). Similar findings have been reported in LTx candidates with COPD and ILD, with objective accelerometry showing an average of 2928 ± 1796 steps/day and 34 ± 19 min/day of walking time, with no significant differences displayed between disease states (Langer et al., 2012). Furthermore, in LTx candidates with advanced ILD undertaking pulmonary rehabilitation, average daily steps were 2736 and moderate-intensity activity time was 3.6 minutes; however, activity levels were higher on the days that exercise-based pulmonary rehabilitation was undertaken (Wickerson et al., 2013).

When investigating the determinants of physical activity behaviour in lung transplant candidates, studies have shown functional exercise capacity (6MWT distance) to be the strongest determinant (Langer et al., 2012; Wickerson et al., 2015). Despite this, the physiological benefit of enhanced exercise capacity does not always translate into enhanced physical activity behaviours (Zwerink, van der Palen, van der Valk, Brusse-Keizer, & Effing, 2013). For instance, a longitudinal study in stable COPD patients has

shown a yearly decrease of approximately 450 steps/day, whilst exercise capacity remained stable, suggesting the decline in physical activity was not due to reductions in exercise capacity (Sievi et al., 2018). Other factors that have been associated with physical inactivity in LTx candidates include the use of long-term oxygen therapy, reduced respiratory muscle force, seasonal variation, and self-reported physical functioning (Langer et al., 2012).

2.5.3 Physical activity in lung transplant recipients

An important goal of LTx is to improve physical function and the ability to perform activities of daily living, leisure and social activities and even return to work (Studer et al., 2004). Whilst there is a paucity of research on the impact of physical activity levels on survival in LTx recipients specifically, physical activity has been shown as an important predictor of all-cause mortality in solid organ recipients (Mathur et al., 2014), patients with COPD (Garcia-Aymerich et al., 2006) and in healthy individuals (Geidl, Schlesinger, Mino, Miranda, & Pfeifer, 2020; Lee & Skerrett, 2001). In a recent meta-analysis including ~50,000 adults, increasing step count was associated with progressively lower mortality risk. For older adults (≥ 60 years) mortality risk plateaued at approximately 6000 to 8000 steps/day, and for younger adults (<60 years) at 8000 to 10,000 steps/day (Paluch et al., 2022) (Figure 2-7).

In a study exploring physical activity levels across the transplant journey, there were no immediate changes in daily steps or time spent in moderate-intensity physical activity from pre-transplant levels (2856 steps/day) to hospital discharge (2760 steps/day). The largest improvement in daily steps occurred over the 3 months following LTx (to 4784 steps/day), however values still remained limited compared to the general population and showed no further improvement at 6 months (Wickerson et al., 2015). Despite the criticism surrounding the evidence base for the 10,000 steps/day recommendation,

according to Tudor-Locke and Bassett (2004), 62% of patients were sedentary (<5000 steps/day), 24% were low active (5000-7499 steps/day), 7% somewhat active (7500-9999 steps/day), 3.5% active (>10,000 steps/day) and 3.5% highly active (>12,500 steps/day).

Even at 1 year following LTx, Langer et al. (2009) demonstrated significantly lower daily steps, standing time, sedentary time and time spent in moderate intensity activity compared to healthy control subjects. Average daily step count in LTx recipients was 4977 ± 2332 steps/day, similar to the step counts reported by Wickerson et al. (2015) at 3- and 6-months post LTx. Time spent in moderate intensity activity averaged 67 minutes/day in LTx recipients, compared to an average of 154 minutes/day in health controls. Thus, most LTx recipients do not return to a normally active lifestyle following their transplant (Langer et al., 2009). There are several factors that may contribute to this. For instance, Langer et al. (2009) found that higher levels of physical activity were correlated with exercise capacity, preserved muscle strength and self-reported physical functioning. The data agreed with previous research, showing that pulmonary function appeared to have little effect on the capacity to perform daily activities following LTx (Langer et al., 2009).

In a qualitative study by van Adrichem et al. (2016), the most common barriers to physical activity in solid organ recipients were physical limitations, energy level, fear, and co-morbidities. Whereas frequent facilitators described were motivation, perceived consequences of physical inactivity, coping, routine/habit, goals, and responsibility of the transplanted organ. In a survey conducted by 113 solid organ recipients in Canada, barriers influencing physical activity included cost of fitness centres, side effects of post-transplant medications, insufficient exercise guidelines and feelings of reduced strength post-transplant. Common facilitators were a feeling of health from activity, motivation, social support, knowledge and confidence about exercise and physician

recommendation (Gustaw et al., 2017). A number of the physical (e.g. physical limitations, lack of energy, co-morbidities) and psychological (e.g. motivation, goals) barriers and facilitators that have been reported in transplant recipients show similarities to those experienced in the general population and individuals with end stage lung disease (Kosteli et al., 2017; Schutzer & Graves, 2004). Thus, most of these factors may also be present in the pre-transplant phase. However, a facilitator specific to transplant recipients was the need to be active to take good care of their new organ, whilst the side-effects of immunosuppressant medications was a specific barrier (van Adrichem et al., 2016).

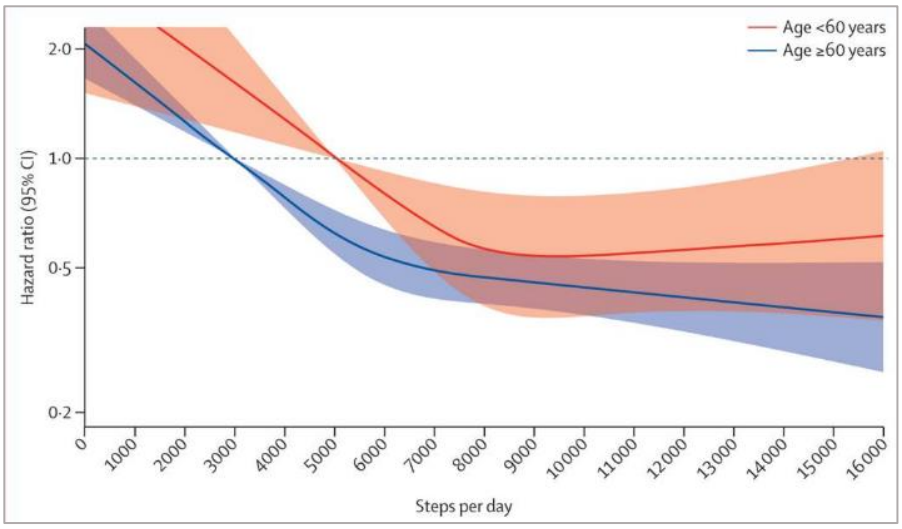


Figure 2-7: Dose-response association between steps per day and all-cause mortality, by age group from Paluch et al. (2022). Thick lines indicate hazard ratio estimates, with shaded areas showing 95% CIs.

2.6 Interventions to enhance physical activity in chronic respiratory disease

2.6.1 Pulmonary Rehabilitation

Pulmonary rehabilitation is a core component in the management of chronic respiratory disease and is defined by the American Thoracic Society (ATS) and European Respiratory Society (ERS) as “a comprehensive intervention based on a thorough patient

assessment followed by patient-tailored therapies that include, but are not limited to, exercise training, education, and behaviour change, designed to improve the physical and psychological condition of people with chronic respiratory disease and to promote the long-term adherence to health-enhancing behaviours" (Spruit, 2014). Individually tailored exercise training is the cornerstone of PR, however a comprehensive programme includes education, psychological support and nutritional counselling (Global Initiative for Chronic Obstructive Pulmonary Disease, 2022).

Pulmonary rehabilitation is recommended for patients before and after LTx. Prior to transplantation, PR can help to maintain or optimise functional capacity before surgery, as well as improve patient knowledge on their upcoming surgery and post-operative care (Spruit, 2014). Following LTx, PR can play and important role in facilitating recovery and improving the limitations that persist following lung transplant surgery (Langer, 2021). A systematic review examining the existing evidence on exercise training to improve exercise capacity, HRQoL and clinical outcomes in lung transplant candidates and recipients can be found in Chapter 3.

Overall, there is a wealth of evidence supporting PR in patients with chronic respiratory disease, with clinically and statistically significant improvements in exercise capacity, HRQoL, dyspnoea, fatigue and emotional function (McCarthy et al., 2015). In LTx recipients, only two studies have investigated the effect of an exercise training programme on daily physical activity levels (Langer et al., 2012; Ulvestad et al., 2021). Langer et al. (2012) reported significantly greater improvements in daily steps, daily walking time and movement intensity following an exercise training intervention compared to usual care (3 months post-discharge). These improvements were also sustained at 12 months following hospital discharge. Additionally at 12 months, time spent in moderate intensity activity was significantly greater in the exercise training group compared to usual care. The authors concluded that improvements in physical fitness

and muscle force elicited during the exercise training intervention, likely facilitated participation in daily physical activities. Furthermore, both the exercise training and usual care groups received physical activity counselling, thus exercise training may have enhanced the effectiveness of this by increasing self-efficacy to participate in regular physical activity (Langer et al., 2012). These findings are supported by a previous study in COPD, which showed the likelihood of improving physical activity after PR was higher in patients with greater exercise capacity (>350m in 6MWT) (Osadnik et al., 2018).

Although exercise capacity is an important component for enhancing physical activity, improvements in exercise capacity do not automatically translate into greater physical activity (Cindy, Mackney, Jenkins, & Hill, 2011). In LTx recipients, Ulvestad et al. (2021) found no significant differences in daily steps, sedentary time or time spent in moderate to vigorous activity following 20 weeks of high intensity interval training compared to usual care. In patients with COPD the effectiveness of PR to elicit improvements in daily physical activity also remains controversial (Spruit, Pitta, McAuley, ZuWallack, & Nici, 2015). Spruit et al. (2015) and Cindy et al. (2011) conducted reviews on this topic in COPD patients and demonstrated inconsistent results between studies. For instance, the systematic review and meta-analysis by Cindy et al. (2011) included seven studies and concluded that exercise training in COPD patients may confer a small benefit on physical activity, however the review was limited by the methodological quality of studies and the lack of RCTs. In a more recent review by Blondeel, Demeyer, Janssens, and Troosters (2018) in which 21 studies were included, 13 studies showed no significant change in physical activity levels (Cruz, Brooks, & Marques, 2015; Dallas, McCusker, Haggerty, Rochester, & Zuwallack, 2009; de Blok et al., 2006; Egan et al., 2012; Mador, Patel, & Nadler, 2011; Mesquita et al., 2017; Nolan et al., 2017; O'Neill et al., 2018; Pitta et al., 2008; Saunders et al., 2015; Steele et al., 2008; Steele et al., 2003; Thyregod, Løkke, & Bodtger, 2018), seven showed significant improvements in physical activity (Coronado et al., 2003; Demeyer et al., 2014; Louvaris et al., 2016; Mercken et al., 2005;

Sewell, Singh, Williams, Collier, & Morgan, 2005; Walker, Burnett, Flavahan, & Calverley, 2008) and one showed a significant decline in physical activity (Altenburg et al., 2015). Overall, the effects of an exercise training programme on physical activity are small, with a weighted mean of 208 steps/day (Burge, Cox, Abramson, & Holland, 2020), 350 steps/day (Blondeel et al., 2018) and 540 steps/day being reported in previous meta analyses (Lahham, McDonald, & Holland, 2016). It has been suggested that longer duration PR programmes (>12 weeks) may elicit greater increases in physical activity outcomes, but findings remain controversial (Mantoani et al., 2016). The research in other disease entities is limited, however the evidence available is in line with the findings in COPD patients. For instance, in patients with ILD undergoing a 6-month PR programme, there was no significant improvement in daily steps and moderate intensity physical activity at 3 and 6 months, compared to usual care (Perez-Bogerd et al., 2018). Similarly, a home-based PR programme in patients with bronchiectasis showed no benefit in terms of daily steps, compared to usual care (José et al., 2021).

As highlighted previously, physical activity as a behaviour can also be influenced by psychological, environmental, social and economic factors (Robinson, Williams, Curtis, Bridle, & Jones, 2018). Thus, physical activity interventions that incorporate a behavioural component are required to facilitate clinically important increases in physical activity, alongside PR (Lahham et al., 2016; Mantoani et al., 2016).

2.6.2 Behavioural Physical Activity Counselling Interventions

Physical activity counselling is an intervention underpinned by theoretical models of behaviour change which incorporates behaviour change techniques such as goal setting, feedback, and self-monitoring. Research investigating physical activity counselling interventions in LTx recipients is scarce (Langer, 2021), however there is a wealth of

evidence in COPD patients, a disease that commonly undergoes LTx (Burge et al., 2020; Lahham et al., 2016; Mantoani et al., 2016).

A common component of physical activity counselling interventions is the use of an activity monitor that can assess and provide direct feedback on a patient's daily physical activity. This is commonly combined with individualised activity goals and/or tailored motivational messages and has been shown as an effective strategy to enhance physical activity levels (Armstrong et al., 2019; Mantoani et al., 2016), demonstrating an improvement of ~1000 steps/day compared to usual care in a recent meta-analysis (Armstrong et al., 2019). This type of intervention can be delivered in a number of ways including face-to-face, alongside rehabilitation or remotely using digital/communication technologies (Demeyer et al., 2017).

A systematic review by Mantoani et al. (2016) included three studies where only physical activity advice was given and 11 in which a coaching programme was delivered with regular activity monitoring. Overall, 11 of the 14 interventions showed a positive influence on physical activity levels, with those including objective activity monitoring rendering the most successful. In the same year, a meta-analysis by Lahham et al. (2016) concluded that interventions combining exercise training and physical activity counselling, demonstrated clinically important increases in daily steps (by 1,452 steps/day). However, physical activity counselling as a stand-alone intervention resulted in small and non-significant effects on physical activity levels. In contrast to this, Armstrong et al. (2019) concluded that physical activity promotion using a pedometer had a positive effect on daily steps compared to usual care (n=12 RCTs; 0.53 (0.29–0.77), $p<0.00001$), which equated to ~1,000 steps/day as a stand along intervention. The disparity in findings could be due to Lahham et al. (2016) including studies that used both subjective and objective physical activity measures. Additionally, Armstrong et al. (2019) included 12 studies with a pooled sample size of 120 COPD patients, whereas (Lahham et al., 2016) only

included two studies with a sample size of 17 patients, thus may be a less robust source of evidence.

The most recent Cochrane review on this topic in COPD patients, highlighted that the evidence encompassing physical activity counselling and its effect on physical activity outcomes is inconsistent, with a wide range of programme durations, patient interfaces and intervention components used (Burge et al., 2020). Therefore, identifying the most effective components of these interventions remains challenging.

2.6.3 Tele-Health Interventions

Tele-health is an evolving approach for providing healthcare at a distance through the use of electronic and communication technologies, where in education, assessment, counselling, treatment or monitoring interventions can be provided remotely (Rochester, 2022). Tele-rehabilitation is a type of tele-health and refers to the provision of rehabilitation services by utilising information and communication technologies. It is an emerging strategy to enhance access to services, as well as improve levels of uptake and completion (Seidman et al., 2017). It can improve service delivery options, particularly for those who are geographically or socially isolated, work full time or have high disease severity, by overcoming practical barriers such as problems with travel (e.g. distance, transport), as well as staffing and resource limitations (Keating, Lee, & Holland, 2011). Tele-rehabilitation interventions may incorporate supervised or unsupervised exercise training, physical activity counselling and/or education, which can be delivered live using real time videoconferencing or via asynchronous interactions using phone or computer applications (Bhatt & Rochester, 2022).

Since the onset of the COVID-19 pandemic, tele-rehabilitation programmes have come to the forefront of healthcare delivery. In response to the COVID-19 pandemic, Wickerson et al. (2021) implemented a rapid and large-scale tele-rehabilitation study in

lung transplant candidates and recipients, demonstrating high levels of usage and satisfaction. Whilst physical activity was only assessed subjectively, 57% of lung transplant candidates self-reported as active at the time of app registration, which increased to 87% at 4 weeks. The only tele-rehabilitation study in lung transplant patients that has objectively assessed physical activity showed that participants walked a median of 1209 daily steps (range 119 to 2481 steps) at baseline, and this increased to 3693 daily steps (range 582 to 5172 steps) following an 8-week home exercise programme (Choi et al., 2016). However, this study was significantly limited by a small sample size (n=4), no control group and lack of diversity in terms of underlying disease entity and gender.

A recent Cochrane review on tele-rehabilitation in chronic respiratory disease included a total of 15 studies and concluded that PR or maintenance PR delivered via tele-rehabilitation achieved similar outcomes to traditional face to face rehabilitation, in terms of exercise capacity and quality of life measures (Cox et al., 2021). For physical activity, the results were inconsistent, with no clear improvement in daily steps (mean difference 489 steps, 95% CI -143 to 1120) or sedentary time (mean difference 42 minutes, 95% CI -26 to 111) for tele-rehabilitation, compared to no rehabilitation. For maintenance rehabilitation, one RCT showed that tele-rehabilitation was equally as effective as hospital-based PR, in terms of maintaining improvements in time spent in sedentary, light, lifestyle and moderate daily physical activities over a 12-month follow up period (Vasilopoulou et al., 2017). When compared to usual care, tele-rehabilitation was superior for improving time spent in sedentary, lifestyle and moderate intensity daily activities (Vasilopoulou et al., 2017). It is important to note that the majority of studies included in the Cochrane review were implemented as an alternative to PR, thus were centred around exercise training rather than modifying physical activity behaviour, which may be a reason for inconsistent findings (Cox et al., 2021). This is supported by the findings of Demeyer et al. (2017) who demonstrated a mean increase of 1,469 steps/day

(95% CI 973 to 1,965 steps/day) when physical activity tele-coaching was implemented, compared to usual care. Thus, highlighting the importance of incorporating behaviour change techniques when trying to induce improvements in physical activity.

Another limitation highlighted by Cox et al. (2021) was that the majority of tele-rehabilitation studies are undertaken in COPD patients, which may have implications for the applicability of findings to other chronic respiratory diseases. Although studies in other diseases entities are lacking, the existing studies do show encouraging results. For instance, a recent study in patients with PAH reported a significant increase in daily step count following completion of a text-based mobile health intervention, compared to usual care (1,409 steps/day [IQR -32 to 2,220] vs -149 steps/day [IQR -1,010 to 735]; p=0.02) (Hemnes et al., 2021). Additionally, in patients with CF, Hebestreit et al. (2022) implemented a partially supervised physical activity intervention consisting of individual counselling sessions to increase vigorous activity, a step counter, web-based diary and regular phone calls from the study team for 6 months, with the step counter and web-based programme continued until 12 months. The results demonstrated increased self-reported physical activity at all time points in the intervention group, along with higher pedometer daily steps at 12 months and exercise capacity at 6 and 12 months, compared to usual care. However, surprisingly the improvement in FEV_1 (% predicted) was significantly higher in the control group, compared to the intervention group (Hebestreit et al., 2022). Thus, despite improvements in physical activity, a steep increase in vigorous physical activity may not be the most suitable approach for improving lung health in patients with CF.

A meta-analysis of tele-rehabilitation interventions in surgical patients reported an overall mean difference of 1.01 (95% confidence interval 0.18 to 1.84) for quality of life, indicating that quality of life improved with tele-rehabilitation compared to usual care (van Egmond et al., 2018). For physical activity, the results were inconsistent, with two studies

demonstrating a significant increase in the 7-day Physical Activity Recall Scale (Pinto, Papandonatos, & Goldstein, 2013; Pinto, Papandonatos, Goldstein, Marcus, & Farrell, 2013) and two studies detecting no differences (Hawkes et al., 2013; Ligibel et al., 2012). However, this evidence was based upon subjective assessment of physical activity and therefore was limited by the lack of objective measurement (van Egmond et al., 2018).

2.7 Summary

As this literature review has outlined, LTx is an established treatment option for a number of chronic respiratory diseases with varying underlying pathologies. Advancements in surgical techniques, donor, and recipient selection, as well as peri-operative management has improved the prognosis and quality of LTx patients. However, it is evident that limitations in physical functioning prevail, which may be largely attributed to physical inactivity and skeletal muscle deconditioning.

The literature in chronic respiratory disease shows that whilst PR is an evidence-based treatment for enhancing exercise capacity, HRQoL, dyspnoea and clinical outcomes, its effects on physical activity can be inconsistent. Incorporating behaviour change strategies such as activity self-monitoring, feedback and goal setting have shown promise in patients with chronic respiratory disease and pose an interesting alternative to supervised exercise training in LTx patients. Importantly, this literature review highlights the dearth of research into interventions to address physical inactivity in LTx patients. Therefore, the following chapter will review the existing evidence on exercise training, which is recommended for lung transplant candidates and recipients, on outcomes related to physical functioning and physical activity such as exercise capacity and HRQoL.

Chapter 3: Systematic Review

3.1 Introduction

As described in Chapter 2, both LTx candidates and recipients exhibit significant limitations in exercise capacity, limiting their physical functioning and ability to undertake daily activities (Langer et al., 2009; Mathur et al., 2004). In LTx candidates with advanced lung disease, several physiological factors contribute to this, predominantly ventilatory limitations, as well as metabolic and gas exchange abnormalities, cardiovascular impairment, and peripheral muscle weakness (Vogiatzis & Zakynthinos, 2012). Since impaired exercise capacity is a predictor of thoracic surgery outcomes, exercise training has the potential to optimise outcomes following LTx surgery (Castleberry et al., 2015; Pestana Caires et al., 2017). A previous systematic review (Hoffman et al., 2017), comprising two randomised controlled trials (RCTs), two quasi-experimental studies and two retrospective studies concluded that pulmonary rehabilitation can be a beneficial treatment for improving functional capacity and HRQoL in LTx candidates. Studies are however still scarce, particularly RCTs. Notably, in the previous review, there were no studies looking at the effect of pulmonary rehabilitation on important outcomes such as survival (Hoffman et al., 2017).

Following LTx there is a marked improvement in pulmonary function. However, patients still experience physical impairments such as limited exercise capacity and skeletal muscle weakness, which persist for years after transplant surgery (Mathur et al., 2004; Reinsma et al., 2006). In the early post-transplant phase, this is likely due to deconditioning from the extended intensive care and hospital stay following surgery, which can vary from three to six weeks or more if complications ensue. Lung transplant patients also face a number of psychological stressors throughout the course of the transplant journey, which can significantly impact HRQoL and recovery of physical functioning (Rosenberger, Dew, DiMartini, DeVito Dabbs, & Yusen, 2012).

It has, therefore, been deemed necessary to implement therapeutic exercise protocols after LTx. Such studies (RCTs, controlled trials, and prospective cohorts) have been presented in a systematic review that was published in 2010 (Wickerson et al., 2010). The overall quality of these studies was deemed fair to moderate and positive outcomes were indicated in areas of maximal and functional exercise capacity, skeletal muscle function, and lumbar bone mineral density. Since the previous systematic reviews (Hoffman et al., 2017; Wickerson et al., 2010), there have been several new studies investigating the effect of exercise therapy protocols before and after LTx.

The American Thoracic Society/European Respiratory Society statement recommends pulmonary rehabilitation for both lung transplant candidates and recipients, and highlights the need to understand the mechanisms of improvement in functional capacity and QoL (Singh, ZuWallack, Garvey, & Spruit, 2013). Accordingly, the aim of the present systematic review is to investigate the effects of exercise training before and after LTx on exercise capacity, QoL, and clinical outcomes (including survival, length of hospital or ICU stay, hospitalisations). Additionally, the safety of exercise training protocols in this patient population will be evaluated.

3.2 Methods

3.2.1 Protocol and registration:

This systematic review was conducted in accordance with the guidelines for the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Moher, Liberati, Tetzlaff, & Altman, 2009). The review protocol is registered in the International Prospective Register of Systematic Reviews (PROSPERO ID: CRD42020166322).

3.2.2 Search strategy:

PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), Nursing and Allied Health, Scopus, and CINAHL databases were searched from inception until February 2020. A re-run of this search was undertaken in March 2022, to identify records published between February 2020 and March 2022. These six databases were chosen due to their relevance in clinical research and use in related systematic reviews (Hoffman et al., 2017; Wickerson et al., 2010). Data-base specific search strategies, developed and pilot tested in consultation with a senior librarian, were based on keywords and MeSH terms related to 'lung transplantation', 'exercise', 'rehabilitation', 'exercise capacity', 'quality of life' and 'survival'. Full details of the PubMed search strategy are detailed in Table 3-1. The reference lists of all relevant systematic reviews identified in the search were also screened for additional studies. The search was restricted to peer reviewed studies written in English, as access to a translator was not available. All search results were collated using EndNote software (Thomson Reuters, New York) and duplicates removed. Remaining references were exported to the systematic review management software program Rayyan (Qatar Computing Research Institute, Doha, Qatar).

3.2.3 Inclusion Criteria:

The titles and abstracts were reviewed independently by two authors (EH and JM) to determine if the studies met the pre-determined PICOS [population (P), intervention (I), comparators (C), outcomes (O), and study design (S)] criteria as follows:

- Population: Lung transplant candidates or recipients (>18 years old) with any lung disease.
- Intervention: Studies evaluating the effects of an exercise training intervention. This was defined as all planned, structured, and repetitive physical activity that

had a final or an intermediate objective of improving or maintaining physical fitness (Caspersen et al., 1985).

- Comparator: no exercise control group, an active control group or a different dose/mode/setting of exercise training were considered acceptable controls in RCTs.
- Outcomes: exercise capacity (assessed through 6MWT, Incremental Shuttle Walk Test (ISWT), Endurance Shuttle Walk Test (ESWT) or cardiopulmonary exercise testing (CPET)), QoL (including health-related quality of life (HRQoL)) and psychological health, assessed through generic or respiratory specific questionnaires), clinical outcomes (survival, hospitalisations, length of hospital or ICU stay).
- Design: studies of all design type were included, as evidence suggests that non-randomized intervention studies, including observational study designs, are key to many areas of healthcare evaluation and can provide complementary evidence to RCTs (Sterne et al., 2016).

Screening of full texts was performed by two independent reviewers (EH and JM) and the reasons for exclusion of ineligible studies was recorded. Any disagreements were resolved through consultation with a third reviewer (IV).

Table 3-1 ; Search strategy for PubMed literature search

Search	Query
#1	(lung transplantation [MeSH Terms] OR lung transplant* [Text Word])
#2	(exercise [MeSH Terms] OR exercise therapy [MeSH Terms] OR physical therapy modalities [Mesh:NoExp] OR rehabilitation [Mesh:NoExp] OR physical exertion [Mesh:NoExp] OR exercise movement techniques [MeSH Terms] OR exercis* [Text Word] OR train* [Text Word] OR rehabilit* [Text Word])
#3	(exercise tolerance [MeSH Terms] OR exercise test [MeSH Terms] OR exercise tolerance [Text Word] OR exercise capacity [Text Word] OR functional capacity [Text Word] OR physical fitness [MeSH Terms] OR fitness [Text Word] OR quality of life [MeSH Terms] OR quality of life [Text Word] OR surviv* [Text Word] OR mortality [Text Word])
#4	1 AND 2 AND 3

3.2.4 Data Extraction and Synthesis:

Data extraction was performed by a single author (EH) using a predesigned, standardized Excel (Microsoft, USA) form. The following study characteristics were extracted: author information (including name of first author and year of publication), participant characteristics (number (N), mean age, gender, baseline lung function), study design, setting (country, inpatient, outpatient or home-based) interventions details, outcome measures (exercise capacity, QoL, and clinical outcomes), and effect sizes for post-intervention differences between intervention and control/comparison groups (RCT and non-randomized controlled trials), or pre- to post- intervention differences (cohort and pilot studies). Effect size was expressed as Cohen's *d* using the mean difference and pooled standard deviation (Higgins et al., 2019). Meta-analyses were planned if three or more studies with clinical and methodological homogeneity were identified (Higgins et al., 2019). For questionnaires with subscales, only those reporting composite scores were extracted, to give a clearer picture of the efficacy of one therapeutic approach versus another (Singer & Singer, 2013).

3.2.5 Quality Assessment

The methodological quality of the studies was evaluated using the Downs and Black checklist (Downs & Black, 1998), designed to assess both randomized and non-randomized study designs. The checklist comprises 27 questions under four sub-scales of reporting, external validity, internal validity (bias and confounding), and power. Each question was scored out of one, except for question five which was scored out of two, with a maximum total score of 28. Scoring of the last item (study power) was modified from a 0-5 scale to a 0-1 scale, where one was scored if a sample size/power calculation was present, while zero was scored if there was no power/sample size calculation or explanation whether the number of subjects was appropriate (Downs & Black, 1998; Knols, Fischer, Kohlbrenner, Manettas, & de Bruin, 2018). A score of 24-28 points was considered excellent, 19-23 good, 14-18 fair, and <14 poor in terms of methodological quality (O'Connor et al., 2015). Each study was scored independently by two authors (EH and JM), with discrepancies resolved through consensus.

3.3 Results

A total of 1962 articles were yielded from the six database searches, of which 393 records were duplicates. Following screening of titles and abstracts, 47 articles remained for full text screening. On completion of full text screening, 21 studies met the eligibility criteria and were included in the original review (Hume et al., 2020). Following a re-run of the search (February 2020 to March 2022), 7 additional studies were added to the review, resulting in a total of 28 studies. A PRISMA flow diagram of the screening process is presented in Figure 3-1. Due to heterogeneity in study designs, interventions, comparison groups, and outcome measures, quantitative synthesis via meta-analysis was not performed, as pooling the data would have led to misleading results that were not clinically meaningful (Haidich, 2010).

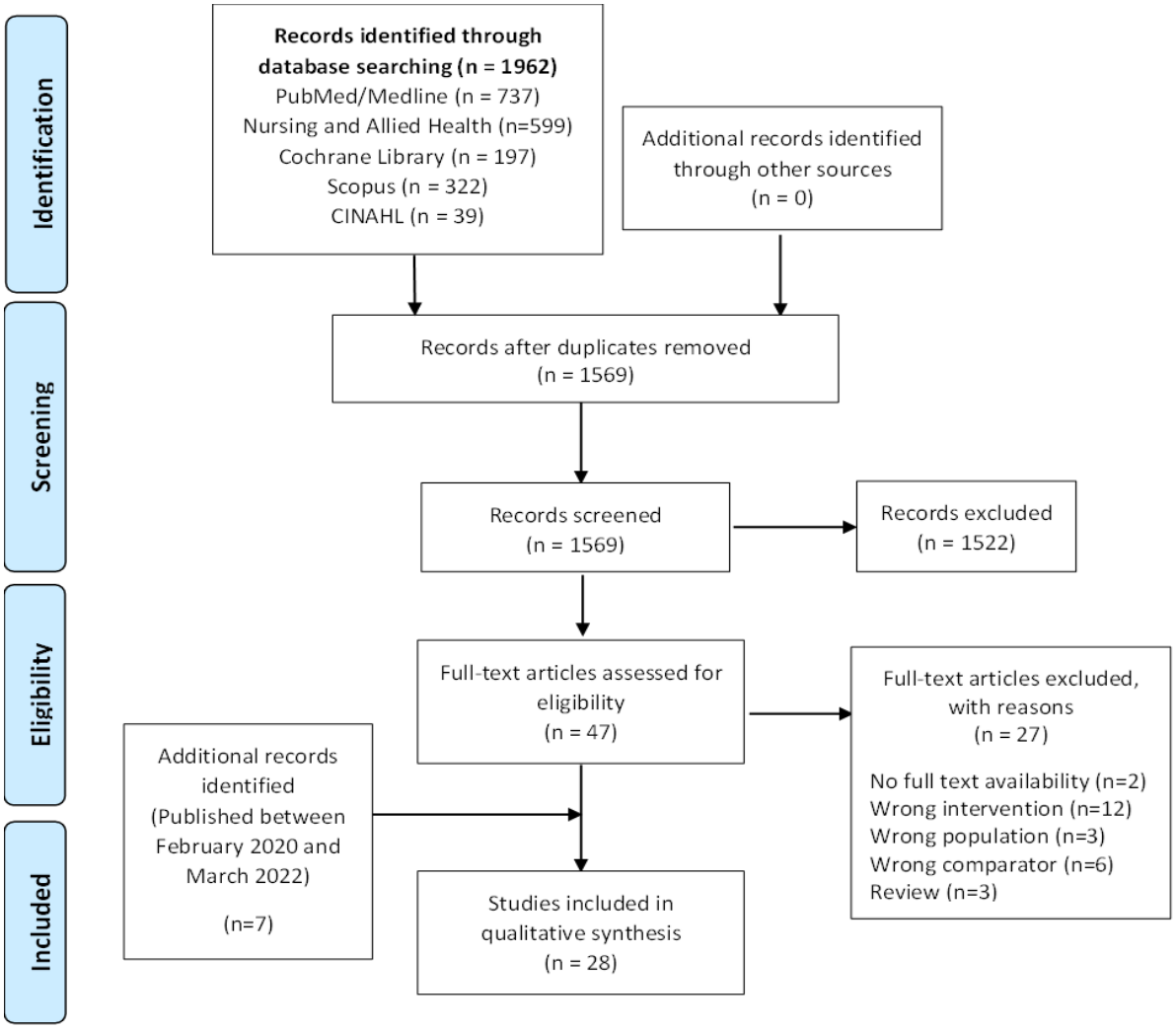


Figure 3-1: PRISMA flow diagram for database search and study selection process.

3.3.1 Study Characteristics and Interventions

The characteristics of the included studies are presented in Table 3-2.

Pre-transplant:

Fourteen of the 28 studies involved pre-transplant patients (N=1830), with a mean age of 50 years (range 30-63 years) and average FEV_1 % predicted range of 22 to 54%. Between 32 and 95% (median = 57%) of participants in each study were male. Of the pre-transplant studies, there was one RCT (Gloeckl, Halle, & Kenn, 2012), two quasi-experimental (Florian et al., 2019; Ochman et al., 2018), eight cohort studies (Da Fontoura et al., 2018; Florian et al., 2013; Kenn et al., 2015; Kerti et al., 2021; Kılıç, Pehlivan, Balcı, & Bakan, 2020; Layton et al., 2021; Li et al., 2013; Massierer et al., 2020; Pehlivan, Balci, Kilic, & Kadakal, 2018) and two single-arm pilot/feasibility studies (Singer et al., 2018; Wickerson et al., 2021). Thirteen of the 14 studies implemented both aerobic and resistance exercise (Da Fontoura et al., 2018; Florian et al., 2013; Florian et al., 2019; Gloeckl et al., 2012; Kenn et al., 2015; Kerti et al., 2021; Kılıç et al., 2020; Layton et al., 2021; Li et al., 2013; Massierer et al., 2020; Pehlivan et al., 2018; Singer et al., 2018; Wickerson et al., 2021) and one study included Nordic walking only (Ochman et al., 2018). Two studies were conducted as inpatient programmes (Gloeckl et al., 2012; Kenn et al., 2015), five were outpatient exercise programmes (Da Fontoura et al., 2018; Florian et al., 2013; Florian et al., 2019; Kerti et al., 2021; Li et al., 2013), three combined outpatient and home-based training (Kılıç et al., 2020; Ochman et al., 2018; Pehlivan et al., 2018), and four were home-based using an online application (Layton et al., 2021; Massierer et al., 2020; Singer et al., 2018; Wickerson et al., 2021). The length of exercise training ranged from 3 to 16 weeks, with exercise session frequency ranging from 2 to 7 exercise sessions per week.

Post-transplant:

Fifteen studies involved exercise training with lung transplant recipients. These studies included 1216 recipients of either single or bilateral lung transplant, with a mean age of 53 years (range 44-59 years), and average FEV_1 % predicted ranging from 64 to 81%. Between 47 and 98% (median = 57%) of participants in each study were male. Included studies comprised five RCTs (Fuller et al., 2017; Gloeckl et al., 2015; Ihle et al., 2011; Langer et al., 2012; Ulvestad, Durheim, Kongerud, Lund, & Edvardsen, 2020), one feasibility RCT (Tarrant et al., 2022), six cohort studies (Candemir et al., 2019; Kerti et al., 2021; Maury et al., 2008; Munro, Holland, Bailey, Button, & Snell, 2009; Schneeberger, Gloeckl, Welte, & Kenn, 2017; Stiebellehner, Quittan, End, Wieselthaler, & et al., 1998) and two single arm pilot studies (Andrianopoulos et al., 2019; Choi et al., 2016). A further controlled trial by Vivodtzev et al. (2011) used healthy individuals as a control group, therefore only the outcomes reported for lung transplant recipients were included in this review. One RCT compared high intensity interval training (HIIT) to usual care (Ulvestad et al., 2020), one compared exercise training to an active control group (physical activity counselling) (Langer et al., 2012), one compared an inpatient programme with outpatient physiotherapy (Ihle et al., 2011), two compared different durations or frequencies of supervised exercise training (Fuller et al., 2017; Tarrant et al., 2022) and one compared exercise training with whole body vibration training (WBVT) to exercise training alone (Gloeckl et al., 2015). Thirteen of the 15 studies implemented exercise programmes comprising both aerobic and resistance exercise (Andrianopoulos et al., 2019; Candemir et al., 2019; Choi et al., 2016; Fuller et al., 2017; Gloeckl et al., 2015; Ihle et al., 2011; Kerti et al., 2021; Langer et al., 2012; Maury et al., 2008; Munro et al., 2009; Schneeberger et al., 2017; Tarrant et al., 2022; Ulvestad et al., 2020) and two comprised aerobic training only (Stiebellehner et al., 1998; Vivodtzev et al., 2011). Five studies implemented inpatient programmes (Andrianopoulos et al., 2019; Gloeckl et al., 2015; Ihle et al., 2011; Schneeberger et al., 2017; Tarrant et al., 2022), seven were

outpatient programmes (Candemir et al., 2019; Kerti et al., 2021; Langer et al., 2012; Maury et al., 2008; Munro et al., 2009; Stiebellehner et al., 1998; Ulvestad et al., 2020) and two were home-based (Choi et al., 2016; Vivodtzev et al., 2011). The length of training varied from 3 to 20 weeks, with session frequency ranging from 3 to 14 times a week.

Table 3-2: Characteristics of included studies

PRE-TRANSPLANT							
Author (ref)	**Setting**	**Sample**	**Study Design**	**Duration & Frequency**	**Intervention**	**Comparison**	**Outcomes** **1) Exercise capacity** **2) QoL** **3) Clinical outcomes**
Gloeckl et al. (2012)	**Country:** Germany Supervised Inpatient Programme	**Sample size:** 60 **Mean age:** 53 **±** 6 **Gender:** 47% male **FEV_1 % pred:** 25 ± 8%	RCT	3 weeks 5-6 x a week	**Exercise programme: Interval training:** 30s cycling alternating with 30s rest. Resistance exercises.	**Exercise programme: Continuous training:** Cycling (60 % PWR). Resistance exercises.	1) 6MWT, PWR 2) SF-36 3) Not assessed
Florian et al. (2019)	**Country:** Brazil Supervised outpatient programme	**Sample size:** 89 **Mean age:** 56 ± 11 **Gender:** 64% male **FEV_1 % pred:** 46 ± 15%	Quasi-experimental	12 weeks (36 sessions) 3 x a week	**Exercise programme:** Aerobic exercises: treadmill walking. Resistance: arm and leg exercises. Breathing exercises associated with arm raising.	**Patients not completing 36 sessions**	1) 6MWT 2) SF-36 3) Survival rate, LOS in hospital & ICU, IMV
Ochman et al. (2018)	**Country:** Poland Outpatient and home-based programme	**Sample size:** 40 **Mean age:** Intervention: 50 ± 8 Control: 54 ± 9 **Gender:** 95% male **FEV_1 % pred:** Intervention: 39 ± 20.5% Control: 43 ± 22.2%	Quasi-experimental	12 weeks	**Exercise programme: Nordic walking**	**No treatment control group**	1) 6MWT 2) SF-36 3) Not assessed
Florian et al. (2013)	**Country:** Brazil Supervised outpatient programme	**Sample size:** 58 **Mean age:** 46 ± 14 **Gender:** 48% male **FEV_1 % pred:** 33 ± 16%	Cohort study	12 weeks 3 x a week (36 sessions)	**Exercise programme:** Aerobic exercises: treadmill walking. Resistance: arm and leg exercises. Breathing exercises associated with arm raising. Stretching: major muscle groups.	**None**	1) 6MWT 2) SF-36 3) Not assessed

Da Fontoura et al. (2018)	**Country: Brazil** Supervised outpatient programme	**Sample size:** 31 **Mean age:** 57 ± 10 **Gender:** 58% male **FEV_1 % pred:** 54 ± 16	Cohort study	12 weeks 3 x a week	**Exercise programme:** Aerobic exercise: treadmill. Resistance exercise: upper and lower body (light weights and resistance bands).	**None**	1) 6MWT 2) SF-36 3) Not assessed
Kenn et al. (2015)	**Country:** Germany Supervised Inpatient programme	**Sample size:** 811 **Mean age:** COPD male: 54 ± 7.6 COPD female: 54 ± 7.4 AATD male: 51 ± 6.3 AATD female: 52 ± 8.2 ILD male: 54 ± 8.7 ILD female: 53 ± 7.9 CF Male: 31 ± 7.4 CF female: 31 ± 8.6 Other male: 45 ± 12.9 Other female: 45 ± 11.3 **Gender:** 43% male **FEV_1 % pred:** COPD male: 25.2 ± 12.6 COPD female: 25.5 ± 7.6 AATD male: 25.6 ± 9.2 AATD female: 27.2 ± 8.9 ILD male: 49.2 ± 19.5 ILD female: 43.5 ± 16.4 CF Male: 23.8 ± 7.8 CF female: 26.2 ± 7.7 Other male: 33.5 ± 15.2 Other female: 33.2 ± 20.5	Cohort study	5-6 weeks 5-6 x a week (25-30 sessions)	**Exercise programme:** Aerobic exercise: cycle ergometer. Resistance training. Breathing exercises. Controlled coughing exercises.	**None**	1) 6MWT 2) SF-36 3) Not assessed
Li et al. (2013)	**Country:** Canada Supervised outpatient programme	**Sample size:** 345 **Mean age:** 51 ± 14 **Gender:** 55% male **FEV_1 % pred:** Not stated	Cohort study	47 ± 59 sessions 3 x a week	**Exercise programme:** Aerobic exercise: arm ergometer, cycle ergometer and treadmill; Stretching and resistance training: biceps, triceps, quadriceps, hamstrings and hip muscles.	**None**	1) 6MWT 2) SF-36, SGRQ, VAS, Standard Gamble, EQ5Q 3) Discharge disposition, hospital & ICU LOS, intubation days

Pehlivan et al. (2018)	**Country:** Turkey Supervised outpatient and home-based programme	**Sample size:** 39 **Mean age:** 37 ± 13 **Gender:** 64% male **FEV_1 % pred:** 26 ± 11	Cohort study	8 weeks (minimum) 5 x a week (2 supervised, 3 at home)	**Exercise programme:** Aerobic exercise: cycle ergometer, treadmill walking, arm ergometer. Resistance exercises. Home exercises: breathing exercises, strengthening exercises using Thera-bands, walking.	**None**	1) 6MWT 2) SF-36, BDI 3) Not assessed
Kılıç et al. (2020)	**Country:** Turkey Supervised outpatient programme with home-based programme	**Sample size:** 23 **Mean age:** 35 ± 10 **Gender: 57**% male **FEV_1 % pred:** 22 (15-43)	Cohort Study	8 weeks 2 x a week	**Exercise Programme:** Aerobic exercise: treadmill, cycling. Resistance exercise: Therabands. Breathing exercises.	**None**	1) 6MWT 2) Not assessed 3) Not assessed
Massierer et al. (2020)	**Country:** Canada Home based programme	**Sample size:** 159 **Mean age: 50** ± 14 **Gender: 57% male** **FEV_1 % pred:** Not stated	Cohort Study	Not specified 3-5 x a week	**Exercise Programme:** Home-based. Aerobic exercise: cycling or treadmill walking. Resistance training: dumbbell, elastic bands or free weights.	**None**	1) 6MWT 2) Not assessed 3) Hospital & ICU LOS, time on mechanical ventilation
Layton et al. (2021)	**Country:** USA Home based programme using App and Outpatient supervised programme	**Sample size:** 19 **Mean age:** **Home: 30** ± 10 **Outpatient: 29** ± 7 **Gender: 32**% male **FEV_1 % pred:** **H**ome: 26 ± 6 Outpatient: 29 ± 14	Pilot Study	12 weeks 24 sessions	**Exercise Programme:** Home-based personalised programme using Peleton App. Aerobic exercise: cycling, treadmill walking, outdoor walking/running, dance. Resistance exercise: Weights, body weight, Plyometrics. Yoga and Stretching.	**Outpatient PR (no description)**	1) 6MWT 2) Not assessed 3) Not assessed

Wickerson et al. (2021)	**Country:** Canada Home-based programme using web-based app with support	**Sample size:** 78 **Mean age:** 59 ± 12 **Gender:**47% male **FEV_1 % pred:** Pre-transplant: Restrictive: 52 ± 16 Obstructive: 26 ± 15 Vascular: 71 ± 17	Programme Evaluation	≥4 weeks 3 x a week	**Exercise programme:** Individually tailored aerobic and resistance training.	**None**	1) 6MWT 2) Not assessed 3) Not assessed
Singer et al. (2018)	**Country: USA** Home-based programme using App	**Sample size:** 15 **Mean age:** 63 ± 6 **Gender:** 67% male **FEV_1 %** pred**:** 42 ± 26	Pilot Study	8 weeks	**Exercise programme:** Home-based exercise using Aidcube App. Aerobic exercise: treadmill or ground walking. Resistance exercises: Thera-bands.	**None**	1) 6MWT 2) Not assessed 3) Not assessed

POST-TRANSPLANT							
Author (ref)	**Setting**	**Sample**	**Study Design**	**Duration and Frequency**	**Intervention**	**Comparison**	**Outcomes:** **1) Exercise capacity** **2) QoL** **3) Clinical outcomes**
Ulvestad et al. (2020)	**Country:** Norway Supervised outpatient Programme	**Sample size: 46** **Mean age:** **Intervention: 52** ± 12 **Control: 51** ± 14 **Gender: 50% male** **FEV_1 % pred:** 81 ± 26%	RCT	20 weeks 3 x a week	**Exercise Programme:** **HIIT:** Treadmill walking. 4 mins at 85-95% HRmax alternating with 2 mins active recovery. Resistance exercises.	**No treatment control group**	1) VO_2peak 2) SF-36 3) Not assessed
Langer et al. (2012)	**Country:** Belgium Supervised outpatient programme	**Sample size:** 36 **Mean age:** 59 ± 6 **Gender:** 50% male **FEV_1 % pred:** Intervention: 79 ± 18% Control: 69 ± 17%	RCT	12 weeks 3 x a week	**Exercise programme:** Aerobic exercises: cycling, walking, stair climbing. Resistance exercises: leg press equipment.	**Physical activity counselling** 6 sessions, 15-30 mins	1) 6MWT (% pred), VO_2max (%pred), PWR (%pred) 2) SF-36 & HADS 3) Not assessed

Ihle et al. (2011)	**Country:** Germany Supervised Inpatient programme	**Sample size:** 60 **Mean age:** Intervention = 49 ± 14 Control = 50 ± 12 **Gender:** 57% male **FEV_1 % pred:** Not reported	RCT	23 ± 5 days	**Inpatient Exercise programme:** Endurance training. Resistance training: upper and lower limb. Stretching: major muscle groups. Range-of-motion exercises: neck, shoulders and trunk.	**Outpatient physiotherapy** Cardiovascular exercise, airway clearance and breathing exercises.	1) 6MWT, PWR, VO_2peak 2) SF-36, SGRQ 3) Not assessed
Fuller et al. (2017)	**Country:** Australia Supervised outpatient programme and home-based unsupervised programme	**Sample size:** 66 **Mean age:** 51 **±** 13 **Gender:** 50% male **FEV_1 % pred:** Intervention: 70 ± 21% Control: 69 ± 23%	RCT	14 weeks 3 x a week	**Exercise programme: 14 weeks supervised** Aerobic training: treadmill and cycle ergometer. Resistance training: upper and lower limb. Functional exercises and core stability.	**Exercise programme: 7 weeks supervised 7 weeks home-based** Aerobic training: treadmill and cycle ergometer. Resistance training: upper and lower limb. Functional exercises and core stability.	1) 6MWT 2) SF-36 3) Not assessed
Gloeckl et al. (2015)	**Country:** Germany Inpatient programme	**Sample size:** 80 **Mean age:** 56 ± 7 **Gender:** 53% male **FEV1 % pred:** 68 ± 20%	RCT	4 weeks 5-6 x a week	**Exercise programme with WBVT:** Aerobic exercise: cycle ergometer. Resistance exercises: major muscle groups + WBVT squats.	**Exercise programme:** Aerobic exercise: cycle ergometer. Resistance exercises: major muscle groups.	1) 6MWT, PWR 2) HADS, CRQ 3) Not assessed
Tarrant et al. (2022)	**Country: Australia** **Inpatient programme**	**Sample size:** 40 **Mean age:** 61 (49-67) **Gender: 60**% male **FEV1 % pred:** Not reported	Feasibility RCT	10 weeks 3 x a week	**Exercise Programme:** Intensive Physiotherapy (twice daily) Early mobility, aerobic exercise and resistance exercise. Additional 30-minute session.	**Exercise Programme** Usual care – Physiotherapy (once daily) Early mobility, aerobic exercise and resistance exercise.	1) 6MWT 2) EQ-5D-5L 3) Inpatient and ICU LOS
Candemir et al. (2019)	**Country:** Turkey Outpatient programme (2 sessions supervised, 1 unsupervised)	**Sample size:** 23 **Mean age:** 47 ± 10 **Gender:** 88% male **FEV_1 % pred:** 75 ± 15	Cohort study	12 weeks	**Exercise programme:** Aerobic exercise: treadmill, cycle ergometer. Resistance exercise: lower and upper extremities	**None**	1) ISWT & ESWT 2) SGRQ, CRQ & HADS 3) Not assessed

Munro et al. (2009)	**Country:** Australia Supervised outpatient programme	**Sample size:** 36 **Mean age:** 46 ± 14 **Gender:** 50% male **FEV_1 % pred:** 71 ± 18	Cohort study	12 weeks 3 x a week	**Exercise programme:** Aerobic exercises: cycling, treadmill walking. Resistance training: upper and lower limb. Stretching: major muscle groups	**None**	1) 6MWT 2) SF-36 3) Not assessed
Maury et al. (2008)	**Country:** Belgium Supervised outpatient programme	**Sample size:** 36 **Mean age:** 57 ± 4 **Gender:** 47% male **FEV_1 % pred:** 70 ± 21	Cohort study	12 weeks 3 x a week	**Exercise programme:** Aerobic exercises: cycling, walking, stair climbing. Resistance exercises: quadriceps muscle.	**None**	1) 6MWT 2) Not assessed 3) Not assessed
Stiebellehner et al. (1998)	**Country:** Austria Supervised outpatient programme	**Sample size:** 9 **Mean age:** 44 ± 6 **Gender:** 67% male **FEV_1 % pred:** 65 ± 17	Cohort study	6 weeks 3-5 x a week	**Exercise programme:** Aerobic exercise: cycle ergometer	**None**	1) VO_2peak 2) Not assessed 3) Not assessed
Schneeberger et al. (2017)	**Country:** Germany Supervised Inpatient programme	**Sample size:** 722 **Mean age:** COPD SLTx: 59 ± 5 COPD DLTx 54 ± 7 ILD SLTx: 58 ± 7 ILD DLTx: 54 ± 9 **Gender:** 55% male **FEV_1 % pred:** COPD SLTx: 51.1 ± 16.6 COPD DLTx: 73.7 ± 20.1 ILD SLTx: 60.2 ± 18.9 ILD DLTx: 65.6 ± 18.1	Cohort study	6 weeks 5-6 x a week	**Exercise programme:** Aerobic training: cycle ergometer. Resistance training: lower extremities. Breathing exercises. Activities of daily living: stair climbing.	**None**	1) 6MWT 2) SF-36 3) Not assessed
Andrianopoulos et al. (2019)	**Country:** Germany Supervised inpatient programme	**Sample size:** 24 **Mean age:** 58 ± 6 **Gender:** 58% male **FEV_1 % pred:** 75.4 ± 22	Pilot study	3 weeks 5-6 x a week (15 sessions minimum)	**Exercise programme:** Aerobic training: cycle ergometer. Resistance training: upper and lower limb. Activities of daily living training: walking and/or calisthenics exercises.	**None**	1) 6MWT 2) Not assessed 3) Not assessed

Choi et al. (2016)	**Country:** USA Home programme using computer programme	**Sample size:** 4 **Mean age:** 55 ± 17 **Gender:** 75% male **FEV_1 % pred:** 71.3 ± 25.2	Pilot Study	8 weeks 8 sessions	**Exercise programme:** Aerobic exercise: walking. Resistance exercises: cuff weights. Balance exercises.	**None**	1) 6MWT 2) Not assessed 3) Not assessed
Vivodtzev et al. (2011)	**Country:** France Home programme (supervised via phone)	**Sample size:** 12 **Mean age:** 47 ± 13 **Gender:** 83% male **FEV_1 % pred:** 74 ± 24	Controlled trial (healthy controls)	12 weeks 3 x a week	**Exercise programme:** Aerobic exercise: cycle ergometer.	**None**	1) VO_2peak, Endurance Time 2) Not assessed 3) Not assessed
PRE & POST-TRANSPLANT							
Kerti et al. (2021)	**Country: Hungary** **Supervised outpatient programme**	**Sample size:** Pre-transplant: 63 Post-transplant: 14 **Mean age:** Pre-transplant: 58 ± 7 Post-transplant: 52 ± 9 **Gender:** Pre-transplant: 54% male Post-transplant: 79% male **FEV_1 % pred:** Pre-transplant: 29±16 Post-transplant: 73±8	Cohort Study	4 weeks Daily	**Exercise programme:** Aerobic exercise: cycling or treadmill. Resistance exercises, Breathing techniques and chest-spine mobilisation.	**None**	1) 6MWT 2) CAT 3) Not assessed

Data are presented as mean ± SD. FEV_1: forced expiratory volume in 1 second; COPD: Chronic Obstructive Pulmonary Disease; ILD: Interstitial Lung Disease; CF: Cystic Fibrosis; AATD: Alpha-1 antitrypsin deficiency; SLTx: single lung transplant; DLTx: double lung transplant; RCT: randomised controlled trial; QoL: quality of life; 6MWT: 6 minute walk test; VO_2peak: peak oxygen uptake; PWR: peak work rate; ISWT: incremental shuttle walk test; ESWT: endurance shuttle walk test; SF-36: Short Form 36 Questionnaire; SGRQ: St George's Respiratory Questionnaire; CRQ: Chronic Respiratory Questionnaire; HADS: Hospital Anxiety and Depression Scale; VAS: Visual Analogue Scale; BDI: Beck Depression Inventory; CAT: COPD Assessment Test; Hospital LOS: hospital length of stay; ICU LOS: intensive care unit length of stay; IMV: invasive mechanical ventilation; WBVT: whole body vibration training; HIIT: High intensity interval training.

3.3.2 Quality Assessment

Quality assessment ratings using Downs and Black are presented in Table 3-3. The mean score for the 28 included studies was 18 out of a possible 28 (range 14 to 25), indicating fair to excellent methodological quality. The RCTs scored highest for methodological quality. Across studies, scoring was low for item 8 (reporting of adverse events), item 12 (representative sample), item 14 (blinding of subjects), item 15 (blinding of assessors), and item 27 (sample size). Poor scoring for item 14 was expected, as it is difficult to blind patients from the condition they are receiving, due to the nature of the intervention. The methodological quality of the non-randomized and cohort studies was limited because of non-random allocation and lack of control for confounding variables.

Table 3-3: Downs and Black Methodological Quality Assessment

	Author (Ref)	Reporting *(/11)*	External Validity *(/3)*	Internal Validity – Bias *(/7)*	Internal Validity – Confounding *(/6)*	Power *(/1)*	Total Score *(/28)*
PRE-TRANSPLANT	**Gloeckl et al. (2012)**	11	2	5	6	1	**25**
	Florian et al. (2019)	8	2	5	4	0	**19**
	Ochman et al. (2018)	7	1	4	3	0	**15**
	Florian et al. (2013)	8	3	5	3	0	**19**
	Da Fontoura et al. (2018)	8	2	5	2	0	**17**
	Kenn et al. (2015)	8	2	5	3	0	**18**
	Li et al. (2013)	7	2	3	3	0	**15**
	Pehlivan et al. (2018)	8	1	5	3	0	**17**
	Singer et al. (2018)	9	3	5	3	0	**20**
	Kılıç et al. (2020)	8	1	4	2	0	**15**
	Massierer et al. (2020)	9	3	2	4	0	**18**
	Layton et al. (2021)	8	2	4	2	0	**16**
	Wickerson et al. (2021)	10	3	4	3	0	**20**
POST-TRANSPLANT	**Langer et al. (2012)**	9	2	6	6	1	**24**
	Ihle et al. (2011)	9	2	5	5	0	**21**
	Fuller et al. (2017)	11	2	6	5	1	**25**
	Gloeckl et al. (2015)	10	2	6	4	1	**23**
	Candemir et al. (2019)	8	1	5	3	0	**17**
	Munro et al. (2009)	7	3	4	3	0	**17**
	Maury et al. (2008)	7	2	4	3	0	**16**
	Stiebellehner et al. (1998)	7	1	5	2	0	**15**
	Schneeberger et al. (2017)	9	1	5	2	0	**17**
	Andrianopoulos et al. (2019)	8	1	5	2	0	**16**
	Choi et al. (2016)	7	1	4	2	0	**14**
	Vivodtzev et al. (2011)	7	1	5	1	0	**14**
	Ulvestad et al. (2020)	11	2	4	5	1	**23**
	Tarrant et al. (2022)	10	1	5	4	0	**20**
Both	**Kerti et al. (2021)**	6	1	5	2	0	**14**

*Maximum score. Cut-off points of the summative score are: excellent (24-28), good, (19-23), fair (14-18), and poor (<14).

3.3.3 Exercise capacity outcomes

The measures of exercise capacity pre- and post- exercise intervention are presented in Table 3-4.

Pre-transplant:

All 14 pre-transplant studies in the review assessed functional exercise capacity using the 6MWT, with nine of the 14 studies reporting a significant improvement in this outcome after exercise training. In addition to the 6MWT, Gloeckl et al. (2012) also assessed peak work rate (PWR) during an incremental test, and found that both interval and continuous training significantly improved both measures of exercise capacity, with no difference in the magnitude of improvement between groups. Florian et al. (2019) reported a significant increase in 6MWT distance in the exercise training group, however no 6MWT data were presented for the control group. Nordic walking elicited a significant improvement in 6MWT distance compared to a control group after 12 weeks (Ochman et al., 2018). Of the eight cohort studies, six showed significant improvements in 6MWT distance following combined aerobic and resistance training (Da Fontoura et al., 2018; Florian et al., 2013; Kenn et al., 2015; Kerti et al., 2021; Kılıç et al., 2020; Pehlivan et al., 2018). A few studies showed a decrease in 6MWT distance from the time of enrolment to the 6MWT conducted before transplantation, following conduction of an outpatient (Li et al., 2013) or home-based exercise programme (Layton et al., 2021; Massierer et al., 2020; Wickerson et al., 2021).

Post-transplant:

Six different measures of exercise capacity were used across the fifteen post-transplant studies: 6MWT distance (Andrianopoulos et al., 2019; Choi et al., 2016; Fuller et al., 2017; Gloeckl et al., 2015; Ihle et al., 2011; Kerti et al., 2021; Langer et al., 2012; Maury et al., 2008; Munro et al., 2009; Schneeberger et al., 2017; Tarrant et al., 2022), ISWT,

ESWT (Candemir et al., 2019), $\dot{V}O_2$peak (Ihle et al., 2011; Langer et al., 2012; Stiebellehner et al., 1998; Ulvestad et al., 2020; Vivodtzev et al., 2011), peak work rate (PWR) (Gloeckl et al., 2015; Ihle et al., 2011; Langer et al., 2012), and endurance time (sustained at 65% PWR) (Vivodtzev et al., 2011). Langer et al. (2012) found a significant increase in 6MWT distance (% predicted) following exercise training compared to a control group; however, there were no significant differences in $\dot{V}O_2$peak (% predicted) or PWR (% predicted). Ulvestad et al. (2020) also reported no significant differences in $\dot{V}O_2$peak following HIIT compared to usual care. Ihle et al. (2011) found no significant difference in the improvement of 6MWT distance, $\dot{V}O_2$peak, or PWR when inpatient rehabilitation was compared to outpatient physiotherapy. Furthermore, improvements in 6MWT distance were not significantly different between 7 and 14 weeks of supervised exercise training (Fuller et al., 2017) or between intensive or standard physiotherapy (Tarrant et al., 2022). Gloeckl et al. (2015) showed significantly greater improvements in 6MWT distance and PWR, with the addition of WBVT to exercise training. Five cohort studies implementing aerobic and resistance training found statistically significant increases in either 6MWT distance (Kerti et al., 2021; Maury et al., 2008; Munro et al., 2009; Schneeberger et al., 2017) or ISWT distance (Candemir et al., 2019). Stiebellehner et al. (1998) showed significant gains in $\dot{V}O_2$peak after an aerobic exercise programme. Furthermore, a pilot study (Andrianopoulos et al., 2019) found a significant increase in 6MWT distance after exercise based pulmonary rehabilitation. However, the pilot study by Choi et al. (2016) showed a 71m improvement in 6MWT distance in four patients with either IPF or CF, but failed to conduct any statistical analysis.

Table 3-4: Effects of Pre- and Post- transplant exercise training interventions on measures of exercise capacity.

PRE-TRANSPLANT								
Author (Ref)	**N**	**Duration**	**Measure**	**Intervention/ Comparison**	**Δ (mean ± SD where reported)**	**Pre-Post P value**	**Between group P value**	**Effect Size**
Gloeckl et al. (2012)	60	3 weeks	6MWT (m)	Interval ET	35.4 ± 28.9	P<0.05	P=0.89	INT < CON; 0.0008
				Continuous ET	35.7 ± 42.2	P<0.05		
			PWR (W)	Interval ET	12.0 ± 8.5	P<0.05	P=0.38	INT > CON; 0.29
				Continuous ET	9.3 ± 10.1	P<0.05		
Florian et al. (2019)	89	12 weeks	6MWT (m)	ET	43 ± 86	P=0.005	-	PRE < POST; 0.5
				Control	NR	NR	-	-
Ochman et al. (2018)	40	12 weeks	6MWT (m)	Nordic walking ET	64	P=0.0378	P=0.034	UTC
				Control	- 57	P=0.0059		
Pehlivan et al. (2018)	39	8 weeks	6MWT (m)	ET	54.3	P=0.001	-	PRE < POST; 0.49
Florian et al. (2013)	58	12 weeks	6MWT (m)	ET	72	P=0.001	-	PRE < POST; 0.57
Da Fontoura et al. (2018)	31	12 weeks	6MWT (m)	ET	58 ± 63	P<0.001	-	PRE < POST; 0.92
Kenn et al. (2015)	811	5-6 weeks	6MWT (m)	ET	55.9 ± 58.5	P<0.001	-	PRE < POST; 0.96
Li et al. (2013)	345	47 ± 59 sessions	6MWT (m)	ET	-6	P=0.002	-	PRE > POST; -0.05
Singer et al. (2018)	15	8 weeks	6MWT (m)	Tele-rehabilitation	-7.8	P=0.73	-	PRE > POST; -0.10
Kılıç et al. (2020)	23	8 weeks	6MWT (m)	ET	60	P=0.018	-	PRE < POST; 0.15
Massierer et al. (2020)	159	Not specified	6MWT (m)	ET	-28	P<0.001	-	PRE > POST; -0.23
Layton et al. (2021)	19	12 weeks	6MWT (m)	Tele-rehabilitation				
				Completers (>24 sessions)	-7 ± 33	NR	-	PRE > POST; -0.21
				Non-Completers (<24 sessions)	-86 ± 108	NR		PRE > POST; -0.79

Wickerson et al. (2021)	78	≥4 weeks	6MWT (m)	Tele-rehabilitation	-39	P=0.002	-	PRE > POST; -0.46
Kerti et al. (2021)	63	4 weeks	6MWT (m)	ET	60	P<0.05	-	PRE < POST; 0.52

POST-TRANSPLANT								
Author (ref)	**N**	**Duration**	**Measure**	**Intervention/ Comparison**	**Δ (mean ± SD where reported)**	**Pre – Post P value**	**Between group P value**	**Effect Size**
Ihle et al. (2011)	60	23 ± 5 days	6MWT (m)	ET (inpatient)	45	P<0.001	P=0.214	INT > CON; 0.24
				Control (outpatient physiotherapy)	24	P<0.001		
			VO_2 peak (ml/min/kg)	ET (inpatient)	1.3	P=0.039	P=0.293	INT < CON; -0.19
				Control (outpatient physiotherapy)	2.2	P=0.005		
			PWR (W)	ET (inpatient)	7.3	P=0.022	P=0.600	INT > CON; 0.09
				Control (outpatient physiotherapy)	4.7	P=0.070		
Langer et al. (2012)	36	12 weeks	6MWT (% pred)	ET	23	-	P=0.008	INT > CON; 0.37
				Control (PA counselling)	19	-		
			VO_2 peak (% pred)	ET	16	-	P=0.149	INT > CON; 0.20
				Control (PA counselling)	12	-		
			PWR (% pred)	ET	16	-	P=0.093	INT > CON; 0.26
				Control (PA counselling)	11	-		
Fuller et al. (2017)	66	14 weeks	6MWT (m)	14 weeks supervised ET	149 ± 169	-	P=0.36	INT < CON; -0.44
				7 weeks supervised ET	202 ± 72	-		
Gloeckl et al. (2015)	80	4 weeks	6MWT (m)	ET + WBVT	83.5	P<0.001	P=0.029	INT > CON; 0.54
				ET	55.2	P<0.001		
			PWR	ET + WBVT	16.8	P<0.001	P=0.042	INT > CON; 0.38
				ET	12.6	P<0.001		
Candemir et al. (2019)	23	12 weeks	ISWT (m)	ET	103	P<0.001	-	PRE < POST; 0.87
			ESWT (min)		8	P<0.01	-	PRE < POST; 1.33

Munro et al. (2009)	36	12 weeks	6MWT (m)	ET	92	P<0.001	-	PRE < POST; 0.79
Maury et al. (2008)	36	12 weeks	6MWT (m)	ET	129	P<0.05	-	PRE < POST; 0.97
Stiebellehner et al. (1998)	9	6 weeks	VO_2 peak (ml/min/kg)	ET	1.9	P<0.05	-	PRE < POST; 0.49
Schneeberger et al. (2017)	722	6 weeks	6MWT (m)	ET in COPD SLTx	109 ± 68	P<0.001	-	PRE < POST; 1.60
				ET in COPD DLTx	117 ± 82	P<0.001	-	PRE < POST; 1.43
				ET in ILD SLTx	115 ± 79	P<0.001	-	PRE < POST; 1.46
				ET in ILD DLTx	132 ± 77	P<0.001	-	PRE < POST; 1.71
Andrianopoulos et al. (2019)	24	3 weeks	6MWT (m)	ET	86 ± 77	P<0.001	-	PRE < POST; 0.73
Choi et al. (2016)	4	8 weeks	6MWT (m)	Tele-rehabilitation ET	71	-	-	PRE < POST; 0.62
Vivodtzev et al. (2011)	12	12 weeks	VO_2 peak (L/min)	Home-based ET	0.13 ± 0.22	P=0.059	-	PRE < POST; 0.59
			Endurance time (65% PWR) (min)		9 ± 12	P<0.05	-	PRE < POST; 0.75
Ulvestad et al. (2020)	46	20 weeks	VO_2 peak (ml/min/kg)	ET (HIIT)	1.5	-	P=0.169	INT > CON; 0.19
				Control	0.8			
Tarrant et al. (2022)	40	10 weeks	6MWT (m)	Intensive Physiotherapy	147	-	P=0.64	INT > CON; 0.04
				Standard Physiotherapy	142			
Kerti et al. (2021)	14	4 weeks	6MWT (m)	ET	104	P<0.05	-	PRE < POST; 0.85

ET: exercise training; WBVT: whole body vibration training; HIIT: High Intensity Interval Training, 6MWT: 6 minute walk test; ISWT: Incremental Shuttle Walk Test; ESWT: Endurance Shuttle Walk Test; VO2 peak: peak oxygen uptake; PWR: Peak Work Rate: SLTx: single lung transplant; DLTx: double lung transplant; COPD: Chronic Obstructive Pulmonary Disease; INT: intervention; CON: control; PRE: Pre-intervention; POST: Post-intervention; UTC: unable to calculate; (Δ): change from baseline.

3.3.4 Quality of Life Outcomes

The measures of QoL are presented in Table 3-5. For the purpose of this review, QoL was operationalised as measures encompassing HRQoL and/or psychological health.

Pre-transplant:

QoL was assessed in eight of the 14 pre-transplant studies using the SF-36 questionnaire, which generates eight sub-scale and two summary scores (physical component summary (PCS) and mental component summary (MCS)). Only the four studies reporting the summary scores were included in the review. Other QOL measures included; St Georges Respiratory Questionnaire (SGRQ) (Li et al., 2013), EQ-5D (Li et al., 2013), Standard Gamble (Li et al., 2013), COPD Assessment Test (CAT) (Kerti et al., 2021) and Beck Depression Inventory (BDI) (Pehlivan et al., 2018). Of the studies using the SF-36 questionnaire, Gloeckl et al. (2012) found significant improvements in SF-36 PCS scores in the continuous training but not the interval training group, whereas enhancements SF-36 MCS scores were found only with interval training. Da Fontoura et al. (2018) found significant improvements in SF-36 PCS scores, but no significant change in SF-36 MCS scores. Whereas Kenn et al. (2015) found significant increases in both SF-36 PCS and MCS scores overall for all disease entities. Kerti et al. (2021) reported significant improvements in CAT score from pre to post rehabilitation. In contrast, Li et al. (2013) revealed a significant decline in SF-36 MCS, SGRQ, and EQ-5D scores, along with no change in SF-36 PCS and Standard Gamble scores from listing to immediately prior to LTx.

Post-transplant:

QoL was assessed in nine of the 15 post-transplant studies. Several measures were used including the SF-36 questionnaire (Fuller et al., 2017; Ihle et al., 2011; Munro et al., 2009; Schneeberger et al., 2017; Ulvestad et al., 2020), Hospital Anxiety and Depression

Score (HADs) (Candemir et al., 2019; Gloeckl et al., 2015; Langer et al., 2012), SGRQ (Candemir et al., 2019; Ihle et al., 2011), EQ-5D-5L (Tarrant et al., 2022), CAT (Kerti et al., 2021) and Chronic Respiratory Questionnaire (CRQ) (Candemir et al., 2019; Gloeckl et al., 2015). Data from three studies were excluded from the results, as summary score data were not provided for the SF-36 (Ihle et al., 2011; Munro et al., 2009), SGRQ (Ihle et al., 2011), CRQ (Gloeckl et al., 2015) and QoL Profile for Chronic Diseases (Ihle et al., 2011) sub-scale questionnaires. Langer et al. (2012) found no significant benefit of 12 weeks exercise training on anxiety and depression scores compared to a control group. Ulvestad et al. (2020) showed significantly greater improvements in SF-36 MCS scores following HIIT compared to usual care, however there was no difference in SF-36 PCS scores between groups. Fuller et al. (2017) concluded that both 7 and 14 weeks of supervised training enhanced SF-36 PCS and MCS scores at 14 weeks, with no significant difference found between the two groups. Gloeckl et al. (2015) found no significant difference in the improvement of HADS scores between WBVT and exercise training compared to exercise training alone. Tarrant et al. (2022) reported no difference in EQ-5D-5L perceived health change scores between standard and intensive physiotherapy. Schneeberger et al. (2017) showed improvements in SF-36 PCS and MCS scores in COPD and ILD patients, with no significant differences found in scores between transplant procedures for either disease entity. Candemir et al. (2019) demonstrated significant increases in HADs, SGRQ, and CRQ scores following a comprehensive outpatient programme. Kerti et al. (2021) reported a significant improvement in CAT scores from pre to post rehabilitation.

Table 3-5: Effects of pre- and post-transplant exercise training interventions on measures of QoL

PRE-TRANSPLANT							
Author (ref)	**N**	**Duration**	**Measure**	**Intervention/ Comparison**	**Pre – Post P value**	**Between group P value**	**Effect Size**
Gloeckl et al. (2012)	60	3 weeks	SF-36	Interval ET Continuous ET	PCS: P>0.05 MCS: P<0.05 PCS: P<0.05 MCS: P>0.05	PCS: P=0.43 MCS: P= 0.066	**PCS:** INT < CON; -0.24 **MCS:** INT > CON; 0.57
Pehlivan et al. (2018)	39	8 weeks (minimum)	BDI	ET	P=0.004	-	PRE < POST; 0.28
Da Fontoura et al. (2018)	31	12 weeks	SF-36	ET	PCS: P=0.004 MCS: P=0.113	-	**PCS:** PRE < POST; 0.43 **MCS:** PRE < POST; 0.15
Kenn et al. (2015)	811	5-6 weeks	SF-36	ET	PCS: P<0.001 MCS: P<0.001	-	**PCS:** PRE < POST; 0.22 **MCS:** PRE < POST; 0.64
Li et al. (2013)	345	~16 weeks (47 ± 59 sessions)	SF-36 SGRQ SG EQ-5D	ET	PCS: P=0.11 MCS: P<0.05 P<0.05 P=0.050 P<0.05	- - - -	**PCS:** PRE > POST; -0.125 **MCS:** PRE > POST; -0.47 PRE > POST; -0.52 PRE > POST; -0.08 PRE > POST; -0.48
Kerti et al. (2021)	63	4 weeks	CAT	ET	P<0.05	-	PRE < POST; 0.33
POST-TRANSPLANT							
Author (ref)	**N**	**Duration**	**Measure**	**Intervention/ Comparison**	**Pre – Post P value**	**Between group P value**	**Effect Size**
Langer et al. (2012)	36	12 weeks	HADs	ET Control (PA counselling)	- -	Anxiety: P=0.812 Depression: P=0.899	**Anxiety:** INT < CON; -0.36 **Depression:** INT < CON; -0.09
Fuller et al. (2017)	66	14 weeks	SF-36	14 wks supervised ET 7 wks supervised ET	- -	PCS: P=0.32 MCS: P=0.74	**PCS:** INT > CON; 0.11 **MCS:** INT < CON; -0.18
Gloeckl et al. (2015)	80	4 weeks	HADs	ET + WBVT ET	Anxiety: P=0.180 Depression: 0.247 Anxiety: P=0.001 Depression: 0.038	Anxiety: P=0.174 Depression: P=0.533	**Anxiety:** INT < CON; 0.33 **Depression:** UTC
Candemir et al. (2019)	23	12 weeks	HADs	ET	Anxiety: P=0.001	-	**Anxiety:** PRE < POST; 3.00

					Depression: P<0.01		**Depression:** PRE < POST; 2.00
			SGRQ		P<0.01	-	PRE < POST; 1.36
			CRQ		P<0.001		PRE < POST; 1.52
Schneeberger et al. (2017)	722	6 weeks	SF-36	ET (COPD SLTx)	PCS: P≤0.001	-	**PCS:** PRE < POST; 1.00
					MCS: P≤0.01		**MCS:** PRE < POST; 0.53
				ET (COPD DLTx)	PCS: P≤0.001		**PCS:** PRE < POST; 0.78
					MCS: P≤0.001		**MCS:** PRE < POST; 0.47
				ET (ILD SLTx)	PCS: P≤0.001		**PCS:** PRE < POST; 0.67
					MCS: P≤0.001		**MCS:** PRE < POST; 0.83
				ET (ILD DLTx)	PCS: P≤0.001		**PCS:** PRE < POST; 1.00
					MCS: P≤0.001		**MCS:** PRE < POST; 0.67
Ulvestad et al. (2020)	54	20 weeks	SF-36	ET (HIIT)	-	PCS: P=0.319	**PCS:** INT < CON; -0.14
				Control	-	MCS: P=0.020	**MCS:** INT > CON; 0.35
Tarrant et al. (2022)	40	10 weeks	EQ-5D-5L (VAS 0-100)	Intensive Physiotherapy	-	P=0.71	INT < CON; 0.04
				Standard Physiotherapy	-		
Kerti et al. (2021)	14	4 weeks	CAT	ET	P<0.05	-	PRE < POST; 0.7

ET: exercise training; WBVT: whole body vibration training; SLTx: single lung transplant; DLTx: double lung transplant; INT: intervention; CON: control; SF-36: Short Form 36 Questionnaire; SGRQ: St George's Respiratory Questionnaire; CRQ: Chronic Respiratory Questionnaire; HADS: Hospital Anxiety and Depression Scale; VAS: Visual Analogue Scale; BDI: Beck Depression Inventory; SG: Standard Gamble; PCS: Physical Component Summary; MCS: Mental Component Summary

3.3.5 Clinical Outcomes

Clinical outcome measures after surgery were reported in three pre-transplant studies (Florian et al., 2019; Li et al., 2013; Massierer et al., 2020). Florian et al. (2019) concluded that patients with IPF who underwent exercise-based pulmonary rehabilitation had a higher survival rate 5 years after transplant (89.9% vs 60.9%, $p<0.001$), a shorter length of stay in the ICU (5 days vs. 7 days, $p=0.004$) and hospital (20 days vs. 25 days, $p=0.046$), along with a lower requirement for more than 24 hours invasive mechanical ventilation (9% vs. 41.6%, $p<0.001$), compared to control subjects. Cox regression models revealed that patients who completed the 12- week exercise programme had a reduced 54% risk of death (hazard ratio = 0.464, 95% CI 0.222-0.970, $p=0.041$). In the single-arm cohort studies, the absence of control data meant it was not possible to interpret the effect of the intervention on clinical outcome measures. However, Li et al. (2013) showed that at the end of hospital admission for transplantation, 79% were discharged home, 13% to inpatient rehabilitation and 8% died. The median hospital length of stay was 18 days (range 7 to 313 days), with a greater pre-transplant 6MWD associated with a short length of hospital stay. In contrast, Massierer et al. (2020) found no associations between 6MWD prior to transplant and post-transplant clinical outcomes (total hospital or intensive care unit length of stay). The median intensive care unit (ICU) and hospital length of stay was 6.6 (IQR: 3 to 12) days and 23 (IQR: 18 to 35) days, respectively. In terms of discharge destination, 72% were discharged home, 19.5% to a transitional post-transplant facility and 8% died.

3.3.6 Safety

Adverse event (AE) reporting was poor, with only 43% of studies (six pre-transplant studies (Gloeckl et al., 2012; Kenn et al., 2015; Layton et al., 2021; Ochman et al., 2018; Singer et al., 2018; Wickerson et al., 2021) and six post-transplant studies (Choi et al., 2016; Fuller et al., 2017; Gloeckl et al., 2015; Schneeberger et al., 2017; Tarrant et al.,

2022; Ulvestad et al., 2020) mentioning AEs. No AEs related to exercise training were reported in any of the 12 studies. One study reported exercise related musculoskeletal pain in four patients following HIIT (Ulvestad et al., 2020).

3.4 Discussion

In this systematic review, evidence from 28 studies including 3046 patients was synthesized to examine the effect of exercise training on exercise capacity, QoL, and clinical outcomes before and after LTx. While there is evidence suggesting positive effects of exercise training interventions on these outcomes, the current evidence is predominantly limited to non-randomized and observational studies and is therefore of lower quality. Prior to and following transplantation, the evidence suggests that exercise training can maintain or improve functional exercise capacity, with effects for improvements ranging from small to large. Furthermore, the enhancements in 6MWT distance tend to exceed the minimal clinically important difference (MCID) defined for chronic lung diseases (Holland & Nici, 2013; Mathai, Puhan, Lam, & Wise, 2012; Nathan et al., 2015). Most studies demonstrate a beneficial impact of exercise training on QoL outcomes. Data on clinical outcomes is sparse; however, it indicates a survival benefit of exercise training, accompanied with favourable post-operative outcomes.

3.4.1 Exercise capacity – Pre-transplant:

Nine of the 14 studies reported improvements in exercise capacity following completion of an exercise programme prior to LTx. Of these studies, two were inpatient (3-6 weeks) and seven were outpatient programmes (8-12 weeks), with no observable benefit of one approach over the other. The 6MWT is commonly used in pre- and post-operative evaluation and has proven beneficial in determining the effect of therapeutic interventions, due to its prognostic value (Martinu et al., 2008; Rejbi et al., 2010). It has also been found to correlate with $\dot{V}O_2$ peak in candidates for LTx (Cahalin,

Pappagianopoulos, Prevost, Wain, & Ginns, 1995). The improvements presented in the nine studies all exceeded the minimal clinically important difference (MCID) for 6MWT distance for patients with chronic lung disease, which have been reported as >30m for COPD (Holland & Nici, 2013), >22-37m for ILD (Nathan et al., 2015), and 33m for PH (Mathai et al., 2012). Currently, evidence for the MCID in CF is lacking. Despite this, direct causation cannot be confirmed, due to the lack of a no-treatment control group in eight of the nine studies.

The RCT comparing interval and continuous training did not confer any benefit of one approach over the other, in terms of functional or maximal exercise capacity (Gloeckl et al., 2012). This finding agrees with that of Beauchamp et al. (2010), where interval and continuous training were deemed comparable in patients with COPD. However, interval training was associated with lower training symptoms and therefore may be used as an alternative, more tolerable method of training (Gloeckl et al., 2012). Of the studies showing no improvement in 6MWT distance, the intervention implemented by Li et al. (2013) was significantly longer (~16 weeks) compared to other pre-transplant studies (3-12 weeks) in this review (Da Fontoura et al., 2018; Florian et al., 2013; Gloeckl et al., 2012; Kenn et al., 2015; Ochman et al., 2018; Pehlivan et al., 2018). Therefore, this longer time period may have resulted in greater disease progression and risk for exacerbation. It is also important to note that a criterion for lung transplant listing is a survival prognosis of less than two years, therefore maintenance of 6MWT distance pre-transplantation could be considered a positive finding, as functional deterioration can occur rapidly during the waiting period.

From the studies identified in the updated search (February 2020 to March 2022), three were home-based programmes, with most utilising a web-based application to support delivery. These studies were timely as they coincided with the start of the COVID-19 pandemic, where there was a rapid need to develop interventions to support patients

remotely, to reduce the risk of infection. Overall, remote interventions (Layton et al., 2021; Singer et al., 2018; Wickerson et al., 2021) were feasible, however most reported a reduction in 6MWT distance, suggesting that in LTx candidates supervised exercise training with an on-site assessment may be favourable to safely achieve the optimal exercise prescription, whilst closely monitoring oxygen saturation and symptoms. The study by Wickerson et al. (2021) was conducted as a rapid response to the COVID-19 pandemic, thus the lack of improvement in 6MWT distance could be due the barriers posed to physical activity during the peak of the pandemic (e.g. no access to gyms, limiting social contact and leaving the house only for essential purposes) and the subsequent deconditioning that entails (Hume et al., 2020; Radtke, Haile, Dressel, & Benden, 2021). Further investigation into tele-rehabilitation in the form of RCTs should be conducted to determine the true effect of this novel intervention that has the potential to impose similar benefits to supervised exercise training, but without the financial and logistical demands (Cox et al., 2021).

The findings from this review confirm and expand those reported in the review by Hoffman et al. (Hoffman et al., 2017), where a significant improvement in 6MWT distance was found in four of the six studies included. Since the review by Hoffman et al. (Hoffman et al., 2017), more observational studies have added to the evidence base; however, RCTs are still lacking. A possible reason for the lack of RCTs in this population is that as exercise-based PR has become a well-recognised treatment in patients with chronic respiratory diseases (Bolton et al., 2013; Spruit, 2014; Spruit et al., 2013), obtaining a non-exercising control group is difficult and potentially unethical.

3.4.2 Exercise capacity - Post-transplant:

Fourteen of the 15 studies conducted post-transplantation reported an improvement in at least one measure of exercise capacity. However as only one study compared

exercise training to a non-exercising control group (Langer et al., 2012), it is difficult to draw definite conclusions. Nevertheless, in this study by Langer et al. (2012) the improvement in 6MWT distance was significantly higher in the intervention group than the control group, both at 12 weeks and 1 year. This study scored well on the quality assessment, providing robust evidence that exercise training has a beneficial effect on functional exercise capacity, which reflects the capacity required to undertake activities of daily living (Mejia-Downs et al., 2018). However, this evidence is restricted to the participant age range of 40 to 65 years highlighting a need for future RCT's in younger lung transplant recipients (Langer et al., 2012). It should be highlighted that the control group in the study by Langer et al. (2012) demonstrated an improvement of 132m over the 12-week intervention period. Thus, the natural course of recovery from LTx can result in clinically significant increases in 6MWT distance, even when additional exercise training is not undertaken. This supports the fact that although all single-arm studies showed significant enhancements in 6MWT distance, definite cause and effect cannot be determined.

Both RCT's by Ulvestad et al. (2020) and Langer et al. (2012) found no significant improvement in maximal exercise capacity ($\dot{V}O_2$peak) following HIIT and exercise training, compared to usual care. This highlights that improvements seen in single arm studies could be largely attributed to the degree of natural recovery occurring after LTx. Despite this, Langer et al. (2012) reported that VO_2peak (% predicted) was 71% in the exercise training group at 12 weeks and 78% at 1 year, which exceeds the values commonly reported in the first year following LTx of 40-60% of predicted normative values (Levy et al., 1993; Williams et al., 1992). The higher $\dot{V}O_2$peak (% predicted) values shown in this study may be due to only patients with an uncomplicated post-operative period being included. Therefore, this does not represent patients having a prolonged hospital stay, who are likely to exhibit lower exercise capacity as a result of prolonged deconditioning. In recipients 12-18 months post-transplant, Stiebellehner et

al. (1998) demonstrated significant improvements in $\dot{V}O_2$peak after aerobic training; however, these values were still limited to 65% predicted. It is noted that prior to initiating the exercise programme, patients were followed for 6 weeks and showed no significant change in $\dot{V}O_2$peak and PWR. The comparison between the control and intervention period improves the internal validity of this cohort study, by attempting to differentiate the effect of the training intervention from natural recovery.

Both inpatient and outpatient exercise training significantly improved $\dot{V}O_2$peak in recipients 4.5 ± 3.2 years following transplant (Ihle et al., 2011). Thus, exercise training is beneficial in the long-term, as well as the short-term management of LTx recipients. It is known that chronic exercise limitation following LTx is predominantly due to impaired oxidative capacity of skeletal muscle which is exacerbated by immunosuppressive medications (Mathur et al., 2004), thus optimising peripheral muscle function is an important goal of exercise training (Studer et al., 2004). Gloeckl et al. (2015) concluded that WBVT may be used as a complimentary therapy to exercise training, demonstrating further enhancements in exercise capacity. This is thought to be due to the mechanical vibration eliciting neuromuscular adaptations.

The previous systematic review looking at exercise training interventions post-transplantation showed a positive effect on exercise capacity (maximal or functional) in four studies (Wickerson et al., 2010). This review expands significantly on those findings, with fourteen studies exhibiting improvements in at least one measure of exercise capacity. In addition to strengthening the evidence base, this review includes studies examining the effect of different modes, doses, and settings of exercise training on exercise capacity.

3.4.3 Quality of life – pre-and post-transplant:

The most common measure of QoL was the SF-36 questionnaire, which is a global measure of HRQoL (Ware & Sherbourne, 1992). Prior to transplantation, improvements in SF-36 PCS scores ranged from 2-4 points and MCS from 2-10 points. Currently, the interpretation of changes in SF-36 scores is challenging, as the MCID for lung transplant candidates has not yet been defined. General recommendations for the tool suggest a MCID of four points (Thabut & Mal, 2017), and a study conducted in IPF patients proposed a MCID of >2-4 units for PCS and MCS scores (Swigris et al., 2010).

Notably, interval training was associated with a significant improvement in SF-36 MCS scores over time, which may be partly attributed to the lower training symptoms (dyspnoea and leg fatigue) associated with this mode of training (Gloeckl et al., 2012; Vogiatzis et al., 2005). Although Li et al. (2013) found no improvement in QoL scores, measures reflecting physical function (SF-36 PCS, SGRQ activity domain) were better preserved than other HRQoL measures (e.g. SF-36 MCS). Comparison of HRQoL in LTx candidates to normative populations has typically shown greatest impairment in physical function rather than mental health domains (Singer & Singer, 2013), highlighting the importance of maintaining or improving this aspect.

After transplant, Langer et al. (2012) found no significant difference in HADS scores between the exercise training and control group. This may be related to low baseline scores indicative of sub-clinical levels of anxiety (Intervention = 5.0 ± 3.4 vs Control = 7.1 ± 4.1) and depression (3.8 ± 3.4 vs 4.5 ± 3.5) (Stern, 2014). As such, there was little scope for improvement in this outcome domain, particularly in the intervention group. This is supported by the significant improvement in HADS scores reported by Candemir et al. (2019), where baseline scores were 10 ± 1 and 9 ± 1 for anxiety and depression, respectively.

The improvements in the SF-36 PCS and MCS scores following exercise training (Fuller et al., 2017; Schneeberger et al., 2017) well exceeded the estimated MCID (>2-3 units) proposed for LTx recipients (Singer & Chowdhury, 2013). A multi-centre study exploring the trajectory of QoL from pre-transplant to 1 year post-transplant without exercise training, reported significant gains in PCS score (+10.9), demonstrating a natural course of physical QoL improvement (Finlen Copeland, Vock, Pieper, Mark, & Palmer, 2013). This is likely due to marked improvements in pulmonary function, resulting in reduced symptom burden and enhancing the ability to complete everyday activities. However, in this observational study MCS remained unchanged. This indicates that exercise training has a beneficial impact on this QoL component, as improvements in this domain were evident in studies implementing exercise training (Fuller et al., 2017; Schneeberger et al., 2017). This is further supported by Ulvestad et al. (2020) showing that HIIT training elicited significantly greater improvements in SF-36 MCS scores, compared to usual care.

Since the review by Wickerson et al. (2010) which incorporated one study evaluating QoL, further studies have shown a beneficial impact of exercise training on QoL (Candemir et al., 2019; Fuller et al., 2017; Gloeckl et al., 2015; Langer et al., 2012; Schneeberger et al., 2017), adding to this preliminary evidence. Besides survival, improving QoL is one of the key objectives of LTx, hence interventions that can enhance QoL following the procedure are of great importance.

3.4.4 Clinical Outcomes

The evidence pertaining to exercise training and post-transplant clinical outcomes is sparse. Since the last systematic review (Hoffman et al., 2017) however, a quasi-experimental study has concluded that PR conducted before LTx halved the risk of mortality and reduced the risk of prolonged ICU and hospital stay (Florian et al., 2019). This study is limited by its design, as lack of randomization may have led to potential

selection bias. Additionally, the study by Florian et al. (2019) only included those with IPF, so findings cannot be extrapolated to all transplant patients.

3.4.5 Safety of exercise training

Limited studies (43%) report data on safety, however in those that did, no adverse events related to exercise training were reported. This highlights the inconsistent and inadequate reporting of safety in exercise training trials in LTx patients, a population that has an increased risk for complications and co-morbidities.

3.4.6 Strengths and Weaknesses of this review

To our knowledge, this is the first systematic review to synthesise the effects of exercise training in both LTx candidates and recipients. The review was conducted in a rigorous manner in accordance with PRISMA guidelines (Moher et al., 2009). Specific search terms were used to identify appropriate articles and bias was minimized through independent screening by two investigators, using pre-defined criteria. Limitations to this review include the lack of RCT's (7 out of 28 studies) and absence of a comparator group or priori sample size calculations in most studies. As such, it was not possible to perform a meta-analysis due to multiple sources of heterogeneity, including type of exercise training intervention, study design, and outcome measures. Additionally, participants across studies varied in underlying respiratory disease and age. Currently, there is little evidence on the effect of exercise training on clinical outcomes, however the single study included does show a survival benefit (Florian et al., 2019). Additional research is needed to establish the efficacy of home-based exercise training interventions. Future studies implementing exercise training should ensure consistent reporting of safety outcomes (e.g. AEs), as this information is important for decision-making by regulators, policy makers and health-care professionals. Findings should be interpreted with caution due to the single-arm study designs implemented in most studies, limiting the ability to

establish definite cause and effect. Nevertheless, the review represents the best available overview of the current evidence base for exercise training pre and post LTx transplantation.

3.5 Conclusions

Both inpatient and outpatient exercise training appears to be beneficial for patients before and after LTx. In general, most studies indicated exercise training interventions to be effective in improving exercise capacity and QoL, however the evidence was significantly limited by the quality of included studies lack of RCTs. Accordingly, exercise training appears valuable in the management of patients both listed for transplantation and following lung transplant surgery.

3.6 Reviews conducted since

Since conducting the initial systematic review (Hume et al., 2020), a Cochrane review (Gutierrez-Arias et al., 2021) has been undertaken on the benefits of exercise training for LTx recipients. In contrast to the current review, only RCT's were included and additional outcomes such as bone fractures were examined, resulting in two additional RCT's being included (Braith et al., 2007; Mitchell, Baz, Fulton, Lisor, & Braith, 2003). The conclusions from the Cochrane review were that the evidence regarding the effect of exercise training on functional exercise capacity, HRQoL and safety is very uncertain due to the low number of studies and participants within studies, high risk of bias and different comparisons included. Similarly to the current review, implications for research were that future studies should include larger RCTs performed with more methodological rigour, including similar forms of measurement so that a meta-analysis can be undertaken, in order to prove that LTx recipients clearly improve in comparison with natural recovery (Gutierrez-Arias et al., 2021).

Chapter 4: General Methods Section

4.1 Introduction

This chapter will detail the methodology used throughout this thesis, including the rationale and justification for the measures used in the following chapters:

- *Chapter 5:* Validity and test re-test reliability of the pedometer in healthy and chronic respiratory disease
- *Chapter 6:* Case control study
- *Chapter 7:* Feasibility and acceptability of a physical activity behavioural modification tele-coaching intervention in lung transplant recipients

4.2 Methodological Framework

The physical activity tele-coaching intervention investigated within this thesis is considered a complex intervention, as it has a number of interacting components, requires new behaviours by those delivering or receiving the intervention and has a variety of outcomes (O'Cathain et al., 2019). Therefore, the development and evaluation of this intervention follows the UK Medical Research Council's framework for complex interventions (Skivington et al., 2021). This framework consists of four phases: development or identification of the intervention, feasibility, evaluation, and implementation (Figure 4-1).

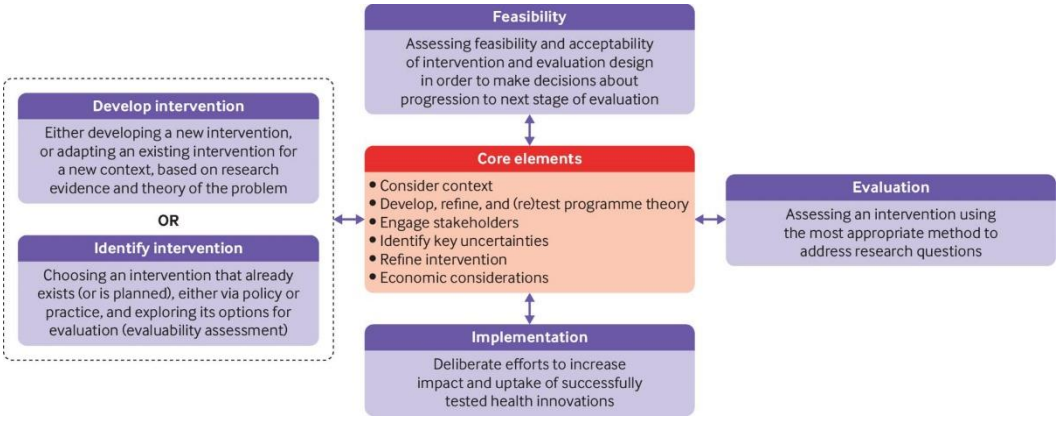


Figure 4-1: Medical Research Council's framework for developing and evaluating complex intervention from Skivington et al. (2021).

The tele-coaching intervention under investigation was previously developed for patients with COPD and was shown to be effective at increasing the amount and intensity of physical activity in a multi-centre randomised controlled trial (Demeyer et al., 2017). However, this thesis adapts the intervention to a new population (LTx recipients), who often undergo significant deconditioning whilst in hospital, experience psychological distress and have a high treatment burden (Blumenthal et al., 2020). Therefore, the main study of this thesis was a feasibility and randomised pilot study, to establish whether a future main study can be done and inform the design and conduct of a future randomised controlled trial (El-Kotob & Giangregorio, 2018). The feasibility study was reported in line with the CONSORT extension checklist for pilot and feasibility trials and was designed to assess predefined progression criteria relating to the evaluation design (e.g. recruitment and retention) and the intervention itself (e.g. acceptability and adherence) (Skivington et al., 2021).

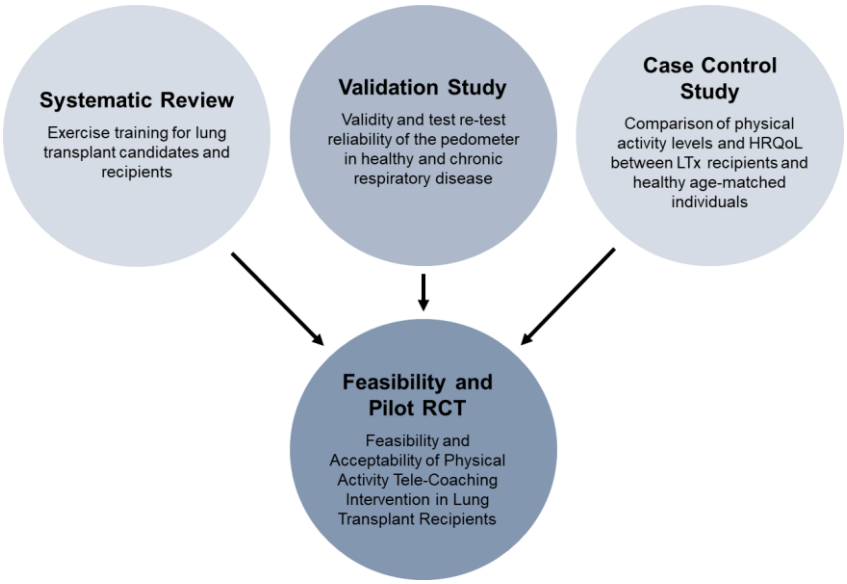


Figure 4-2: Diagram of studies culminating in the feasibility and pilot randomised controlled trial.

4.3 Ethical Approvals

Obtaining ethical approval is an established part of the research process to ensure that the research is conducted in compliance with the law, respecting human rights and avoiding unnecessary risk to patient's safety and wellbeing (Smajdor, Sydes, Gelling, & Wilkinson, 2009). Accordingly, as the research in this thesis was conducted at Northumbria University, Newcastle and Newcastle upon Tyne NHS Foundation Trust hospitals, ethical approval was obtained from both ethical committees as appropriate.

4.3.1 Northumbria University Ethical Approval

Prior to commencing, institutional ethical approval was obtained for Chapters 5, 6 and 7 from Northumbria University Faculty of Health and Life Sciences Research Ethics Committee. Ethical approval from the university for Chapter 5 and 6 (ref: 16428) was obtained in May 2019 and for Chapter 7 (ref: 13989) in February 2019.

4.3.2 NHS Ethical Approval

To initiate the process of obtaining NHS ethical approval, the study protocol was developed (Appendix 4a) and an Integrated Research Application System (IRAS) submission was created (ref: 257479). The study documents including the participant information sheet (Appendix 4b), informed consent form (Appendix 4c) and GP letter (Appendix 4d) were then created and uploaded to the IRAS system. Following submission, the study team were invited to attend an ethical review meeting and a Research Ethics Committee (REC) favourable opinion was issued (Appendix 4e), along with Health Research Authority (HRA) approval (ref: 19/NE/0119) (Appendix 4f) in May 2019. All ethical approvals and study documents were then submitted to the Trust R&D department for approval. Confirmation of capacity and capability was granted by the Newcastle upon Tyne NHS Foundation Trust R&D department on the 18th of December

2019 (ref: 09258). Given the nature of the research, an NHS research passport and honorary letter of access was obtained (Appendix 4g).

4.4 Data Management

Data collected in this thesis were carried out in compliance with appropriate laws, rules, regulations, and guidelines applicable to the collection, use, handling, processing, and disposal of personal data, such as the General Data Protection Regulation (GDPR) and Data Protection Act (2018). In line with the NHS Trust requirements, Caldicott approval (ref: 7372) was obtained prior to commencing the clinical trial to ensure adherence to the seven Caldicott principles. Additionally, to comply with Good Clinical Practice guidelines, participant data was collected in a coded, deidentified manner, using paper case report forms (Appendix 4h). To conform with NHS trust recommendations, patient assessments were recorded in case report forms and stored securely at Northumbria University, along with a copy of the completed consent form, participant information sheet, GP letter, and adverse event log in a locked filing cabinet. A copy of these documents was also uploaded to the patient's hospital record. To ensure accuracy and completeness, data were checked manually by the study co-ordinator (EH) and inputted electronically into Microsoft Excel. Data stored electronically was stored on a password-protected computer and backed up on a password protected cloud storage. Any identifiable data was destroyed as soon as possible, within 6 to 12 months of the study end date. Research data generated from the clinical trial will be retained for 15 years following study completion.

4.5 Recruitment

4.5.1 Lung Transplant Recipients

A single cohort of LTx recipients was recruited for this thesis, who had undergone either single or bilateral LTx at Freeman Hospital, Newcastle upon Tyne. Potentially eligible

patients were identified by designated cardiothoracic transplant co-ordinators working within the trust, who provided initial information about the trial. If the patient was interested, they were contacted by a designated investigator (EH) who then confirmed eligibility and discussed full details of the trial. Eligible patients received a letter of invitation and a participant information sheet (Appendix 4b). Patients were given time to consider participation in the trial before written informed consent was obtained, either face to face in the transplant outpatient clinic or through the post.

Inclusion criteria included:

- Undergone single or bilateral LTx with a primary diagnosis of Interstitial Lung Disease (ILD), COPD, Cystic Fibrosis, Bronchiectasis or Pulmonary Vascular Disease.
- Within two months of discharge following LTx.
- Aged >18 years
- Able to speak and read English.
- Able to provide informed consent.

Exclusion criteria included:

- Severe post-transplant critical illness neuromyopathy
- Bilateral diaphragmatic weakness
- Presence of any other significant disease or disorder which, in the opinion of the investigators, may either put the participant at risk because of participation in the study, or may influence the result of the study, or the participant's ability to participate in the study.

4.5.2 Healthy Participants

Healthy participants were recruited for Chapter 5 and 6 of this thesis, to assess the validity and reliability of the physical assessment (pedometer) tools during treadmill walking and to compare physical activity levels and HRQoL with LTx recipients, respectively. Healthy participants were recruited through a number of methods including: 1) a central database of individuals who had expressed an interest in participating in research; 2) advertisement through recruitment posters (Appendix 4i); 3) word of mouth. A host of recruitment methods were used to gain a representative sample with a range of ages and demographics. If interested in the study, participants were provided with a participant information sheet (Appendix 4j) and were given adequate time to consider participation, before written informed consent (Appendix 4k) was obtained.

Inclusion criteria:

- Males and females aged 18-75.
- Normal spirometry results (FEV_1/FVC >0.70 & FEV_1 >80% predicted).
- Able to provide informed consent

Exclusion criteria:

- Orthopaedic, neurological, other complaints that impair normal movement patterns.
- Unstable ischaemic heart disease, including myocardial infarction within 6 weeks.
- Moderate or severe aortic stenosis or hypertrophic obstructive cardiomyopathy.
- Uncontrolled hypertension.
- Another condition likely to limit life expectancy to less than one year (principally metastatic malignancy).
- Cognitive impairment that precludes participation.

4.6 Outcome Measures

All demographic and outcome measures for this thesis were collected between January 2019 and June 2022. Outcome measures obtained throughout this thesis are detailed in Table 4-1.

Table 4-1: Overview of thesis outcome measures

Outcome Measure	***Validity & Reliability Study***	***Case Control Study***	***Tele-Coaching RCT***
Accelerometer derived PA		✓	✓
Pedometer derived PA	✓		✓
SF-36		✓	✓
HADs		✓	✓
Patient experience of PA (C-PPAC)			✓
Hospitalisations			✓
Survival			✓

4.6.1 Assessment of Anthropometric Measures

Stature and body mass were measured in LTx recipients and healthy participants using a stadiometer (Seca 213, Seca GmbH & Co., Hamburg, Germany) and digital scales (Seca 703, Seca GmbH & Co., Hamburg, Germany) to the nearest 0.1cm/kg. For LTx recipients, this was undertaken at Freeman Hospital Lung Function Department as part of their lung function assessment.

For stature, participants were instructed to remove any footwear and adjust any hairstyles or accessories that could interfere with the measurement. They were then asked to stand on the stadiometer with feet slightly apart (in line with hips), facing forward, as tall and as straight as possible with their arms by their side. The researcher

would ensure the participant's head was in the 'Frankfort plane' and then ask the participant to take a deep breath in and use the head plate to take the measurement.

When measuring body mass, participants were asked to remove footwear, any heavy clothing and items from their pockets and then stand in the centre of the scales. Body mass index (BMI) was calculated using the following equation: BMI = body mass (kg) / stature (m^2).

4.6.2 Assessment of Pulmonary Function

Pulmonary function testing was performed in LTx recipients and healthy individuals at Freeman Hospital Lung Function Department and Northumbria University laboratories, respectively. These tests were carried out by respiratory physiologists in accordance with The Association for Respiratory Technology & Physiology (ARTP) published guidance (Sylvester et al., 2020).

4.6.3 Assessment of Physical Activity

Within this thesis, physical activity was objectively measured using both a triaxial accelerometer (Actigraph GT3X, Actigraph LLC Pensacola, Florida, USA) and a pedometer (iChoice Shark A20, Choice MMed America Co., Bristol, PA) (Figure 4-3), in line with recommendations recently published by an international expert task force for COPD patients (Demeyer et al., 2021). The pedometer was used as a motivational tool in the tele-coaching intervention to record physical activity and provide direct feedback to the patient. The validity and test re-test reliability of the iChoice pedometer in patients with chronic respiratory disease, as well as in healthy individuals is presented in Chapter five.

Figure 4-3: iChoice pedometer and Actigraph (GT3X) Accelerometer

The Actigraph GT3X (Actigraph LLC Pensacola, Florida, USA) is a triaxial accelerometer which was used to assess physical activity in LTx recipients and healthy individuals throughout this thesis. Variables derived from the Actigraph GT3X include step counts, movement intensity (vector magnitude units) and time spent in each domain of physical activity intensity (sedentary, light, moderate and vigorous) (Table 4-2). Vector magnitude units is the sum of movements in three planes of movement over each minute, which is used to quantify the intensity of daily activity levels (Louvaris et al., 2016). The device also contains an inclinometer which indicates whether a subject is standing, sitting, or lying down, as well as if the device is not being worn at all. The Actigraph GT3X was positioned using an elasticated waistband on the participants dominant side on the iliac crest at the anterior axillary line (Figure 4-4). This position was chosen as monitors worn closer to the centre of mass, tend to have higher validity than wrist worn monitors (Gaz et al., 2018). Prior to wearing the accelerometer, participants were given written instructions (Appendix 4l) and a visual demonstration on 1) the correct positioning of the device; 2) the start and end date of the physical activity assessment; 3) the wearing period (I.e. wear the device during waking hours and continue wearing during sedentary time); 4) when the device should be removed (I.e. during water based activities such as showering or bathing). An overview of the accelerometer methodology is outlined in Table 4-3.

Figure 4-4: Image depicting correct positioning of Actigraph GT3X accelerometer.

4.6.3.1 Physical activity measurement period

Throughout this thesis, participants were instructed to wear the accelerometer during waking hours (07:00 to 22:00 hours) for 7 days. Participants were given the initialised accelerometer in delay mode and were asked to commence the measurement the following morning, with a seven day stop time indicated. Although the pattern of physical activity may differ between countries, patients with COPD typically perform most activity between 7am and 10pm, with 95% of steps taken within this timeframe (Demeyer et al., 2014; Furlanetto et al., 2017), which is similar to that reported in middle-aged adults (Jansen, van Kollenburg, Kamphuis, Pierik, & Ettema, 2017). Additionally, the studies of this thesis focus on the total amount (e.g. steps, total time in different intensity activities) and intensity (e.g. vector magnitude units) of physical activity, therefore limiting the sampling period to only waking hours standardizes the sampling period, whilst having little influence on the outcome. It also aims to optimise adherence of wearing the monitor, by reducing the burden placed on the participant.

Table 4-2: MET intensity and activity count cut points.

	MET intensity Thresholds	Activity Count Cut Points
Sedentary PA	<1.5 METs	0 - 99 CPM
Light PA	≥ 1.5 and <3 METs	100 – 1951 CPM
Moderate PA	≥3 and <6 METs	1952 – 5724 CPM
Vigorous PA	>6 METs	5725 – 9498 CPM

Abbreviations: PA: Physical activity, MET: metabolic equivalent, CPM: counts per minute

4.6.3.2 Physical activity assessment duration

In all studies, participants were asked to wear the Actigraph GT3X for 7 consecutive days. In COPD patients, this has been deemed an acceptable duration to wear the activity monitor (Rabinovich et al., 2013). By instructing the participant to wear the monitor for seven days, it was likely that enough days would be captured for analysis. Furthermore, a previous study assessing physical activity over 21 consecutive days demonstrated no differences between the first and concluding days, supporting seven days as a suitable duration for assessment (Bowler et al., 2019).

4.6.3.3 Defining a valid day of assessment

Throughout this thesis, a valid day of physical activity measurement was defined as at least 8 hours of wearing time in the standardized timeframe (7:00am to 10:00pm), in line with previous recommendations to obtain a representative physical activity assessment (Demeyer et al., 2021). Thus, any day with less than 480 minutes of wear time were considered non-compliant days and were excluded from the analysis.

4.6.3.4 Type and number of days used in the analysis of physical activity

The types of days used within this thesis varied between studies, depending on the objective of the individual study. For instance, in the case control study (Chapter 6) both weekdays and weekends were included, to fully characterize the level of physical activity

in the patient and healthy participant cohorts. Previous data shows that the exclusion of weekend days did not impact the intervention effect but did decrease the sample size needed to achieve statistical power (Demeyer et al., 2014). Thus, in an interventional design where the physical activity variable is an outcome, excluding weekends allows for a lower sample size to be used. Therefore, in Chapter 7 weekends were excluded from the analysis.

Regarding the number days used, previous studies have shown that a reliable assessment may be obtained from two weekdays (Demeyer et al., 2014; Pitta et al., 2005), however if physical activity is the primary endpoint in an interventional trial, including up to 4 weekdays is optimal to reduce the variability of the outcome measure (Demeyer et al., 2014). Thus, in the tele-coaching trial in Chapter 7 the best four weekday step counts were used for analysis. In the case control study in Chapter 6, the five best valid days (weekdays and weekends) were used to fully characterize the LTx and healthy participant cohorts.

Table 4-3: Summary of accelerometer methodology

Information	**Detail**
Accelerometer Model	Actigraph GT3X Version 6
Piezosensor Orientation	Tri-axial
Sampling Rate	60 Hz
Location worn	Dominant Hip
Sampling Period	07:00 – 22:00
Instructions	Wear during waking hours
Initialisation	Initiated in delay mode on day 0 (day of visit) to begin on day 1 at 7:00am with a 7 day stop time indicated
Valid day	≥ 8 hours of wear time (480 minutes)
Valid recording	At least 4 valid weekdays
Epoch length	60 seconds

Abbreviations: Hz: Hertz

4.6.3.5 Validity of the Actigraph GT3X

The Actigraph GT3X is a commonly used accelerometer within the research setting. Whilst it hasn't been validated in LTx recipients specifically, it has been validated in a number of populations, including patients with COPD (Albaum et al., 2019; Rabinovich et al., 2013; Santos-Lozano et al., 2013). In COPD patients, both laboratory and field-based studies have shown the Actigraph GT3X to be one of the most valid and responsive activity monitors, when validated against the doubly labelled water method which is considered to be 'gold standard' (Rabinovich et al., 2013). The monitor has also demonstrated the ability to capture variability in physical activity levels across different days, as well as differences between weekdays and weekends (Rabinovich et al., 2013). Literature on inter-instrument reliability of the Actigraph GT3X has deemed the accelerometer as reliable, which improved with increased length of data-accumulation, therefore several days of measurement is suggested (Aadland & Ylvisåker, 2015).

4.6.4 Health-related quality of life - 36-Item Short Form Survey (SF-36)

The SF-36 was administered in Chapter 6 and 7 to assess HRQoL of LTx recipients and healthy individuals (Appendix 4m). The questionnaire is a widely used HRQoL survey, which is commonly used to provide an indication of health status and to evaluate the impact of clinical or social interventions (Hays, Sherbourne, & Mazel, 1993). In the absence of a lung transplant specific HRQoL questionnaire, the SF-36 the most commonly used questionnaire in interventional studies in this population, as evidenced in the systematic review of this thesis. The questionnaire was developed in the US and comprises 36 items that assess eight health domains: physical functioning (10 items), role limitations caused by physical health problems (4 items), role limitations caused by emotional problems (3 items), social functioning (2 items), emotional well-being (5 items), energy/fatigue (4 items), pain (2 items) and general health perceptions (5 items). Each dimension was scored separately, and scores transformed to a 0-100 scale, with higher

scores indicating better HRQoL. Physical component and mental component summary scores were then calculated using published scoring algorithms (Ware & Sherbourne, 1992). Previous research reports that a 4 point change in the SF-36 is considered clinically meaningful (Thabut & Mal, 2017). The SF-36 has been previously validated in a number of cohorts including LTx patients (Stavem et al., 2000), patients with COPD (Mahler & Mackowiak, 1995) and healthy individuals (Walters, Munro, & Brazier, 2001).

4.6.5 Hospital Anxiety and Depression Scale (HADs)

Anxiety and Depression levels were assessed in LTx recipients and healthy individuals in Chapter 6 and 7 (Appendix 4n). The HADs was developed over 30 years ago by Zigmond and Snaith (1983) to measure anxiety and depression in a general medical outpatient clinic. Nowadays, it is widely used in both clinical practice and research with a range of populations, likely due to its simplicity, speed and ease of use (Stern, 2014). Research highlights that a substantial proportion of LTx patients report feelings of anxiety and depression, which has a large impact on HRQoL (Limbos, Joyce, Chan, & Kesten, 2000). The HADs has been shown to be a valid, reliable and responsive tool to assess the severity of symptoms of mood disorders, however it should not be used to diagnose mood disorders (Snaith, 2003). The questionnaire comprised 14 questions (seven for anxiety and seven for depression) and was administered in paper format in all chapters. Scores for each sub-scale ranged from 0 to 21, with a higher score reflecting higher levels of anxiety and depression. A review of studies concluded good to very good concurrent validity of the HADs, with correlations between 0.6 and 0.8 with other commonly used questionnaires for anxiety and depression (Bjelland, Dahl, Haug, & Neckelmann, 2002). Furthermore, Cronbach's coefficient alpha averaged 0.83 for HADS-A and 0.82 for HADS-D, showing the instrument to be reliable (Bjelland et al., 2002). Evidence looking at the minimal clinically important difference (MCID) report estimates between -1.8 and -1.3 points for HADS-A, and -1.7 to -1.5 points for HADS-D

in COPD patients (Smid et al., 2017). Currently there are no studies reporting the estimated MCID for lung transplant recipients.

4.6.6 Clinical Visit of Proactive Physical Activity in COPD (C-PPAC)

The C-PPAC instrument is a tool used to quantify the level of physical activity and the difficulties of performing activities in everyday life. The tool was used in Chapter 7 of this thesis and was administered in paper format (Appendix 4o). Although this is a COPD specific instrument, the instrument was developed by the PROactive consortium to provide a global measure of physical activity, by encompassing qualitative assessment of how patients perceive their daily engagement in physical activity, as well as quantitative analysis via an activity monitor (Gimeno-Santos et al., 2015). Thus, we thought it would be interesting to explore experiences of physical activity in LTx recipients, whilst acknowledging that the questionnaire has only been validated in COPD patients. The qualitative aspect comprises 12 questions and covers dimensions such as social, cultural along with behavioural psychology and their influence on physical activity. The quantitative part used two variables (steps and vector magnitude units) collected by the Actigraph which was worn simultaneously. This results in the attainment of three distinct scores; 1) amount of physical activity; 2) difficulty with physical activity; 3) total physical activity experience. The raw C-PPAC scores were converted to rasch scaled scores, ranging from 0 (worse) to 100 (better).

A multi-centre study conducted by the PROactive consortium showed the C-PPAC to have good internal consistency (Cronbach's $\alpha>0.8$), test re-test reliability (intraclass correlation coefficient ≥ 0.9) and moderate-high correlations ($r>0.6$) with related constructs, therefore confirming the tool to be a valid and reliable measure of physical activity in patients with COPD (Gimeno-Santos et al., 2015). The estimated minimal important difference for the C-PPAC tool is 6 for the amount and difficulty scores and 4 for the total score (Garcia-Aymerich et al., 2021)

Chapter 5: Validity and test re-test reliability of the iChoice pedometer

5.1 Introduction

Undertaking regular physical activity is vital in the maintenance of physical and mental health in both healthy and diseased populations (Reid & Foster, 2017). In chronic respiratory diseases, physical inactivity is often a cardinal feature, both as a cause and a consequence (Watz et al., 2014). Physical activity has become increasingly popular as an outcome measure, as it encompasses not only physical fitness but also psychological, social, cultural, environmental, and economic factors. Previous studies have shown that although PR enhances exercise capacity and quality of life, this does not always translate into improvements in self-directed physical activity (Coronado et al., 2003; Dallas et al., 2009; Steele et al., 2003). Consequently, this has led to the increased development of interventions focused on promoting long term physical activity behaviour. Key components of these interventions include the use of an activity monitor in combination with established behaviour change and self-regulatory techniques (e.g. self-monitoring, goal setting, self-reinforcement and feedback provision) (Troosters et al., 2013).

Whilst subjective measures of physical activity assessment such as questionnaires, diaries/logs and surveys are common and can be useful for gaining insight into the physical activity levels of large populations, these measures are prone to recall and response bias (Reilly et al., 2008). Therefore, objective methods (e.g., activity monitors) are becoming the most optimal method for quantifying the frequency, intensity, accumulated time, and type of physical activity undertaken (Demeyer et al., 2021). Types of physical activity monitors typically encompass pedometers, accelerometers, and integrated multisensory systems. Accelerometers determine the intensity as well as the quantity of movement by detecting acceleration in one, two or three directions (Shephard, 2017). The Actigraph GT3X is a commonly used accelerometer, which will be used to assess physical activity throughout this thesis. This accelerometer has been validated in patients with COPD, showing good correlation with the doubly labelled water

indirect calorimetry method for activity energy expenditure (Rabinovich et al., 2013). On the other hand, pedometers provide more limited physical activity information, detecting vertical deflections at the hip to quantify step counts (Strath et al., 2013). The benefit of these devices is that they are simple, inexpensive, and often contain a digital display, rendering them more accessible and user friendly (Prince et al., 2008). This has led to their increasing use in physical activity interventions, as a motivational tool to self-monitor walking behaviour. In chronic disease, walking is often a favourable form of physical activity to promote and maintain health status, as it requires no additional physical skills and can be achieved with minimal risk of injury (Williams, Matthews, Rutt, Napolitano, & Marcus, 2008). Pedometer based interventions have elicited beneficial effects on physical activity in other chronic diseases including type 2 diabetes (Baskerville, Ricci-Cabello, Roberts, & Farmer, 2017), cardio-metabolic conditions (Hodkinson et al., 2019) and musculoskeletal disorders (Mansi, Milosavljevic, Baxter, Tumilty, & Hendrick, 2014). A recent meta-analysis by Armstrong et al. (2019) also concluded that pedometers were an effective tool for promoting physical activity in COPD patients, either as a stand-alone intervention or alongside pulmonary rehabilitation, inducing meaningful improvements in steps per day.

Consequently, pedometers are a practical and valuable tool for assessing and promoting physical activity in chronic respiratory disease patients, both in research and practice. However, their effectiveness is dependent on them being validated as an accurate and reliable measure of physical activity. Previous research has highlighted the need to be cautious when using pedometers at slower walking speeds (Martin, Krc, Mitchell, Eng, & Noble, 2012). It is common for patients with chronic respiratory disease to ambulate at slower speeds than healthy individuals, therefore it is important to determine the validity of devices in this population (Karpman & Benzo, 2014). Accordingly, the purpose of this study was to assess the criterion validity (i.e. accuracy) and test re-test reliability of the iChoice Shark A20 pedometer (Choice MMed America Co., Bristol, PA) in patients with

chronic respiratory disease and healthy individuals. This pedometer will be used in the clinical trial investigating the feasibility of physical activity tele-coaching in LTx recipients. The iChoice pedometer was chosen due to it interoperability with the tele-health application and platform that will be used for the tele-coaching intervention.

5.2 Methods

5.2.1 Participants and Study Design

The investigation was made up of two studies: 1) assessment of criterion validity in chronic respiratory disease patients during a 6MWT; 2) assessment of criterion validity and test re-test reliability in a group of healthy individuals using a treadmill protocol. A sample of 24 chronic respiratory disease patients who were participating in a PR programme at Royal Victoria Infirmary hospital (Newcastle upon Tyne) took part in the study, along with a convenience sample of 24 healthy individuals. The study received institutional ethical approval from the Northumbria University Health and Life Sciences Research Ethics Committee (submission reference: 16428) and Newcastle upon Tyne Hospitals NHS Foundation Trust (IRAS ID: 248697; REC ref: 18/YH/0376). Participants provided written informed consent prior to participation in the study. Individuals were excluded if they had: any orthopaedic, neurological, or other concomitant diseases that significantly impair biomechanical movement patterns; unstable ischaemic heart disease, including myocardial infraction within 6 weeks; moderate or severe aortic stenosis or hypertrophic obstructive cardiomyopathy; uncontrolled hypertension; another condition likely to limit life expectancy to less than one year or cognitive impairment that precludes participation.

5.2.2 Study Protocol 1: Patients with CRD

Patients with chronic respiratory disease undertook a 6MWT as part of their outpatient PR discharge assessment. During this test, the pedometer was attached on the dominant

hip at the mid-clavicular line using an elasticated waist band. A recording of the pedometer reading was taken before the patient began the 6MWT. The 6-minute walk test was performed according to the instructions of the American Thoracic Society ("ATS Statement," 2002). Patients were instructed to walk along a 30-metre hospital corridor from end to end at their own pace, whilst attempting to cover as much distance as possible in the allotted 6 minutes. Throughout the test, the steps undertaken by the patient were manually counted by two researchers using a hand tally device (RS Components Ltd., Corby, UK). Upon completion of the test, the patient was asked to stand stationary whilst the step counts from the pedometers were recorded. Walking speed was calculated by dividing the total 6MWT distance by the total walking time (Walking speed (m/s) = 6MWT distance (m) / walking time (sec)). For example, in a 6MWT distance of 400 m during which patient have unintended stop(s) of a total duration of 30s, the walking speed would be 1.2 m/sec (e.g. 400 m/330sec) (Andrianopoulos et al., 2015).

5.2.3 Study 2 Protocol: Healthy participants

Healthy participants were required to visit the laboratory at Northumbria University on two separate occasions to perform a walking treadmill protocol. Upon arrival to the laboratory, participant demographic data including age, stature and mass was collected. Participants received verbal instruction on how to use the treadmill, which was followed by a 5-minute familiarization/warm up period to experience the different speeds that were going to be used during the walking protocol. An elasticated belt was then placed around the waist of the participant and the pedometer attached, ensuring that the pedometer was placed on the dominant side, at hip level on the mid-clavicular line. A recording of the baseline number of pedometer steps was then taken. The walking protocol consisted of four different speeds (2.5, 3.0, 3.5 and 4km/h). These walking speeds were chosen to cover the full range of walking speeds commonly undertaken by patients with chronic

respiratory disease, both during the 6MWT (study 1) and within the literature (McClellan, Amiri, Limsuwat, & Nugent, 2014; Nolan et al., 2018). Each speed was performed at a 0% gradient for a 2-minute duration. Participants were given a 5 second warning before the treadmill was stopped. Between each stage participants stood motionless for a minute, whilst the researchers recorded the device step count. Throughout the protocol, a video camera focused on the participant's lower limbs was used to record walking activity, as a criterion method for step counting. Visit 2 was undertaken approximately 7 days later and the walking protocol was repeated as described for visit 1, to determine the test re-test reliability of the pedometer.

5.2.4 Statistical Analysis

Video recorded steps were independently analysed by two observers by manually counting the steps recorded for each speed. Criterion validity of the iChoice pedometer was assessed in three ways. Firstly, Deming regression was employed to assess the agreement between iChoice step count and manual step count. Agreement was confirmed if the 95% confidence interval for the slope contained 1 and the intercept contained 0 (Martin, 2000). Bland and Altman plots were also constructed to visually inspect the data and determine absolute systematic and random error of the iChoice device (Altman & Bland, 1983). The percentage relative error was also calculated, in order to allow comparison with previously assessed pedometers. This was calculated using the equation: Percentage relative error = [(iChoice step count – visual count)/(visual count)] x 100. Values close to zero indicated more accurate pedometer results (Takacs et al., 2014). A Positive value indicated overcounting (extra steps detected), and a negative value indicated undercounting by the pedometer (missed steps).

The test-retest reliability of the pedometer in the laboratory study was calculated using intra-class correlation coefficient (ICC), using a two-way mixed effects model with absolute agreement, where an ICC >90, 0.75-90, 0.50-0.75 and <0.50 indicate excellent, good, moderate and poor reliability, respectively (Koo & Li, 2016). Additionally, typical error of measurement was used to assess the absolute reliability of the iChoice device. All statistical analyses were conducted using SPSS v26 (IBM Statistics) or GraphPad Prism 5.03.

5.3 Results

Participant characteristics for chronic respiratory disease patients and healthy individuals are presented in Table 5-1.

Table 5-1: Characteristics of healthy participants and chronic respiratory disease patients.

Characteristic	Chronic Respiratory Disease Patients (n=24)	Healthy (n = 24)
Gender (M/F)	8/16	13/11
Age (years)	71 ± 9	58 ± 17
Height (cm)	163.6 ± 9.5	170.7 ± 9.0
Weight (kg)	74.0 ± 5.8	76.2 ± 15.1
BMI (kg/m^2)	27.2 ± 7.7	26.1 ± 5.0
FEV_1 (litres)	1.31 ± 0.48	3.19 ± 0.94
FEV_1 (% predicted)	60 ± 19	108 ± 14
FVC (litres)	2.18 ± 0.67	3.90 ± 1.13
FEV_1/FVC	63 ± 23	82 ± 7
Diagnosis (n): COPD/Asthma/ILD/Bronchiectasis	13 / 5 / 3 / 3	N/A

5.3.1 Criterion Validity of pedometer in Chronic Respiratory Disease Patients

Deming regression showed no systematic [intercept (95% CI) = -18.87 (-77.94 to 40.21) steps] or proportional bias [slope (95% CI) = 1.045 (0.947 to 1.144) steps] of the iChoice

pedometer compared to manually counted step counts during a 6-minute walk test (Figure 5-1a). A Bland-Altman plot with systematic bias and limits of agreement is displayed in Figure 5-1b. The distance achieved during the 6MWT ranged from 190 to 490 metres. After excluding unintended stops, average walking speed during the 6MWT was 0.97 m/s (range 0.69 to 1.36 m/s), which equates to 3.5 km/h (range 2.5 to 4.9 km/h).

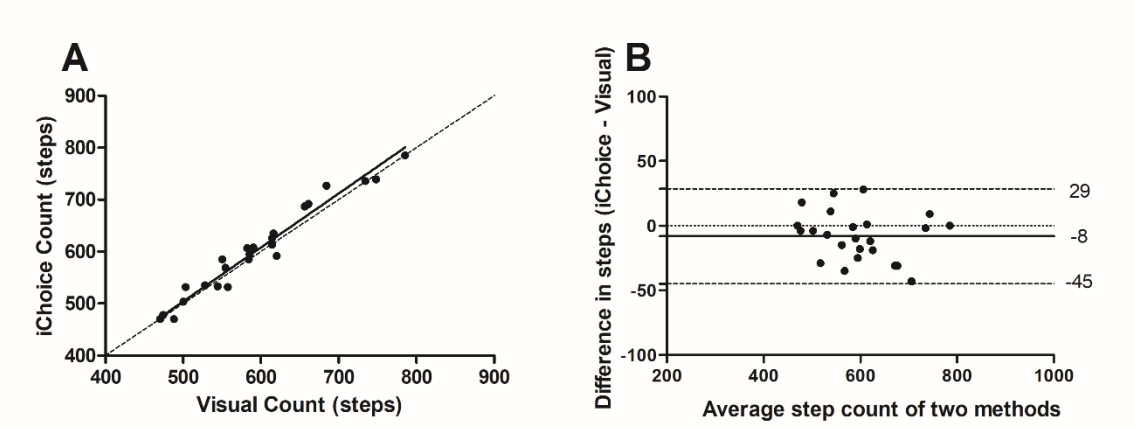


Figure 5-1: Comparison of steps obtained from the iChoice pedometer and manual count during a 6MWT. A) Deming regression (left), dotted line represents line of equality and solid line denotes the regression line. B) Bland-Altman plot (right) with systemic bias (solid line) and 95% limits of agreement (±1.96 SD) (dashed lines).

5.3.2 Criterion Validity of pedometer in Healthy Participants

At 2.5 km/h, deming regression systematic [intercept (95% CI) = -306.1 (-436.2 to -176.1) steps] and proportional bias [slope (95% CI) = 2.53 (1.83 to 3.25) steps] was evident, with iChoice under recording step counts (Figure 5-2a). However, at 3.0 km/h, deming regression analysis revealed no systematic [intercept (95% CI) = -109.1 (-223.5 to 5.36) steps] or proportional bias [slope (95% CI) = 1.52 (0.94 to 2.11) steps] of the iChoice pedometer compared to visually counted steps via video recording (Figure 5-2c). This was also the case at 3.5 km/h and 4.0km/h, demonstrating no systemic [3.5km/h intercept (95% CI) = -5.56 (-17.15 to 6.03) steps; 4.0km/h intercept (95% CI) = -11.99 (-49.46 to 25.48) steps] or proportional bias [3.5 km/h slope (95% CI) = 1.03 (0.98 to 1.09) steps (Figure 5-2e); and 4.0km/h slope (95% CI) = 1.07 (0.89 to 1.24) steps] (Figure 5-

2g). Bland Altman plots with systematic bias and limits of agreement are displayed in Figure 5-2b, d, f, h. The percentage relative error was -18.9%, -7.7%, -1.9% and 0.8% for 2.5, 3.0, 3.5 and 4.0 km/h walking speeds, respectively.

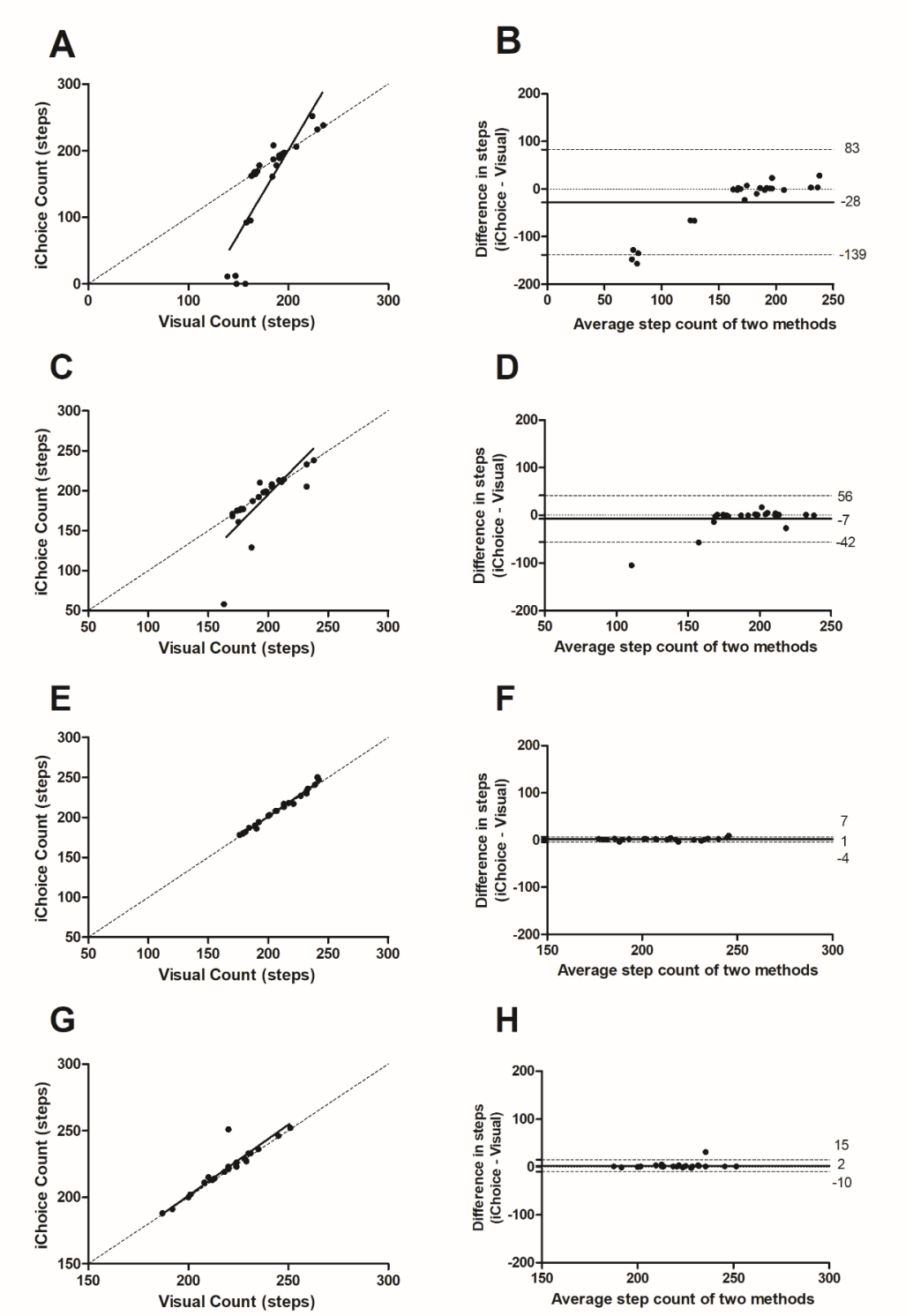


Figure 5-2: Comparison of steps obtained from the iChoice pedometer and visual recording at A & B) 2.5 km/h, C & D) 3.0 km/h, E & F) 3.5 km/h and G & H) 4.0 km/h. Deming regression (left), dotted line represents line of equality and solid line denote the regression line. Bland-Altman plots (right) with systemic bias (solid line) and 95% limits of agreement (±1.96 SD) (dashed lines).

5.3.3 Pedometer test re-test reliability

The iChoice pedometer demonstrated good to excellent test re-test reliability for step count at all speeds (ICC >0.9 and 95% CI >0.75) (Table 5-2). Typical error was 17.8% for 4.0km/h, 10% for 3.0km/h, 3.1% for 3.5km/h and 3.3% for 4.0km/h.

Table 5-2: Intraclass correlation coefficients (ICC) and typical error (%) of test-retest reliability of iChoice pedometer at 2.5, 3.0, 3.5, 4.0 km/h.

Speed (km/h)	ICC	95% confidence interval	Typical Error (%)
2.5	0.936	0.835 to 0.973	17.8%
3.0	0.907	0.785 to 0.960	10.0%
3.5	0.945	0.868 to 0.977	3.1%
4.0	0.916	0.807 to 0.963	3.3%

5.4 Discussion

The primary aim of this study was to evaluate the criterion validity of step count output from the iChoice pedometer in patients with chronic respiratory disease and healthy individuals, as well as determine the test re-test reliability of the device. Our findings indicate that in chronic respiratory disease patients, the iChoice pedometer is a valid device for monitoring step counts during over-ground walking at an average speed of 3.5 km/h (range 2.5 to 4.9 km/h). Furthermore, when assessed at regulated speeds in healthy individuals the pedometer was accurate at measuring step counts at 3.0, 3.5 and 4.0 km/h. However, accuracy of the pedometer was more limited at the slowest walking speed of 2.5km/h, demonstrating greatest deviation from the criterion method (direct observation). The test re-test reliability was good to excellent for all walking speeds (2.5, 3.0, 3.5 and 4,0 km/h).

Currently, the literature on pedometer accuracy predominantly covers a speed range of 3.2 to 6.5 km/h, which reflect walking speeds commonly undertaken by healthy individuals (Martin et al., 2012). Cyarto, Myers, and Tudor-Locke (2004) assessed the accuracy of the Yamax Digiwalker pedometer in nursing home residents at self-selected slow, normal, and fast walking speeds. The normal and fast walking speeds corresponded closely to the speeds used in the present study, equating to 0.64 (± 0.28) m/s (equivalent to 2.3 km/h) and 0.8 (± 0.28) m/s (equivalent to 2.9 km/h). The results showed mean percentage errors of -55.1% and -46.3% for medium and fast speeds, respectively, when compared to actual steps taken. When looking at performance of the iChoice pedometer at treadmill speeds of 2.5 and 3.0 km/h, mean percentage error of the iChoice was -18.9% and -7.7% respectively, demonstrating less error. However, this was in healthy individuals and performed on a treadmill. Notably, Cyarto et al. (2004) found that the presence of gait disorders, assessed through the Tinetti's Performance-Oriented Mobility Assessment (POMA) (Tinetti, 1986) was associated with an increased error in pedometer step count, highlighting the influence of gait characteristics as well as walking speed on pedometer accuracy.

In studies involving chronic respiratory disease patients, the lack of accuracy seen at slower speed was also evident when comparing pedometer to actual step counts (Furlanetto et al., 2010; Turner, Houchen, Williams, & Singh, 2012). Similarly to the present study, Furlanetto et al. (2010) found the Digiwalker SW701 pedometer to be valid in COPD patients at 100% of 6MWT speed, with an average walking speed faster than the present study (4.8 vs 3.5 km/h). The pedometer significantly underestimated steps at 30% and 60% of 6MWT speed, which corresponded to 1.6 ± 0.2km/h and 3.3 ± 0.5 km/h in healthy and 1.4 ± 0.3 and 2.9 ± 0.5 km/h in COPD patients. This was attributed to the slower speeds producing reduced vertical movement at the hip, resulting in the pedometer sensor failing to register some of the movement and therefore underestimating steps (Furlanetto et al., 2010). This may have also been the case in the

present study, however the iChoice pedometer appears to perform better than the Digiwalker SW701, as it was deemed accurate at 3.0 km/h treadmill speed, suggesting it might have higher sensitivity.

Additionally, the iChoice appears to demonstrate greater accuracy than the Yamax CW-700 pedometer at slower speeds. Turner et al. (2012) assessed pedometer accuracy in healthy individuals and patients with chronic respiratory disease, during an endurance shuttle walk test which controlled walking speed. The Yamax CW-700 pedometer demonstrated good accuracy at faster walking speeds (>3.79 km/h), however significant differences in step counts were observed at slow and medium walking speeds (between 1.78 km/h and 3.79 km/h). It should be noted that agreement between pedometer and visual step count in this study was determined using a one-way ANOVA, which is a test of difference rather than agreement (Phatak & Nimbalkar, 2017). Additionally, in agreement with the present study the pedometer was shown to be reproducible within the same wearer, on consecutive occasions. However, the Yamax CW-700 was shown not to be interchangeable between devices. This aspect was not assessed in the present study, but this suggests that in a clinical or research environment patients should use the same pedometer to minimise any inconsistencies between devices.

Overall, the pedometer was shown to be inaccurate at 2.5km/h, which corresponds to 0.7 m/s. Previous research looking at gait characteristics in chronic respiratory disease patients has shown that the vast majority of patients have gait speeds exceeding this (Ilgin et al., 2011; Nolan et al., 2019). For instance, in patients with COPD, average gait speeds of 1.3, 1.1 and 1.0 m/sec were shown in moderate, severe and very severe COPD patients (Ilgin et al., 2011). Furthermore, in a cohort of 130 patients with IPF average gait speed was 0.91 m/s (Nolan et al., 2019). Despite its overall inaccuracy at 2.5 km/h, the iChoice appeared to perform well in more than half of the participants (see figure 2a and b). This could be due to the varied gait characteristics between participants,

with some exhibiting more light or heavier footed steps than others. Additionally, it has been previously shown that accuracy of pedometers improves as cadence increases (Martin et al., 2012). Thus, as the protocol was performed on a treadmill, individuals with a longer stride length may have ambulated at slower cadences, leading to under detection by the pedometer. Nevertheless, if using the pedometer to facilitate behaviour change, underestimation of steps by the pedometer could have an unfavourable effect on an individual's motivation.

5.4.1 Limitations

This study has some limitations that should be considered. Firstly, although the study assessed pedometer accuracy in both regulated (lab-based on treadmill) and self-regulated (six-minute walk test) walking speeds, both assessments were conducted in controlled settings, and therefore may not reflect activities and movement patterns undertaken in normal daily life. Secondly, actual step count was measured visually, thus may be subject to a small degree of error. However, we aimed to minimise this by having two independent observers for the treadmill and 6MWT protocols, as well as video recording the steps in the treadmill protocol. Additionally, Deming regression is a statistical approach that aims to accommodate for differences in measurement errors between the test and reference methods (Martin, 2000). Furthermore, for the treadmill assessment in healthy individuals, gait pattern may have been altered by forcing participants to walk at specific cadences, although this is the approach is commonly adopted to control walking speeds in previous analyses of human walking (Martin et al., 2012). Future studies should aim to investigate pedometer accuracy in both controlled and real-world settings to ensure their practical use, as well as the effect of placement position on pedometer accuracy and the interchangeability between different pedometers.

5.5 Conclusion

In conclusion, the iChoice pedometer was shown to be accurate for measuring step counts during a 6MWT in patients with chronic respiratory disease with an average walking speed of 3.5km/h or 0.97 m/s. When assessed at controlled speeds in healthy individuals, the pedometer demonstrated good accuracy at speeds above 3.0km/h. Caution should be taken when using the device in individuals who ambulate at slower walking speeds (<3.0km/h), as the device was shown to underestimate steps in some individuals. Furthermore, the iChoice was shown to be reliable at all walking speeds from 2.5 to 4.0 km/h.

Chapter 6: Case Control Study

6.1 Introduction

The evidence endorsing the promotion of physical activity is compelling, with physical activity recommended as one of the main lifestyle behaviours in the management of chronic conditions worldwide (Chudasama et al., 2019). In both healthy and those with chronic conditions, the World Health Organisation (WHO) recommends at least 150 to 300 minutes of moderate intensity aerobic physical activity or at least 75 to 150 minutes of vigorous intensity aerobic activity per week, with muscle strengthening activities undertaken on 2 or more days per week (World Health Organisation, 2010). Maintaining a physically active lifestyle has been shown to significantly reduce the risk of all-cause mortality and morbidity in older adults, as well as reduce the risk of disability and functional limitation, improve quality of life and enhance cognitive functioning (Cunningham, O' Sullivan, Caserotti, & Tully, 2020; Paluch et al., 2022).

As detailed throughout this thesis, the evidence regarding physical activity levels in LTx candidates and recipients is limited. However, it is evident that LTx candidates with advanced lung disease demonstrate very low levels of physical activity (Langer et al., 2012; Wickerson et al., 2013; Wickerson et al., 2015). Overall, there is limited research comparing physical activity levels in LTx recipients to healthy controls (Langer et al., 2009; Ulvestad et al., 2020; Wickerson et al., 2015), with no studies examining physical activity levels of LTx recipients living in the UK. Furthermore, only Wickerson et al. (2015) has examined physical activity levels of LTx recipients at the point of hospital discharge. The existing evidence demonstrates a degree of improvement in physical activity levels from pre-transplant to post-transplant, however levels remain significantly lower than the general population (Wickerson et al., 2015). Additionally, when considering physical activity recommendations, a study of Norwegian LTx recipients 6 to 60 months post-transplant, showed that 86% of patients were classified as physically inactive based on WHO recommendations (Ulvestad et al., 2020).

In LTx recipients, disparities in the amount of moderate intensity physical activity undertaken have been reported between Canadian and Belgium patient cohorts (Langer et al., 2009; Wickerson et al., 2015). Furthermore, in COPD patients, a prospective study of five European centres showed that physical activity levels varied between countries, with patients in the UK performing fewer daily steps (Boutou et al., 2019). Due to the host of geographical factors (e.g. environmental, socio-economic and socio-cultural) that can influence physical activity (Aspvik et al., 2018; Boutou et al., 2019), data from different regions of the world is needed to increase the generalisability of results and establish the degree of physical inactivity in our specific patient population, in comparison to healthy individuals living in the same region. Thus, the aim of this study was to evaluate physical activity levels, HRQoL and psychological wellbeing in LTx recipients compared to healthy-age matched individuals in the UK.

6.2 Methods

This study received institutional ethical approval from Northumbria University Health and Life Sciences Research Ethics Committee (ref: 16428) and NHS Research Ethics approval from the Northeast, Tyne and Wear South Research Ethics Committee (REC Reference 19/NE/0119; IRAS project ID 257479).

6.2.1 Participants

Lung Transplant Recipients:

Lung transplant recipients who had undergone single or bilateral LTx were recruited from Freeman Hospital, Newcastle upon Tyne, UK as part of the clinical trial in Chapter 7. Potentially eligible patients were identified by cardio-thoracic transplant co-ordinators working within the Trust, eligibility was then confirmed by a designated researcher. Patients were given time to consider participation in the trial before written informed consent was obtained.

Inclusion criteria included:

- Undergone single or bilateral LTx with a primary diagnosis of ILD, COPD, CF, Bronchiectasis or Pulmonary Vascular Disease.
- Within two months of discharge following LTx.
- Aged >18 years
- Able to speak and read English.
- Able to provide informed consent.

Exclusion criteria included:

- Severe post-transplant critical illness neuromyopathy
- Bilateral diaphragmatic weakness
- Presence of any other significant disease or disorder which, in the opinion of the investigators, may either put the participant at risk because of participation in the study, or may influence the result of the study, or the participant's ability to participate in the study.

Healthy Participants

Healthy individuals with no underlying medical conditions were recruited from Northumbria University and the local area, after being matched for age (+/- 3 years) and gender. Full details of recruitment and eligibility criteria are detailed in Chapter 4.

Inclusion criteria included:

- Males and females aged 18-70 years
- Normal spirometry results age (FEV_1/FVC >0.70 & FEV_1 >80% predicted).

Exclusion criteria included:

- Orthopaedic, neurological, other complaints that impair normal movement patterns.
- Unstable ischaemic heart disease, including myocardial infarction within 6 weeks.
- Moderate or severe aortic stenosis or hypertrophic obstructive cardiomyopathy.
- Uncontrolled hypertension.
- Another condition likely to limit life expectancy to less than one year (principally metastatic malignancy).
- Cognitive impairment that precludes participation.

6.2.2 Study Design

This case control study was conducted to establish daily physical activity levels in lung transplant recipients, compared to healthy individuals living in the UK, to gauge the degree of impairment in daily physical activity. Data for LTx recipients were collected remotely upon hospital discharge as part of their baseline assessment for the clinical trial in Chapter 7. Healthy individuals attended the laboratory at Northumbria University on two separate occasions to perform spirometry and demographic measurements, complete questionnaires and collect/return the accelerometer.

6.2.3 Experimental Procedure

Lung Transplant Recipients

Demographic data was collected from patients' hospital records, along with Spirometry results which was conducted as part of patient's routine clinical assessment prior to hospital discharge following their lung transplant surgery. Eligibility to the study was then confirmed and written informed consent was obtained. An accelerometer (Actigraph GT3X; Actigraph LLC, Pensacola, FL, USA), SF-36 HRQoL questionnaire and the

Hospital Anxiety and Depression Scale (HADs) were then sent out to the patient in the post, along with instructions. The patients were instructed to wear the accelerometer for 7 full days during waking hours and then return the accelerometer and questionnaires in a pre-paid envelope. Details of the study outcomes are described below and more extensively in Chapter 4.

Healthy individuals

Healthy individuals attended the laboratory and demographic data such as age, sex, stature, and body mass were collected. Eligibility to the study was then confirmed and written informed consent was obtained. Following this, spirometry assessment was undertaken (detailed in chapter 4) and questionnaires to assess HRQoL (SF-36) and anxiety and depression (HADS) were then administered. Participants were then provided with an Actigraph accelerometer to undertake the physical activity assessment. Following completion of the 7-day physical activity assessment, the accelerometer was returned to the researcher at the laboratory.

6.2.4 Study Outcomes

6.2.4.1 Primary Outcome – Physical Activity Assessment

Daily physical activity in all participants was assessed using an accelerometer (Actigraph GT3X; Actigraph LLC, Pensacola, FL, USA). Participants were instructed to wear the accelerometer around their waist for 7 consecutive days during waking hours (07:00 – 22:00). Full details of the physical activity assessment are detailed in Chapter 4. Parameters used to characterise physical activity levels in LTx recipients and healthy participants were daily steps, movement intensity (vector magnitude units), time spent in sedentary, light, and moderate to vigorous physical activity intensities.

6.2.4.2 Secondary Outcomes

Health Related Quality of Life

The 36-Item Short Form Health Survey questionnaire (SF-36) was used to evaluate self-reported domains of HRQoL (detailed in Chapter 4) in LTx recipients and healthy controls.

Anxiety and Depression

Levels of anxiety and depression were evaluated using the Hospital Anxiety and Depression Scale (detailed in Chapter 4) in LTx recipients, healthy controls, and COPD patients.

6.2.5 Sample Size Justification

Using the effect size from Langer et al. (2009) for the difference in daily steps between LTx recipients (4977 ± 2332 steps/day) and healthy individuals (8645 ± 3491), a power calculation (alpha 0.05, power 0.90) determined that a sample size of 15 participants per group was required to detect significant differences between lung transplant recipients and healthy age-matched controls.

6.2.6 Statistical Analysis

SPSS version 27.0 (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses. Data are presented as mean ± SD or median (ranges) as appropriate. Prior to analysis, normal distribution of data was confirmed using the Shaprio-Wilk test. Independent samples T-tests were undertaken to determine between group differences in outcome variables between LTx recipients and age-matched healthy individuals. If data were not

normally distributed, Mann Whitney U Test was used. Significance for all tests was set at P<0.05.

6.3 Results

In total, 20 LTx recipients were recruited from Freeman Hospital, Newcastle upon Tyne as part of the clinical trial in Chapter 7. For healthy participants, 32 individuals expressed interest in the study and 26 returned the pre-screening eligibility questionnaire. Following confirmation of eligibility, 15 healthy individuals who were age-matched (+/- 3 years) to LTx recipients were recruited to the study. Reasons for exclusion included not meeting age criteria (n=10) and musculoskeletal injury that impacted physical activity (n=1). The flow of participants through the study is depicted in Figure 6-1 and characteristics of LTx recipients and healthy individuals are presented in Table 6-1.

Table 6-1: Baseline characteristics of participants

	Lung Transplant Recipients (n=20)	**Healthy Individuals (n=15)**	***p-value***
Age (years)	56 ± 10	58 ± 8	0.508
Sex (male/female)	12/8	9/6	N/A
Height (cm)	172 ± 9	173 ± 10	0.742
Body Mass (kg)	69 ± 12	79 ± 17	0.044
BMI (kg/m^2)	23.3 ± 3.3	26.4 ± 5.1	0.036
FEV_1 (Litres)	2.1 ± 0.5	3.41 ± 0.69	<0.001
FEV_1 % predicted	69 ± 14%	107 ± 12%	<0.001
FVC (Litres)	2.5 ± 0.7	4.10 ± 0.84	<0.001
FVC % predicted	66 ± 16%	101 ± 11%	<0.001
FEV_1/FVC (%)	86 ± 9%	83 ± 4%	0.232
Disease diagnosis:	COPD: n=5 ILD: n=11 CF: 2 PAH: 2	N/A	N/A

Abbreviations: cm: centimetres, kg: kilograms, BMI: body mass index, m^2: metres squared, FEV_1: Forced expiratory volume in one second, FVC: forced vital capacity, COPD: Chronic Obstructive Pulmonary Disease, ILD: Interstitial Lung Disease, CF: Cystic Fibrosis, PAH: Pulmonary Arterial Hypertension. Data are mean ± SD.

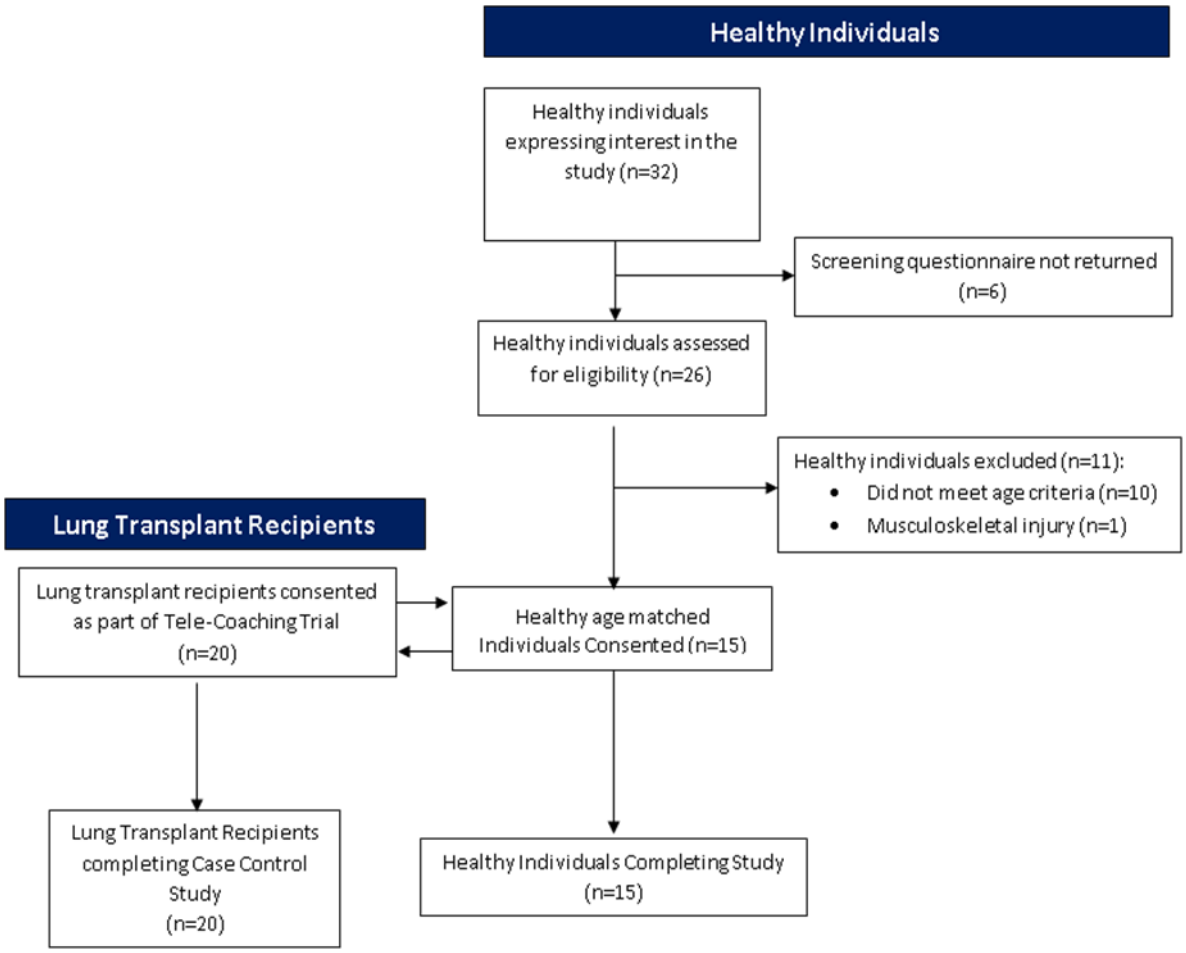


Figure 6-1: Flow of healthy individuals and lung transplant recipients through the study.

6.3.1 Physical activity outcomes

Daily steps, movement intensity (VMU), light activity time (mins/day) and time spent in moderate to vigorous physical activity (MVPA) (mins/day) are shown in Figure 6-2. The number of daily steps undertaken was significantly lower in LTx recipients (3642 ± 2614 steps/day) compared to healthy controls (9412 ± 4476 steps/day) (mean difference: 5770 ± 1226 steps/day; $p<0.001$). Additionally, movement intensity was significantly reduced in LTx recipients (260 ± 122 VMU) compared to healthy individuals (714 ± 326 VMU) (mean difference: 454 ± 81 VMU; $p<0.001$). Lung transplant recipients spent significantly less time in light intensity physical activity (157 ± 45 mins/day) compared to healthy controls (235 ± 95 mins/day) (mean difference: 77 ± 25 mins/day; $p=0.004$). Furthermore,

time spent in moderate to vigorous intensity physical activity was significantly lower in LTx recipients (13 ± 20 mins/day), compared to healthy participants (45 ± 27 mins/day) (mean difference: 32 ± 8 mins/day; p<0.001). There was no significant difference in sedentary time between LTx recipients (511 ± 105 mins/day) and healthy individuals (470 ± 85 mins/day) (mean difference: -41 ± 34 mins/day; p=0.229).

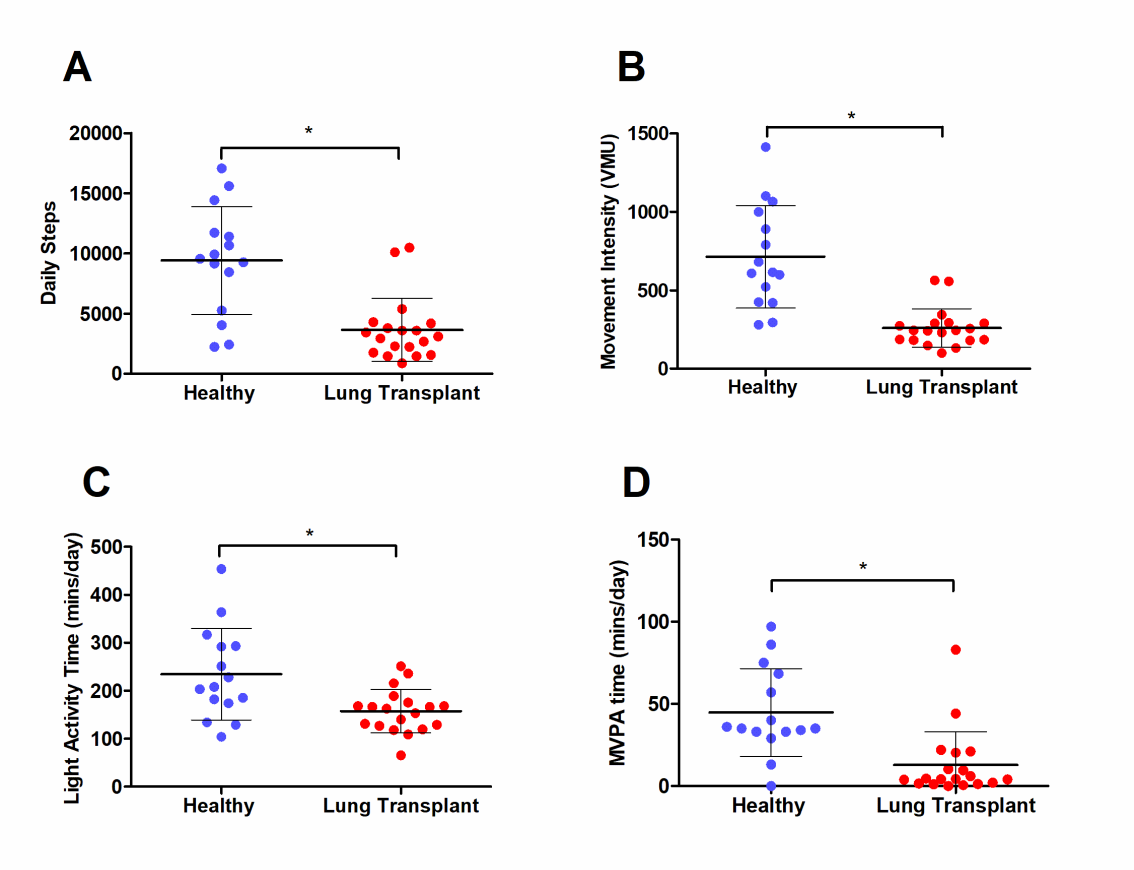


*Figure 6-2: A) Daily steps, B) Movement intensity, C) Light intensity activity time, D) Moderate to vigorous activity time for lung transplant recipients and healthy individuals. Data expressed as mean ± SD. *Statistically significant difference between groups.*

6.3.2 Physical activity in different underlying disease entities

Daily steps, movement intensity (VMU), light activity time (mins/day) and time spent in moderate to vigorous physical activity (MVPA) (mins/day) for the different underlying disease entities are shown in Figure 6-3. When looking at mean values for the underlying disease entities of LTx recipients, the highest number of daily steps were undertaken by patients with PAH (7030 ± 4868 steps/day; n=2), followed by ILD patients (3736 ± 2546

steps/day; n=11), COPD patients (2686 ± 870 steps/day; n=5) and finally patients with CF (2349 ± 832 steps/day; n=2). Similarly, patients with PAH had the highest movement intensity (404 ± 224 VMU), followed by ILD patients (263 ± 124 VMU), COPD patients (217 ± 78 VMU) and patients with CF (214 ± 45 VMU). Time spent in light intensity activity was highest in ILD patients (173 ± 48 mins/day), followed by patients with PAH (153 ± 19 mins/day), CF (143 ± 35 mins/day) and COPD (134 ± 48 mins/day). Whereas, for time spent in moderate intensity activity, patients with PAH displayed the highest values (42 ± 59 mins/day), followed by ILD patients (12 ± 13 mins/day), COPD patients (6 ± 8 mins/day) and then CF patients (2 ± 2 mins/day).

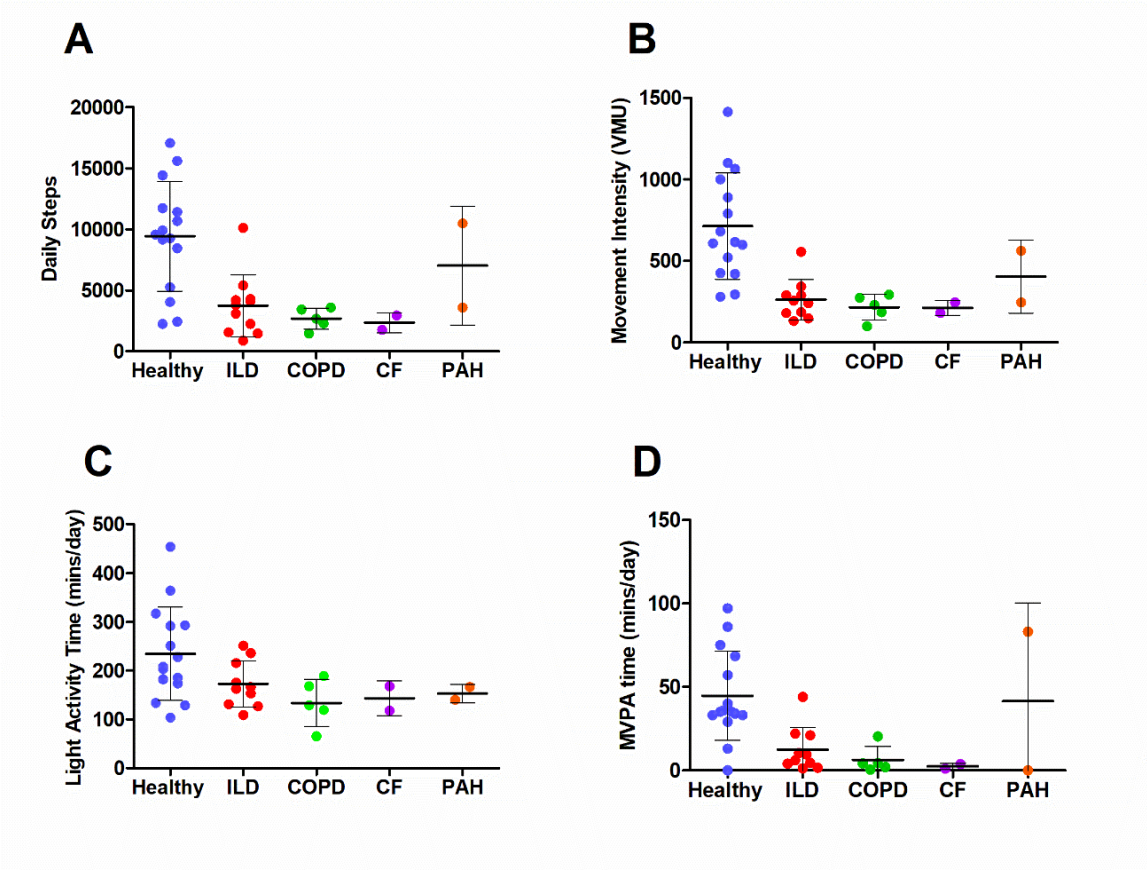


Figure 6-3: A) Daily steps, B) Movement intensity, C) Light intensity activity time, D) Moderate to vigorous activity time for healthy individuals and lung transplant recipients by underlying disease entity. Data expressed as mean ± SD.

6.3.3 Health related quality of life

Scores for the eight sub-scales of the SF-36 questionnaire in LTx recipients and healthy are presented in Table 6-2. In terms of SF-36 summary scores, LTx recipients had significantly and clinically important reductions in physical component summary (PCS) scores compared to healthy controls ($p<0.05$). For mental component summary (MCS) scores, there were clinically important reductions in LTx recipients compared to healthy controls, however the difference in scores did not reach statistical significance ($p>0.05$). When examining the eight SF-36 domains, LTx patients had significantly reduced scores for all health domains compared to healthy controls ($p<0.05$), apart from the mental health domain ($p=0.051$).

6.3.4 Anxiety and Depression

Anxiety and Depression Scores assessed through the HADs questionnaire are presented in Table 6-2. Lung transplant recipients reported significantly higher levels of depression compared to healthy participants ($p<0.05$). For anxiety, scores did not differ significantly between groups ($p>0.05$).

Table 6-2: SF-36 scores and anxiety and depression scores reported by lung transplant recipients and healthy age matched individuals.

	Lung Transplant Recipients	**Healthy Individuals**	**∆ (95% CI)**	***P value***
SF-36 Domain				
Physical Functioning	45.8 ± 22.1	93.0 ± 8.2	47.2 (32.2 to 62.1)	<0.001
Role - Physical	22.4 ± 37.2	100 ± 0	77.6 (53.3 to 102.0)	<0.001
Role – Emotional	70.2 ± 36.7	100 ± 0	29.8 (5.8 to 53.8)	0.017
Vitality	54.5 ± 18.9	81 ± 12.6	26.5 (12.8 to 40.2)	<0.001
Mental Health	80.0 ± 16.1	91.2 ± 8.6	11.2 (0 to 22.4)	0.051
Social Functioning	56.6 ± 31.0	98.6 ± 4.2	42.1 (21.8 to 62.5)	<0.001
Bodily Pain	49.9 ± 26.3	94.8 ± 7.7	44.9 (27.3 to 62.5)	<0.001
General Health	51.3 ± 25.1	88.0 ± 9.2	36.7 (19.7 to 53.7)	<0.001
SF-36 Summary Scale				
Physical component (PCS)	30.7 ± 9.5	55.2 ± 2.0	24.5 (18.2 to 30.8)	<0.001
Mental component (MCS)	53.2 ± 9.5	58.5 ± 3.7	5.3 (-1.1 to 11.7)	0.103
HADs				
Anxiety	3 (2 to 7)	1 (1 to 5)		0.123
Depression	2 (1 to 5)	0 (0 to 0)		<0.001

Data expressed as SF-36 mean ± SD, HADs median (IQR)

6.4 Discussion

This is the first study evaluating physical activity levels and HRQoL in LTx recipients living in the UK, in comparison to healthy age-matched individuals. The findings show that during the early stages of LTx recovery, recipients demonstrate significantly lower daily physical activity, HRQoL parameters and levels of depression, compared to healthy age matched individuals. Given the wealth of evidence supporting the benefits of physical activity to reduce the risk of mortality, co-morbidities and improve health

outcomes in chronic respiratory disease and healthy individuals (Anokye, Trueman, Green, Pavey, & Taylor, 2012; Garcia-Aymerich et al., 2006; Ramakrishnan et al., 2021), developing interventions to enhance physical activity in LTx recipients is important.

6.4.1 Physical activity outcomes

For physical activity outcomes the findings demonstrate significantly lower daily steps, movement intensity and time spent in light and moderate to vigorous intensity activity in LTx recipients, compared to healthy age matched individuals. These findings support previous studies that have objectively measure physical activity in LTx recipients (Langer et al., 2009; Ulvestad et al., 2020; Walsh, Chambers, Yerkovich, Hopkins, & Morris, 2021; Wickerson et al., 2015). Specifically, at the point of hospital discharge, the number of daily steps reported in the current study (3088 steps/day) are comparable to those reported by Wickerson et al. (2015) (2760 steps/day). This was also the case for the time spent in at least moderate intensity activity (9 mins/day and 8 mins/day, respectively).

In studies looking at LTx recipients in the later stages of recovery, (6 to 60 months post-transplant), a higher number of daily steps have been reported with values ranging from ~4700 to 5500 steps/day (Langer et al., 2009; Ulvestad et al., 2020; Wickerson et al., 2015), however these remain markedly lower than the general population. This demonstrates that although there is some natural recovery following LTx, physical activity levels do not return to normative values. When examining moderate to vigorous intensity physical activity in this study, only two out of the 20 patients met the WHO recommendations of at least 150 min of moderate-to-vigorous physical activity, performed in bouts lasting at least 10 min per week. This may be expected at this early stage of recovery due to patient's extended hospital stay and subsequent deconditioning, however the majority of LTx recipients at 6 to 60 months post-transplant also failed to reach these recommendations in a previous study (Ulvestad et al., 2020). Interestingly,

Ulvestad et al. (2020) showed that the 14% of patients that did meet the WHO physical activity recommendations had significantly higher exercise capacity ($\dot{V}O_2$ peak) than those who did not. Langer et al. (2009) also reported that physical inactivity was related to reduced exercise capacity, muscle force and HRQoL.

With regards to the specific underlying disease entities, PAH patients displayed the highest values for most physical activity variables, followed by ILD, COPD and CF, respectively. However, this was using mean values only and no statistical analysis. On average, patients with PAH were younger than ILD and COPD patients, therefore likely exhibit less age-related decline in skeletal muscle strength and function, which have been related to physical inactivity in LTx recipients (Langer et al., 2009). Furthermore, PAH and ILD patients tended to have shorter stays in hospital following LTx (28 and 29 days, respectively), compared to COPD (62 days) and CF (51 days) patients. Prolonged immobility whilst in hospital has been related to reductions in muscle mass, strength, and physical function (Falvey, Mangione, & Stevens-Lapsley, 2015), thus extended ICU and hospital stay in COPD and CF patients likely increased the degree of deconditioning in these patients. Furthermore, despite the younger age of CF patients compared to other conditions, multisystemic complications such as diabetes, pancreatic insufficiency, osteoporosis and malignancy are common and may influence physical activity levels (Jardel, Reynaud, & Durieu, 2018). It is important to emphasise that this data should be interpreted with caution, due to the small sample sizes and large standard deviation within some disease entities. However, understanding how physical activity levels may differ between disease entities due to different underlying pathophysiology of exercise limitation, may be important when developing physical activity interventions and could be explored further in future larger studies.

6.4.2 HRQoL and Psychological Wellbeing

HRQoL assessed through the SF-36 questionnaire showed that LTx recipients exhibited diminished scores for most domains of the SF-36 questionnaire, compared to healthy age matched controls. Lung transplant recipients demonstrated significant and clinically important reductions in PCS scores, compared to healthy individuals. Mental summary scores were more preserved, with scores not significantly different from healthy controls, however the difference between groups was still clinically meaningful. These findings are similar to those of Langer et al. (2009), who showed significant reductions in physical health components, however mental components were similar to reference values. Our findings also demonstrated no significant difference in anxiety scores between lung transplant recipients and healthy controls. This is perhaps surprising given that patients have undergone major surgery and experience many uncertainties with regards to acute allograft rejection, infections and secondary illnesses (Knoop & Estenne, 2006). Nevertheless, improving quality of life from the pre-transplant state is an important goal of LTx, thus a number of studies report improved HRQoL following LTx (Anyanwu, McGuire, Rogers, & Murday, 2001; Gross, Savik, Bolman, & Hertz, 1995; Künsebeck et al., 2007; Ramsey, Patrick, Lewis, Albert, & Raghu, 1995; Stavem et al., 2000), with a study reporting that ~90% of patients were satisfied with their decision to undergo LTx (Ramsey et al., 1995).

Although depression levels in LTx recipients were significantly higher than healthy individuals in the current study, median scores remained well below the cut off score of ≥8 points, which has been reported for detecting anxiety and depressive disorders (Olssøn, Mykletun, & Dahl, 2005). Previous research has shown prevalence rates of 22% for anxiety disorders, 30% for depression disorders, and 15% for transplant related post-traumatic stress disorder, during the first two years after LTx (Dew et al., 2012). Additionally, the development of complications, particularly bronchiolitis obliterans

syndrome, has been shown to significantly impact well-being and HRQoL (Künsebeck et al., 2007), which may lead to increased levels of anxiety and depression further along the transplant journey.

6.4.3 Limitations

There are some limitations that should be considered in this study. Firstly, this was a single centre study which may limit the generalisability of the results; however, Freeman Hospital has a large geographical catchment and are the main LTx site for Scotland, Northern Ireland and the North of England, therefore have a varied demographic of patients. Secondly, due to restrictions related to COVID-19 and the requirement to assess LTx recipients remotely, we were unable to conduct additional measures such exercise capacity and upper and lower body strength, which would have helped us to understand the level of deconditioning in these patients. Finally, although the sample size met the *a priori* sample size calculation for comparing physical activity levels in LTx recipients to healthy individuals, a larger sample size of LTx recipients would be required to make more robust comparisons between disease entities.

6.5 Conclusion

In conclusion, physical activity parameters are significantly reduced in LTx recipients living in the UK, compared to healthy individuals. Given the overwhelming benefit of physical activity for improving health outcomes in chronic disease, developing interventions to enhance physical activity in LTx recipients is vital to facilitate recovery and optimise long term outcomes.

Chapter 7: Feasibility and Acceptability of a Physical Activity Behavioural Modification Tele-Coaching Intervention in Lung Transplant Recipients

7.1 Introduction

As detailed in previous literature and Chapter 6, LTx recipients in the UK and worldwide exhibit significantly lower physical activity levels in comparison to healthy age-matched individuals (Langer et al., 2009; Ulvestad et al., 2020; Wickerson et al., 2015). Collectively, these data are concerning as physical activity is a strong predictor of all-cause mortality, both in patients with chronic respiratory disease and healthy individuals (Garcia-Aymerich et al., 2006; Lee & Skerrett, 2001). Furthermore, in other transplant populations physical activity has been associated with preserved graft functioning (Romano, Lorenzon, & Montanaro, 2012). Despite improvements in lung function following LTx, significant skeletal muscle weakness and reduced exercise capacity persist, which may limit improvements in daily physical functioning and HRQoL (Mathur et al., 2004). This is due to a host of factors including deconditioning as a result of persistent sedentary time, as well as immunosuppressant medications and episodes of organ rejection which may hinder functional recovery (Langer, 2015).

To date, there is little research investigating interventions to improve daily physical activity in LTx recipients (Langer, 2021). One RCT implementing a12-week supervised exercise training programme, demonstrated significantly greater improvements in daily physical parameters compared to usual care (Langer et al., 2012). Exercise training in the form of PR is recommended for LTx recipients (Spruit, 2014). From the systematic review conducted earlier in this thesis (Chapter 3), it appears to be beneficial for enhancing exercise capacity and quality of life, albeit the quality of studies was limited. Despite this, access, uptake, and completion of these programmes is limited in the UK and worldwide (Rochester et al., 2015; Steiner, 2016). With only six lung transplant centres across the UK, patients often live far away from the transplant centre (NHS Blood and Transplant, 2021), therefore rehabilitation beyond the immediate post-transplant hospital phase is typically only undertaken by a small minority of patients who have a

prolonged hospital stay, and this will vary depending on the patient's geographical location.

Physical activity tele-coaching is a digital intervention that aims to promote physical activity in COPD by facilitating behaviour change techniques such as individually tailored feedback, self-monitoring, and goal setting (Demeyer et al., 2017; Loeckx et al., 2018). However, LTx recipients experience significant deconditioning and psychological distress throughout their transplant journey and already have a high treatment burden, involving intensive medication regimes, self-monitoring, diet management and regular hospital appointments (Wessels-Bakker et al., 2022; Xu et al., 2012). Thus, it is not known whether physical activity tele-coaching will be feasible and improve outcomes in these patients.

Therefore, the primary objectives of this study were to evaluate: 1) the proportion of LTx recipients accepting participation in the trial; 2) retention of LTx recipients; 3) feasibility of randomisation; 4) participants' acceptability of the tele-coaching intervention and 5) compliance with the intervention and physical activity goals. The secondary objectives were to obtain preliminary data on the short (3-month)- and longer-term (6-month) impact and safety of tele-coaching, by comparing physical activity, anxiety/depression, HRQoL outcomes and rates of adverse events, following tele-coaching in comparison to usual care.

7.2 Methods

7.2.1 Ethics Approval

This study received ethical approval from the Northeast, Tyne and Wear South Research Ethics Committee (REC Reference 19/NE/0119; IRAS project ID 257479) and was prospectively registered on the clinicaltrials.gov database (NCT03873597).

7.2.2 Study design

This study was a single centre, parallel two-arm, feasibility and randomised pilot study. The trial consisted of four visits, which were all conducted remotely and included: a screening assessment (T0), a baseline assessment (T1), a post-intervention assessment (3 months) (T2) and a follow up assessment (6 months) (T3).

7.2.3 Participants

Patients who had undergone single or bilateral LTx and were discharged between February 2020 and February 2022 were recruited from Freeman Hospital, Newcastle upon Tyne NHS Foundation Trust, UK. Potentially eligible patients were identified by designated cardiothoracic transplant co-ordinators, who provided initial information about the trial. Patients received an invitation letter with a participant information sheet and were given time to consider participation in the trial before written informed consent was obtained upon confirmation of eligibility. Patients were consented within two months following hospital discharge, to coincide with the first outpatient appointment.

<u>Inclusion criteria included:</u>

- Undergone single or bilateral LTx with a primary diagnosis of ILD, COPD, CF, Bronchiectasis or Pulmonary Vascular Disease.
- Within two months of discharge following LTx

- Aged >18 years
- Able to speak and read English.
- Able to provide informed consent.

Exclusion criteria included:

- Severe post-transplant critical illness neuromyopathy
- Bilateral diaphragmatic weakness
- Presence of any other significant disease or disorder which, in the opinion of the investigators, may either put the participant at risk because of participation in the study, or may influence the result of the study, or the participant's ability to participate in the study.

7.2.4 Randomisation and Concealment

Participants were assigned to one of two conditions using a computer-generated random sequence, managed by a researcher not involved in the recruitment process. Randomisation (1:1) was stratified by 6MWT distance (6MWD: <300 or ≥300m) (Maury et al., 2008; van Adrichem et al., 2015) which was performed routinely before hospital discharge, using a block size of two following T1. The tele-coaching group received usual care in addition to the intervention. The control group received usual care, which included a motivational interview session. Given the nature of the intervention, it was not possible to conceal the treatment that participants were assigned to.

7.2.5 Physical Activity Tele-Coaching Intervention

The 3 month physical activity behavioural modification tele-coaching intervention was delivered by the PhD researcher (EH) and consisted of a: 1) one-to-one motivational interview exploring motivational factors, barriers, preferred and non-preferred activities

and strategies to become more active; 2) a pedometer (iChoice Shark A20, Choice MMed America Co., Bristol, PA) providing direct feedback; 3) smartphone app (Linkcare v2.7.1) which used data collected from the pedometer, transmitted to the smart phone via Bluetooth and simultaneously to the Linkcare web-based platform; 4) home exercise booklet containing general strengthening and stretching exercises in 3 levels of difficulty and 5) telephone support from the researcher. An overview of the intervention is depicted in Figure 7-1.

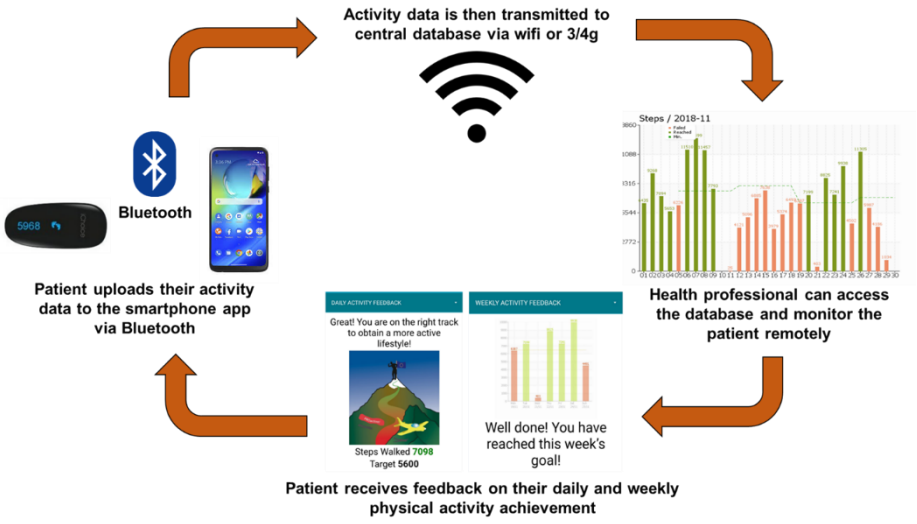


Figure 7-1: Overview of physical activity behavioural modification tele-coaching intervention.

Patients were asked to wear the pedometer during waking hours and interact with the smartphone application every day by reviewing and completing the automated application tasks. Every evening (after 8pm), patients were required to upload their step data to the smartphone application (via Bluetooth) by pressing the button on the pedometer. Each week an activity goal was set by the app, based on the patient's physical activity levels (steps/day) in the previous week (Demeyer et al., 2017). The goals were calculated using the mean and median of the 4 most active days (Demeyer et al., 2014). If the mean value exceeded the weekly goal, the application displayed the option to increase their median goal by 500 steps/day or to keep it the same as the

previous week. If the mean value was lower than the weekly goal and the median was more than 500 steps/day below the goal, the goal was reduced to the median of the 4 most active days +500 steps/day (Demeyer et al., 2017). Otherwise, the goal remained the same. The app also provided patients with daily feedback, encouragement, and educational messages, which were displayed in text or picture format (Figure 6-2). Throughout the intervention, researchers could access patient data via their app linked web-based platform (Linkcare app v2.7.1, Caldicott approval: 7372) and monitor their physical activity progress and adherence to the intervention. Telephone contact from the researcher was triggered if patients: (1) did not send their step count data for 3 consecutive days, (2) did not reach their step target for 2 consecutive weeks, (3) reached the step target but were not willing to increase their goal for 2 consecutive weeks. Prior to commencing the intervention, all patients received an instruction guide on how to use the smartphone application.

Following the 3-month intervention period, the smartphone app and support from the researcher was removed, but patients were advised to keep the pedometer and monitor and adjust their physical activity levels independently.

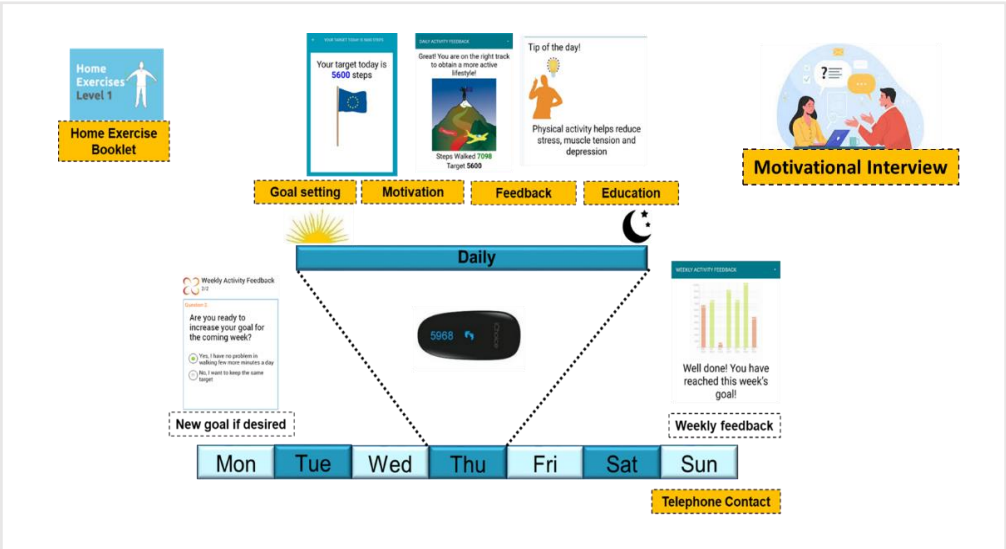


Figure 7-2: Overview of physical activity tele-coaching intervention components.

7.2.6 Usual Care

Usual care for LTx recipients included physical mobilisation whilst in the intensive care unit and post-transplant ward provided by physiotherapists working within the hospital trust. During this time, patients were provided with a set of individualised rehabilitation exercises to conduct at home following hospital discharge. Additionally, as part of the study, participants assigned to usual care underwent a motivational interview to encourage patients to be physically active. This included education on the benefits of being physically active, goal setting and self-monitoring of physical activities.

7.2.7 Outcomes to Assess Feasibility

A priori progression criteria were used to consider whether it would be appropriate to progress to a full-scale study. Based on other similar feasibility studies (Haines, 2020; Hawkins et al., 2019; Ward et al., 2018) these included: 1) feasibility to recruit participants, 2) retention of participants, 3) feasibility of randomisation processes, 4) intervention acceptability, and 5) intervention usage.

*7.2.7.1 **Criterion 1:** Screening, Eligibility and Recruitment*

The screening rate was defined as the number of patients that were approached by the research team and assessed for eligibility against the inclusion and exclusion criteria. This included those who decided not to take part. Eligibility was determined by dividing the number of people screened by the number who met inclusion criteria.

The research team recorded all patients that met the eligibility criteria and decided not to take part in the trial, along with the reason for their decision.

7.2.7.2 ***Criterion 2****: Retention*

The retention rate was defined as the number of participants who remained in the study and did not drop out.

7.2.7.3 ***Criterion 3:*** *Randomisation Feasibility*

Randomisation feasibility was assessed by the number of participants that were willing to be randomised to either the intervention or usual care group.

7.2.7.4 ***Criterion 4:*** *Patient Acceptability*

Acceptability of the intervention by patients was assessed through a project specific questionnaire (Appendix 7a) at T2 (Loeckx et al., 2018), consisting of 16 multiple choice questions on their experiences with the intervention, including 10-point Likert scales to rate the usefulness of the intervention components. Patients were asked to complete this 15-minute questionnaire at T2.

7.2.7.5 ***Criterion 5:*** *Actual Usage of the Intervention and Step Goal Compliance*

Actual usage of the pedometer throughout the intervention was assessed objectively using the data on the web based LinkCare Platform, specifically the pedometer readings on a day-to-day basis. Usage of the pedometer was determined by the presence of step count data (>70 steps for that day) (Demeyer et al., 2017; Loeckx et al., 2018), to verify actual usage of the pedometer each day. Compliance with the step goal was assessed using the step data and goals set on the platform. Self-reported usage of the pedometer and home exercise booklet was also assessed within the acceptability questionnaire.

7.2.7.6 Contact Time

All contact with patients was recorded in a case file, including details on the duration and reason for each contact.

7.2.8 Adverse Events

An adverse event was defined as any untoward occurrence that occurred during the conduct of the study. All adverse events were recorded in the adverse event log within the patients notes and were classified as serious or not, and attributable to the study or not, as per the 'Decision Tree for Adverse Event reporting' from the National Institute for Health Research, Clinical Research Network, Introduction to Good Clinical Practice Toolkit (National Institute for Health Research., 2018).

7.2.9 Outcomes to Assess Clinical Effectiveness

7.2.9.1 Physical Activity

Physical activity was assessed objectively using an Actigraph accelerometer (Actigraph LLC Pensacola, Florida, USA) in the week following T1 (baseline), the week following T2 (post-intervention at 3 months) and T3 (follow up at 6 months). Patients in both the tele-coaching and usual care groups were instructed to wear the accelerometer for seven consecutive days during waking hours. A valid physical activity measurement was defined as a minimum of four weekdays, with at least 8 hours of wear time. The physical activity parameters assessed included daily steps, movement intensity, time spent in sedentary and at least light activity intensities. A detailed explanation of the set-up, implementation, analysis, as well as the validity and reliability of the accelerometer physical activity assessment are provided in Chapter 4.

The pedometer was used by the intervention group as part of the tele-coaching intervention, to provide direct feedback to patients on their daily steps (Chapter 4, Figure 4-3).

7.2.9.2 Additional Assessments

Additional outcomes assessed at T1, T2 and T3 included:

1) HRQoL through the SF-36 questionnaire (Ware & Sherbourne, 1992);

2) Anxiety and Depression using the Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983)

3) Patient experiences of physical activity using the C-PPAC instrument (Gimeno-Santos et al., 2015).

4) All-cause mortality at T3 only.

A detailed description of the SF-36 questionnaire, HADS and C-PPAC, along with the validity and reliability of these instruments is detailed in Chapter 4 of this thesis.

7.2.10 Analyses

All statistical analyses were performed using SPSS version 27 (IBM, UK). Prior to analysis, the assumption of normality for outcomes was assessed using the Shapiro Wilk Test. Descriptive statistics were reported to better understand the distribution and potential for change of the proposed outcomes.

Data from the project-tailored questionnaire were scored as categorical variables and reported as frequencies and percentages (number of patients indicating each answer), except for the usefulness ratings of the components, which were expressed as medians (IQR). Actual usage of the pedometer was expressed as the percentage of patients who wore the pedometer for at least 90% of the days, as well as the median (IQR) wear time

(days per week). The 90% cut off point was derived from a study utilising a similar intervention in COPD patients (Loeckx et al., 2018), to allow comparison between studies. Weekly compliance to the goal was presented as the percentage of goals met over the intervention period (12 weeks).

Paired t-tests or Wilcoxon Signed Ranks Test were employed to assess the within group differences from T1 to T2, as well as T2 to T3, to identify whether the intervention or natural recovery had a significant effect on physical activity and HRQoL outcomes and explore whether any improvements made were maintained in either the tele-coaching or usual care groups. Data for T2 to T3 included only n=7 for Tele-Coaching and n=5 for Usual Care, as investigation into the longer-term effects of the initial 3-month intervention is ongoing.

Given that this was a feasibility study, the main aim of the study was not to test the effectiveness hypotheses associated with any planned main large-scale trial. However, between-group differences were analysed using an analysis of covariance (ANCOVA) model to adjust for potentially confounding factors judged to be distributed unevenly between groups. End-of-study variables were used as the dependent variable, the baseline variable as a covariate and the group factor as the explanatory variable whose effect is to be tested. If the data were not normally distributed, transformation using common logarithm was performed (Feng et al., 2014). Statistical significance was set at $P<0.05$ for all analyses.

7.3 Results

7.3.1 Participants

In total, 20 LTx recipients provided consent for the study and were randomised to the tele-coaching intervention (n=11) or usual care (n=9). Eighteen patients completed T2 (Table 7-1) and at present 12 patients have completed T3 (Figure 7-3).

Table 7-1: Characteristics of patients at baseline (hospital discharge).

Characteristic	**Tele-Coaching (n=10)**	**Usual Care (n=8)**
Age (years)	56 ± 9	57 ± 12
BMI (kg/m^2)	22.8 ± 3.5	24.5 ± 2.6
Sex (Male/Female)	6/4	6/2
FEV_1 (L)	2.18 ± 0.49	2.25 ± 0.57
FEV_1 (% predicted)	69 ±13	71 ± 17
FVC (L)	2.48 ± 0.69	2.70 ± 0.87
FVC (% predicted)	64 ± 14	69 ± 22
FEV_1/FVC %	89 ± 7	85 ± 10
6MWD (m)	324 ± 85	333 ± 43
Diagnosis:		
COPD	4	1
CF	2	0
ILD	3	7
PAH	1	0
Hospital Length of Stay (days)	44 ± 22	35 ± 27

Definitions of abbreviations: BMI = Body mass index, COPD = Chronic Obstructive Pulmonary Disease, CF = Cystic Fibrosis, ILD = Interstitial Lung Disease, PAH = Pulmonary Arterial Hypertension. Values are mean ± SD.

7.3.2 Feasibility Outcomes

A summary of the feasibility progression criteria and outcomes are displayed in Table 7-2.

Table 7-2: Overview of progression criteria for feasibility outcomes

Progression Criteria	Assessment of Criteria	Outcome	Decision
1) Feasibility to recruit a sufficient proportion of LTx recipients.	Recruitment: percentage of eligible patients recruited; if > 30% recruited = proceed, if < 10% = unlikely to be feasible; if 10–30% = consider feasibility of proceeding based on screening rate and possible steps to increase recruitment (Haines, 2020; Ward et al., 2018).	Recruitment: 22 were eligible (29 were screened); 91% of eligible patients (76% of those screened) were recruited.	Proceed
2) Retention to 12-week follow-up (T2).	Retention: percentage of participants retained; if > 80% = proceed, if < 60% = unlikely to be feasible, if 60–80% = consider feasibility of proceeding based on available data and possible steps to increase retention (Hawkins et al., 2019; Ward et al., 2018).	Retention: 90% of participants enrolled in the study were retained.	Proceed
3) Randomisation Feasibility	>80% of participants randomised to the intervention or usual care following baseline assessment (Ward et al., 2018).	All patients consented (100%) were randomised to either to tele-coaching or usual care group following their baseline assessment.	Proceed
4) Acceptability of intervention	Intervention acceptability was considered by a project specific questionnaire and compared to previous findings in COPD patients (Loeckx et al., 2018).	Acceptability of the intervention was good (see Table7-3). 88% enjoyed taking part in the programme, 89% willing to use at least one aspect of the intervention in the future.	Proceed
5) Intervention Usage	Actual usage of pedometer was defined as presence of >70 steps for that day present on the LinkCare Platform (Loeckx et al., 2018).	80% of patients wore the pedometer for >90% of days.	Proceed

7.3.2.1 ***Criterion 1:*** *Screening, Eligibility and Recruitment*

A total of 33 LTx recipients were discharged between February 2020 and February 2022. Of those 33, four were unable to be approached, due to the suspension of trial recruitment at the start of the COVID-19 pandemic. In total, 29 patients were screened by accessing patient records or by direct contact in clinic. Of the 29 patients screened, 7 (24%) were not eligible to participate in the trial. The remaining 22 patients received information about the trial (Figure 7-3).

In total, 20 LTx recipients were recruited between February 2020 and February 2022. No patients were recruited from March to October 2020, as well as mid-January to May 2021 due to the suspension of LTx in response to the COVID-19 pandemic (Hardman et al., 2021). The consent rate for the study was high at 91%, with 20 out of 22 patients accepting participation.

7.3.2.2 ***Criterion 2:*** *Retention*

The retention rate was 90% for patients that consented to take part in the study. The dropout rates were equal between the tele-coaching and usual care group and the reasons for drop out were: 1) extenuating personal circumstances and 2) chronic lung allograft dysfunction resulting in palliative care.

7.3.2.3 ***Criterion 3:*** *Randomisation*

All 20 patients were willing to be randomised to either the intervention or usual care group following T1.

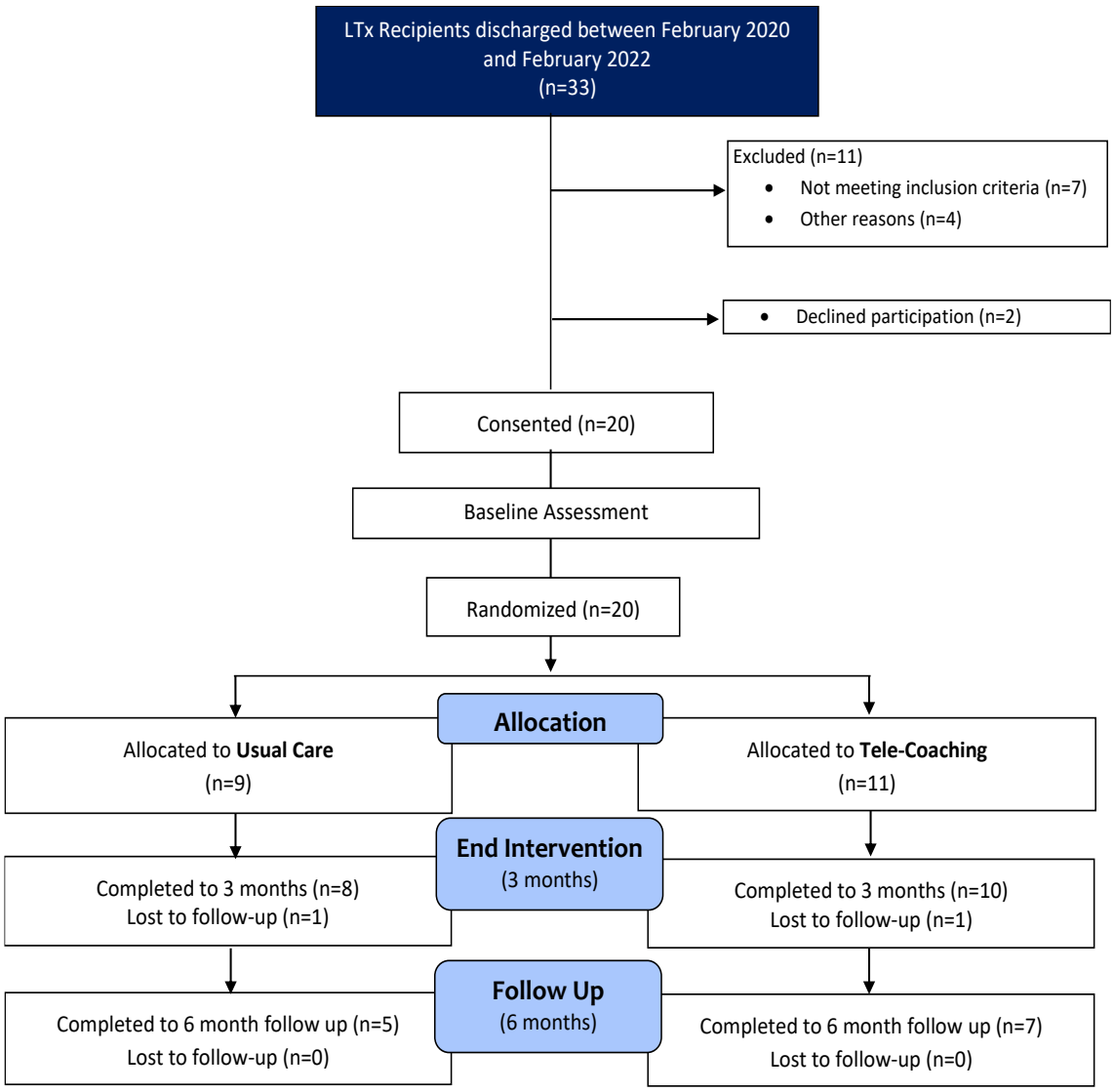


Figure 7-3: CONSORT participant flow diagram

*7.3.2.4 **Criterion 4:** Acceptability of Intervention*

Data from the acceptability questionnaire are presented in Table 7-3. Overall, patient feedback on the intervention was positive, with 88% of patients indicating that they either “liked” (44%) or “liked the intervention a lot” (44%). Furthermore, 78% of patients reported that the intervention “helped them a lot” to improve their physical activity levels, with 89% of patients indicating that the smartphone app was either “very easy” (33%) or “easy” (56%) to use. Importantly, 89% of patients were willing to use at least one aspect

of the intervention in the future. For the importance of intervention components, patient rated the telephone calls with the researcher, pedometer, and daily goal as the most important aspects of the intervention (Figure 7-4).

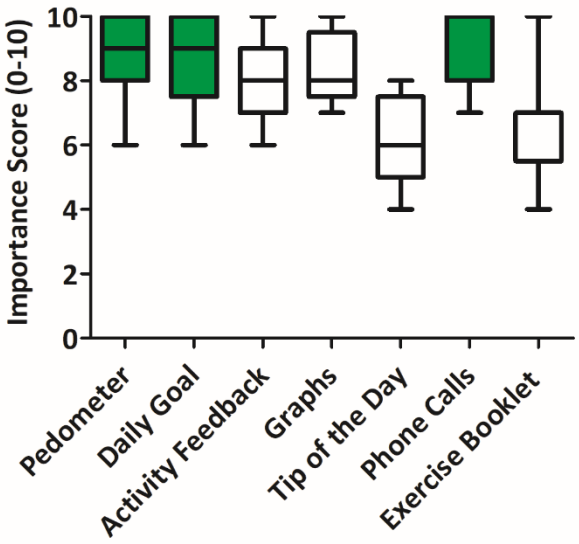


Figure 7-4: Boxplots depicting the usefulness scores (1-10 likert scale) of the different intervention components rated by patients.

*7.3.2.5 **Criterion 5:** Actual Usage of the Intervention and Step Goal Compliance*

Of those completing the intervention, 80% wore the pedometer for more than 90% of days over the 12-week intervention. Overall, patients wore the pedometer for a median of 7 (IQR: 6-7) days per week. The most common reason for not wearing the pedometer or not uploading steps on to the platform was due to transplant-related complications (e.g., infection, acute rejection, or hospital readmission).

In terms of self-reported usage, 78% of patients indicated that they looked at the pedometer “several times a day”, 11% indicated “once daily” and 11% “sometimes”.

The number of weekly step goal targets met throughout the 12-week intervention was good, with a mean (SD) of 69 ± 12% of step goals achieved (Figure 7-5).

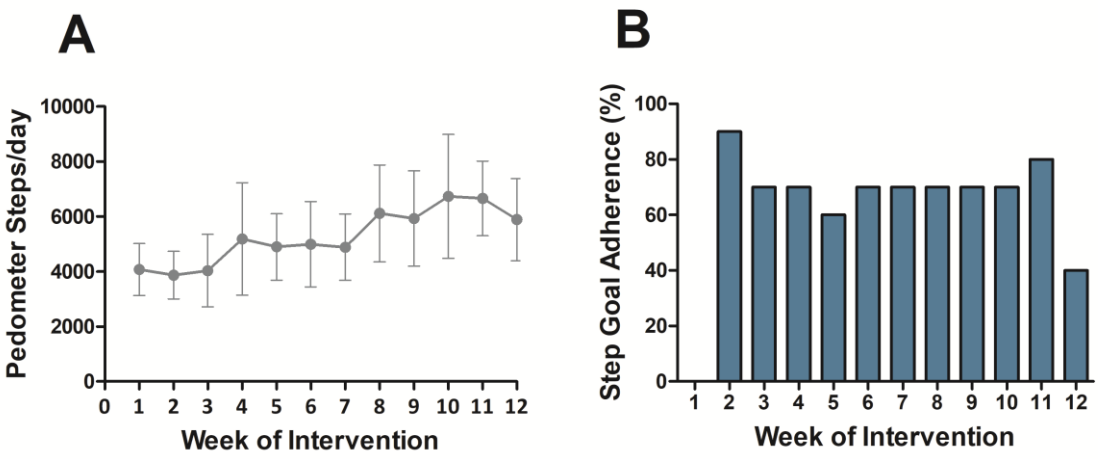


Figure 7-5: A) pedometer steps/day and B) step goal compliance over 3-month intervention

7.3.2.6 Contact Time

The total mean ± SD contact time per patient was 46±23 minutes per patient. On average, patients had to be contacted 9±4 times over the 3 months. If the patient was progressing well and no contact was triggered, general well-being checks were conducted every 2 weeks via brief phone calls. For instances where the patient did not send their step data for 3 consecutive days, did not reach their step target for 2 consecutive weeks, or chose not to increase their goal for 2 consecutive weeks, the mean number of contacts was increased as well as the time for consultation. This was to provide troubleshooting solutions and explore barriers of engagement with goal adjustment.

7.3.3 Adverse events

Over the study period, there were no adverse events related to the intervention and the effort of patients to progressively increase their activity levels or related to the study protocol or procedures.

7.3.4 Hospital Admissions and Complications

Throughout the 3-month intervention period, 10 patients (Tele-Coaching: n=6 and Usual Care: n=4) were admitted to the hospital for more than 72 hours. In the tele-coaching group, the reasons for admission were acute rejection resulting in reduction in pulmonary function (n=4), fever and suspected infection (n=1) and dyspnoea due to right main bronchus anastomotic stricture (n=1). In the usual care group, hospital admissions were for acute rejection resulting in reduction in pulmonary function (n=3) and acute kidney injury (n=1).

Table 7-3: Overview of patient responses from acceptability questionnaire

Question 1)	**Liked it a lot**	**Liked it**	**Neutral**	**I disliked it**	**No opinion**
How much did you enjoy taking part in the activity programme?	44%	44%	11%	0%	0%
Question 2)	**Yes, helped a lot**	**Yes, helped a little**	**Not noticeable**	**No, not at all**	**No, it discouraged me**
Did the intervention help you to increase your physical activity levels?	78%	11%	11%	0%	0%
Question 3)	**Much too low**	**A little bit too low**	**Reasonable**	**A little bit too high**	**Much too high**
How did you experience the weekly goal increases during the intervention?	0%	0%	89%	11%	0%
Question 4)	**Very Easy**	**Easy**	**Not easy, but managed**	**Difficult**	**Very difficult**
How was it for you to work with the smartphone intervention?	33%	56%	0%	11%	0%
Question 5)	**Step Counter**	**Smartphone App**	**Telephone Contact**	**Exercise booklet**	**Other**
In your opinion, what was the most important part of the intervention?	44%	11%	33%	0%	0%
Question 6) How often did you perform the following actions?	**Several times per day**	**Once per day**	**Sometimes but not everyday**	**Once or twice per week**	**Never**
a) Look at the step counter	78%	11%	11%	0%	0%
b) Do any home exercises	44%	11%	11%	11%	22%
Question 7)	**Very helpful and supportive**	**Helpful and supportive**	**Neutral**	**Poor, not supportive**	**Very Poor, not supportive at all**
How would you rate the graphics used on the smartphone application?	11%	44%	33%	11%	0%
Question 8)	**Very quick**	**Quick**	**Neutral**	**Slow**	**Very Slow**
How would you rate the interaction between you and the app?	0%	56%	33%	0%	11%
Question 9)	**Nothing**	**Step Counter**	**Step counter, phone & feedback messages**	**Step counter, phone & contact**	**Whole Intervention**
Which part of the intervention would you be willing to use in the future?	11%	22%	11%	33%	33%

7.3.5 Outcome measures

Data for all outcome measures at T1 (baseline) and T2 (3 months) for the tele-coaching and usual care groups are presented in Table 7-4.

7.3.5.1 Accelerometer-derived Physical Activity (0 to 3 months)

The effect of the tele-coaching intervention and usual care on accelerometer derived physical activity outcomes is presented in Table 7-4 and Figure 7-6. At 3 months there were significant and clinically important (Demeyer et al., 2016) improvements in steps/day for both the tele-coaching (by 2945±3056 steps/day; p=0.014) and usual care (by 1566±1400 steps/day; p=0.016) groups, however the increase in the tele-coaching group exceeded the usual care group by clinically important margins (Demeyer et al., 2016) (by 1379 steps/day). However, the difference between groups was not significant ($F_{1, 15} = 2.980$, p=0.105).

Accelerometer movement intensity significantly improved within the tele-coaching group (by 138±148 VMU; p=0.023), but not the usual care group (by 53±119 VMU; p=0.249), with no significant difference found between groups ($F_{1, 14} = 2.998$, p=0.105). For time spent in at least light activity, there was a significant increase within the tele-coaching group (by 43±28 min/day; p=0.002) at 3 months, but not in the usual care group (by 31±63 min/day; p=0.249), with no significant difference between groups ($F_{1, 14} = 0.164$, p=0.692). For sedentary time, results showed no significant change in the tele-coaching (by -49±113 mins/day; p=0.234) or usual care (by 18±53 mins/day; p=0.203) group over the intervention period, with no significant difference displayed between the two groups ($F_{1, 14}=0.002$, p=0.964).

Individual changes in steps/day and movement intensity for each disease entity in the tele-coaching and usual care groups are presented in Appendix 7b. For daily steps and

movement intensity the mean improvement in the tele-coaching group was 3148±4153 steps/day and 127±175 VMU, respectively for ILD (n=3), 1554±1370 steps/day and 108±52 VMU, respectively for COPD (n=4), 8717±0 steps/day and 479±0 VMU, respectively for PAH (n=1) and 2537±1554 steps/day and 42±4 VMU, respectively for CF (n=2). For usual care, the mean improvement in daily steps and movement intensity were 1721±1436 steps/day and 73±113 VMU, respectively for ILD (n=7) and 479±0 steps/day and -87.9±0 VMU, respectively for COPD (n=1).

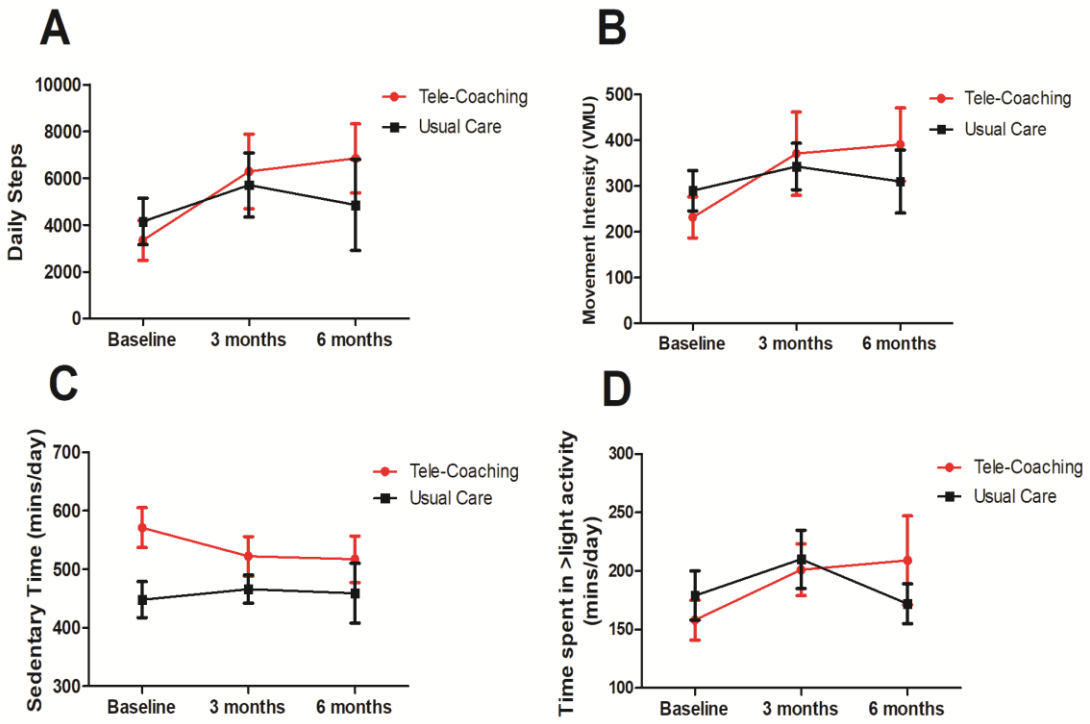


Figure 7-6: A) Daily steps, B) Movement Intensity, C) Sedentary time, D) Time spent in at least light intensity activity at baseline (hospital discharge), 3 months and 6 months for lung transplant recipients assigned to the Tele-coaching and Usual Care group. Data at Baseline and 3 months is n=18 (TC: n=10, UC: n=8), data at 6 months is n=12 (TC: n=7, UC: n=5). Data are mean ± SEM.

7.3.5.2 HRQoL (0 to 3 months)

Data for SF-36 PCS and MCS summary scores at T1 and T2 are presented in Table 7-4 and all eight individual SF-36 domains in Appendix 7c. At 3 months, there were clinically important (>3 units) (Singer & Chowdhury, 2013) increases in SF-36 PCS

scores, in both the tele-coaching (10±14 points; p=0.062) and usual care (5±9 points; p=0.141) groups. There was a clinically important difference in the improvement between the two groups (5 points), however this did not reach the level of significance ($F_{1, 14}$=0.454, p=0.511). There were no significant or clinically important differences in SF-36 MCS scores in either the tele-coaching (-2±14 points; p=0.624) or usual care (1±7 points; p=0.824) group over the intervention period. Furthermore, there was no significant difference shown between the two groups ($F_{1, 14}$=0.031, p=0.863).

For the eight individual domains, there was a significant improvement in the Physical Functioning (p=0.049) and Role Physical (p=0.043) domains in the tele-coaching group over the 3 months, but not in any of the other six SF-36 domains. In the usual care group, there were no significant changes in any of the eight SF-36 domain scores (Appendix 7c). There were no significant differences between the tele-coaching and usual care for any of the eight SF-36 domains over 3 months (p>0.05).

7.3.5.3 Psychological Well-being (0 to 3 months)

There were no significant or clinically important changes in HADs anxiety scores in either the tele-coaching (-1±4 points; p=0.225) or usual care group (-1±5 points; p=0.634) following the intervention period, with no significant difference shown between the two groups ($F_{1, 14}$=1.009, p=0.332). For HADs depression scores, there were no significant or clinically important changes in either the tele-coaching (-1±5 points; p=0.848) or usual care group (0±2 points; p=0.722) following the intervention period, with no significant difference shown between the two groups ($F_{1, 14}$=0.002, p=0.966).

7.3.5.4 Patient experiences of physical activity (0 to 3 months)

As shown in Table 7-4, clinically important increases in C-PPAC total scores were shown in both the tele-coaching (10±11 points) and usual care (6±15 points) groups over 3 months, with only the tele-coaching group improving significantly (p=0.038). Similarly, C-PPAC amount scores improved by clinically important margins in both the tele-coaching (16±13 points) and usual care (10±17 points) groups, with only tele-coaching improving scores significantly over 3 months (p=0.016). There were no clinically important or significant changes in C-PPAC difficulty scores in the tele-coaching (5±12 points; p=0.264) or usual care (2±15 points; p=0.834) groups. Furthermore, there were no significant differences between tele-coaching and usual care in C-PPAC total ($F_{1,14}$=0.169, p=0.687), amount ($F_{1,14}$=0.051, p=0.825) or difficulty ($F_{1,14}$=0.296, p=0.595) scores over 3 months.

Table 7-4: Physical activity, HRQoL, Psychological Wellbeing and patient physical activity experience outcomes at baseline (hospital discharge) and 3 months (post-intervention).

Outcome	Group	Baseline (T1) (n=18)	3 months (T2) (n=18)
Accelerometer Outcomes:			
Daily Steps (steps/day)	TC	3342 ± 2684	6287 ± 5069*#
	UC	4148 ± 2806	5714 ± 3860*#
Movement intensity (VMU)	TC	232 ± 135	371 ± 274*
	UC	290 ± 125	343 ± 144
Time spent in sedentary activity (min/day)	TC	571 ± 101	522 ± 102
	UC	448 ± 87	466 ± 69
Time spent in at least light activity (min/day)	TC	158 ± 51	201 ± 67*
	UC	185 ± 71	221 ± 61
SF-36:			
PCS Score	TC	30 ± 13	40 ± 13#
	UC	33 ± 6	38 ± 10#
MCS Score	TC	56 ± 9	53 ± 13
	UC	51 ± 10	52 ± 12
HADS:			
Anxiety	TC	5 ± 4	4 ± 3
	UC	4 ± 3	4 ± 4
Depression	TC	4 ± 4	3 ± 4
	UC	3 ± 2	3 ± 4
C-PPAC:			
Total Score	TC	60 ± 14	70 ± 18*#
	UC	64 ± 12	70 ± 16#
Amount Score	TC	52 ± 17	68 ± 21*#
	UC	61 ± 23	71 ± 16#
Difficulty Score	TC	68 ± 18	73 ± 21
	UC	73 ± 5	74 ± 18

Abbreviations: VMU = Vector Magnitude Units, MVPA = moderate to vigorous physical activity, HADS = Hospital Anxiety and Depression Scale, SF-36 = Short Form 36 Questionnaire, PCS = Physical Component Summary, MCS = Mental Component Summary, TC = Tele-Coaching, UC = Usual Care. Values are mean ± SD.
**: Significant within group change #: Clinically important within group change*

7.3.5.5 Accelerometer-derived Physical Activity (3 to 6 months)

Physical activity outcomes for the tele-coaching and usual care groups at 3 and 6 months is presented in Table 7-5 and Figure 7-6. Please note that for data analysis the data presented in Table 7-5 at 3 and 6 months is for n=12, whereas in Figure 7-6 the data at 3 months is for n=18. For patients completing T3 (TC: n=7, UC: n=5), there were no

significant changes in daily steps from T2 (post-intervention) to T3 (6 months) for the tele-coaching (-190±2780 steps/day; p=0.862) or usual care (- 604±1032 steps/day; p=0.261) groups, however the decline seen in the usual care group is considered clinically important (Demeyer et al., 2016). There was no significant difference in daily steps between the tele-coaching and usual care groups at T3 ($F_{1, 9}$=0.836, p=0.384).

For movement intensity, there were no significant changes in the tele-coaching (1±169 VMU; p=0.999) or usual care (-4±71 VMU; p=0.910) groups from T2 to T3. Additionally, there was no difference in VMU between the tele-coaching and usual care group at T3 ($F_{1, 9}$ = 0.026, p=0.876).

Similarly, for sedentary time there were no significant change from T2 to T3 for the tele-coaching (4±97 mins/day; p=0.913) or usual care (-4±145 mins/day; p=0.951) groups, with no significant difference shown between groups ($F_{1, 9}$=0.235, p=0.640).

For time spent in at least light activity there were no significant changes in the tele-coaching (12±77 mins/day; p=0.690) and usual care (-22±60 mins/day; p=0.453) groups from T2 to T3, with no significant difference shown between groups ($F_{1, 9}$=0.724, p=0.417).

7.3.5.6 HRQoL (3 to 6 months)

For patients completing T3 (n=12), there was no significant change in SF-36 PCS scores in the tele-coaching (1±6 points; p=0.577) or usual care (-3±10 points; p=0.571) groups from T2 to T3, however the worsening in the usual care group was clinically important (Singer & Chowdhury, 2013). There was no significant difference in SF-36 PCS scores shown between the two groups at T3 ($F_{1,9}$=0.846, p=0.382). For SF-36 MCS scores, there was no significant change in the tele-coaching (-2±7; p=0.400) or usual care (1±10;

p=0.835) groups, as well as no significant difference shown between the two groups ($F_{1,9}$=0.391, p=0.547).

7.3.5.7 Psychological Well-being (3 to 6 months)

For patients completing T3 (TC: n=7, UC: n=5), there was no significant difference in HADs anxiety scores between T2 and T3 for both the tele-coaching (-1±2 points; p=0.156) and usual care (2±2 points; p=0.129) groups, however the worsening of scores in the usual care group (2±2 points) exceeded the MCID previously proposed for COPD patients (Smid et al., 2017). There was no difference identified between the two groups ($F_{1,9}$=0.689, p=0.428). Additionally, for HADs depression scores there was no significant change in either the tele-coaching (0±2 points; p=0.225) or usual care (0±1 points; p=1.000) groups, with no significant difference displayed between the two groups ($F_{1,9}$=1.479, p=0.255).

7.3.5.8 Patient experiences of physical activity (3 to 6 months)

For patients completing T3 (TC: n=7, UC: n=5), there were no significant or clinically important changes in C-PPAC total scores in the tele-coaching (1±9 points; p=0.745) or usual care (-3±5 points; 0.254) groups from T2 to T3, with no significant difference between the two groups ($F_{1,9}$=0.006, p=0.941). For C-PPAC amount scores, there was no significant change from T2 to T3 for the tele-coaching (4±16; p=0.617) or usual care (-8±11 points; p=0.200) groups, however the decline in the usual care group was clinically important (Gimeno-Santos et al., 2015). There was a clinically important difference between the tele-coaching and usual care group, however this did not reach the level of significance ($F_{1,9}$=4.526, p=0.062). For C-PPAC difficulty scores, there was no significant change between T2 and T3 in the tele-coaching (-2±5 points; p=0.544) or usual care (1±11 points; p=0.783) groups, with no significant difference between the two groups ($F_{1,9}$=0.296, p=0.595) at 6 months.

7.3.5.9 All-cause Mortality

There were no deaths in either the tele-coaching or usual care groups up to T3 (6 months).

Table 7-5: Physical activity, HRQoL, Psychological Wellbeing and patient physical activity experience outcomes at 3 months (post-intervention) and 6 months (follow up).

Outcome	**Group**	**3 months (T2) (n=12)**	**6 months (T3) (n=12)**
Accelerometer Outcomes:			
Daily Steps (steps/day)	TC	7033 ± 5944	6843 ± 3904
	UC	5408 ± 4444	4804 ± 4372[#]
Movement intensity (VMU)	TC	390 ± 118	391 ± 212
	UC	314 ± 129	310 ± 154
Time spent in sedentary activity (min/day)	TC	513 ± 43	517 ± 105
	UC	463 ± 85	459 ± 113
Time spent in at least light activity (min/day)	TC	197 ± 72	209 ± 101
	UC	194 ± 58	172 ± 39
SF-36:			
PCS Score	TC	39 ± 14	40 ± 13
	UC	38 ± 12	35 ± 13[#]
MCS Score	TC	53 ± 14	51 ± 17
	UC	51 ± 13	52 ± 13
HADS:			
Anxiety	TC	4 ± 4	5 ± 4
	UC	4 ± 5	6 ± 6[#]
Depression	TC	3 ± 3	3 ± 3
	UC	3 ± 5	3 ± 4
C-PPAC:			
Total Score	TC	70 ± 19	71 ± 12
	UC	71 ± 13	68 ± 12
Amount Score	TC	68 ± 23	72 ± 10
	UC	68 ± 11	60 ± 14[#]
Difficulty Score	TC	71 ± 22	69 ± 21
	UC	75 ± 18	76 ± 13

Abbreviations: VMU = Vector Magnitude Units, MVPA = moderate to vigorous physical activity, HADS = Hospital Anxiety and Depression Scale, SF-36 = Short Form 36 Questionnaire, PCS = Physical Component Summary, MCS = Mental Component Summary, TC = Tele-Coaching, UC = Usual Care. Values are mean ± SD.

**: Significant within group change [#]: Clinically important within group change*

7.4 Discussion

This is the first study investigating the feasibility of a physical activity behavioural modification tele-coaching intervention in LTx recipients. The findings showed that tele-coaching was a feasible, safe, and well accepted intervention by LTx recipients. Patient uptake and retention, acceptability and usage of the tele-coaching intervention was high, without occurrence of adverse events. When compared to usual care, tele-coaching elicited improvements in accelerometer derived physical activity parameters that exceeded clinically important margins, highlighting the potential effectiveness of this intervention to support patients post LTx. Furthermore, follow up data appears to show that the benefits gained in physical activity and HRQoL outcomes following tele-coaching are maintained at 6 months when the tele-coaching intervention is removed, whilst the usual care group showed clinically important declines in daily steps, SF-36 PCS and anxiety scores.

7.4.1 Feasibility Outcomes

Recruitment for the trial was significantly affected by the COVID-19 pandemic and the suspension of LTx during the early stages of the pandemic. Thus, the main reason for slow patient recruitment was due to the limited number of transplants performed. A centre-specific investigation reported this as a 77% reduction during the first peak of the pandemic (Hardman et al., 2021). Although the number of transplants was limited, uptake of the study was high with 91% of eligible participants accepting participation. This well exceeds criteria previously used to proceed to a full-scale trial (>30% of eligible patients recruited) (Hawkins et al., 2019). As per the findings of Wietlisbach et al. (2020), LTx recipients value the importance of physical activity and are motivated by desires to lead long and healthier lives, pay gratitude to their organ donor and capitalise on their renewed physical capabilities. Additionally, there were low rates of attrition in both the tele-coaching and usual care groups (14% overall) over the 12-weeks. According to

previous literature, attrition of <20% is unlikely to threaten the validity of a trial (Schulz & Grimes, 2002). Additionally, this is significantly lower than the dropout rate previously reported in a meta-analysis of app-based interventions in chronic disease (Meyerowitz-Katz et al., 2020).

Overall, the tele-coaching intervention was well accepted by patients, who rated their enjoyment similarly to a study using the same intervention in COPD patients (Loeckx et al., 2018). Most patients (78%) reported that the intervention 'helped them a lot' to improve their physical activity, which is higher than that previously reported in COPD patients (59%) (Loeckx et al., 2018). A recent evaluation of a tele-rehabilitation programme in LTx candidates and recipients also reported high satisfaction with a rehabilitation application. Whilst the questionnaire used was project specific and therefore different to that used in the current study, 88% stated that they liked the virtual care features (videoconferencing, texting, education etc.) of the programme and 83% reporting that the programme helped them to prepare for surgery (Wickerson et al., 2021). Similarly, Choi et al. (2016) implemented an 8 week aerobic and strengthening tele-rehabilitation programme, consisting of 8 home exercise sessions using videoconferencing and home monitoring of arterial oxygen saturation, heart rate and daily steps. Following the programme, all patients reported a positive experience with the programme and reported that the intervention helped them to improve their physical function. Similarly, to the current study, the main reason for non-adherence to exercise sessions, or in our case uploading of physical activity data, was due to transplant-related complications (e.g., infection, acute rejection or hospital readmission) which temporarily led to postponement of the scheduled exercise session. Hence, this highlights the importance of allowing flexibility and individualised adjustment throughout an exercise training or physical activity intervention. Another important finding in the study by Choi et al. (2016) and Wickerson et al. (2021) was that there were no adverse events reported related to the intervention, which was also the case in the current study. This is promising

given that there is a lack of data around the optimal prescription of exercise and physical activity in an unsupervised environment in lung transplant patients (Dechman et al., 2020).

The simplicity of the smartphone application in the current study may have contributed to the good acceptability of the intervention, as most patients reported finding it easy to use. In COPD patients, 47.8% rated the goal increases as either 'high' or 'much too high' (Loeckx et al., 2018) compared to only 11% in the current study in LTx recipients, which is supported by high step goal compliance (69±12%). This may suggest that LTx recipients are more ambitious with their physical activity targets, because of improved lung function and diminished symptoms of breathlessness (Pêgo-Fernandes et al., 2009).

Alike to the findings in COPD patients (Loeckx et al., 2018), LTx recipients considered the pedometer and telephone contact with the researcher as the most important components of the intervention. A study exploring desired features for digital health tools in organ recipients, showed physical activity guidance, particularly focused on safety of specific activities was a common desire expressed by patients (Mathur et al., 2021). Thus, the regular contact with the researcher to resolve and advise on any safety concerns in the current study, may have enhanced patient's self-efficacy to undertake more physical activity (Hartman, Boezen, de Greef, Bossenbroek, & ten Hacken, 2010; McAuley, Szabo, Gothe, & Olson, 2011). The perceived importance of health care professional (HCP) support also reinforces the wealth of evidence highlighting the significance of a collaborative approach between the patient and HCP in facilitating patient behaviour change and self-management (Benzo, 2012).

Although HCP contact was important, the average contact time required for each patient was only 46 minutes over the 12-week intervention. This is significantly less resource

intensive than an intervention such as pulmonary rehabilitation, where it is recommended that patients attend a minimum of two classes per week for 6 weeks, with a minimum supervision ratio of two HCP to eight patients (British Thoracic Society, 2014), equating to around four hours of HCP time per week. In the current study, coaching eight patients simultaneously over 12 weeks, would equate to around 31 minutes of HCP time per week. The low contact time could have been facilitated by several factors, such as the semi-automated nature of the intervention, the instruction booklet provided to help with working the app, as well as the simplicity of the app, as 89% of patients indicated that they found the app either “very easy” or “easy” to use. The contact time in the current study was similar to that reported by Demeyer et al. (2017), with patients contacted a median (IQR) of 6 (4-9) times, with 50 minutes of contact time per patient.

The high-level of perceived importance of the pedometer by patients was also reflected by the excellent actual and self-reported usage of the pedometer. Most patients (80%) wore the pedometer for over 90% of the 12-week programme, which was higher than that previously reported in the study in COPD patients (59%) (Loeckx et al., 2018). This is an important finding as the foundations of an effective physical activity behavioural intervention are based upon patients being able to accurately record their physical activity habits (Mantoani et al., 2016). A meta-analysis of 70 RCTs reported that high tech fitness trackers that incorporate features such as distance walked, elevation, activity intensity and heart rate monitoring offered no clear advantage over simpler pedometer-based interventions in improving steps/day in the general population (Chaudhry et al., 2020). Thus, the minimal pedometer display in the current study was able to provide simple self-monitoring information to the patient, with an easily understandable output. Furthermore, compared to internet interventions requiring either a desktop or laptop computer, mobile application interventions have the capacity to interact with patients at a greater frequency and allow data transmission via Bluetooth, so that the intervention

can be tailored to changing physical activity behaviours, which may also facilitate adherence (Riley et al., 2011).

7.4.2 Physical Activity Outcomes

In terms of accelerometer physical activity outcomes, there were statistically significant and clinically important improvements in steps/day in both groups. The improvement in the usual care group highlights the natural recovery occurring in the early stages of LTx recovery. This supports the work by Langer et al. (2012) who demonstrated an improvement of 750 steps/day in a usual care group within an exercise training study. It is clear from the systematic review (Chapter 3) of this thesis (Hume et al., 2020), that the majority of rehabilitation studies conducted post-transplantation are limited by the lack of a control group, making it difficult to differentiate the true effect of the intervention. Literature on interventions to improve physical activity in LTx recipients is scarce (Langer, 2021). Improvements in daily steps in the current study exceeded those shown following exercise training (Choi et al., 2016; Langer et al., 2012). This is likely due to step counts being the central focus of the intervention and the incorporation of behavioural techniques such as self-monitoring, goal setting and feedback, which have been deemed important for enhancing healthy activity behaviours (Sullivan & Lachman, 2017). For instance, Choi et al. (2016) reported an increase of ~2400 steps in a small cohort of four patients undergoing a tele-rehabilitation programme. However, this was only an 8-week programme, which focused primarily on exercise training without the incorporation of behavioural change strategies.

Although peripheral muscle abnormalities have been shown to be the predominant limiting factor to exercise capacity in lung transplant recipients (Mathur et al., 2004), the underlying lung disease entity and pathophysiology may also influence an individual's exercise capacity and physical activity behaviour. When examining individual changes

following tele-coaching (Figure 4), the largest improvements in daily steps and movement intensity were seen in PAH, whereas the lowest was in COPD. The degree of natural recovery (steps/day and VMU) was also lowest in COPD patients, which could be attributed to the older age of COPD patients, compared to other respiratory disease entities. Although the maximum age for undergoing LTx is increasing, older recipients demonstrate considerably lower 1- and 5-year survival, compared to patients under 60 years old (Lane & Tonelli, 2015). Furthermore, age-associated processes/co-morbidities such as frailty, sarcopenia, osteoporosis, cardiovascular abnormalities, and immune dysfunction, may limit recovery from lung transplant and subsequent daily physical activity (Schaenman et al., 2021). Second to COPD patients, CF patients demonstrated the least improvement in daily steps. Although CF recipients are often younger compared to other disease entities such as COPD, CF is a multi-organ disease in which co-morbidities such as diabetes mellitus and bone disease are common both pre- and post-transplant (Meachery et al., 2008). It is important to note that definitive conclusions cannot be drawn from this data due to the limited sample size, however this poses an interesting question for future research.

For VMU and time spent in at least light activity, only the tele-coaching group demonstrated a significant improvement over the 3-month intervention period, however the difference between groups was not significant, likely due to the small sample size. In the study by Langer et al. (2012) walking movement intensity (m/s^2) improved significantly in the exercise training group compared to usual care, however this was assessed using a different unit of measurement to VMU, making it challenging to compare with the findings of the current study. Of note, the study by Langer et al. (2012) had a sample size of 36 patients, thus was adequately powered to detect differences between the intervention and control group. The improvement elicited by physical activity tele-coaching (138±148 VMU) in the current study exceeded those reported previously in COPD patients following high intensity interval training (Louvaris et al., 2016), as well

as an intervention combining physical activity behavioural modification alongside pulmonary rehabilitation (Armstrong et al., 2021) in COPD. Specifically, Louvaris et al. (2016) showed a significant increase in movement intensity of 84 VMU following high intensity interval training, compared to a 5 VMU increase in the usual care group. Comparably, Armstrong et al. (2021) showed an increase of 78 VMU in the physical activity behavioural modification and pulmonary rehabilitation group, compared to a decline of 20 VMU following pulmonary rehabilitation alone. As well as the limited sample, the lack of difference between the tele-coaching and usual care groups could be because there is no decline in the usual care group, and patients potentially have a higher ceiling due to the removal of lung disease.

7.4.3 Patient's physical activity experience

The findings showed that both tele-coaching and usual care elicited clinically important improvements in C-PPAC total and amount scores over the 3 months, however only the tele-coaching group improved significantly, which aligns closely with the findings on steps/day and movement intensity. Although this is not surprising as steps/day and VMU constitute the objective component of the C-PPAC instrument, it presents additional understanding by assessing patient reported outcomes. For instance, patient's perceptions on the amount of walking and household activities they undertake, as well as the symptoms during daily activities and the subsequent adaptations to physical activity that need to be made.

As this is an instrument specific to COPD patients, results can only be compared to this patient population. Although COPD is one of the main respiratory diseases undergoing LTx, symptoms impacting LTx recipients' physical activity may differ to those in COPD and be less dominated by breathlessness (Mathur et al., 2004). Therefore, these results are exploratory and should be interpreted with caution. Nevertheless, in the current

study, C-PPAC total and amount scores improved significantly following 3 months of tele-coaching, however there was no significant change in C-PPAC difficulty scores. In the study implementing a similar physical activity tele-coaching intervention in COPD patients (Demeyer et al., 2017), C-PPAC total scores and amount scores were superior compared to usual care, however scores in the usual care group declined, whereas this was not the case in the current study due to the natural recovery occurring after LTx. On the other hand, Armstrong et al. (2021) showed that the addition of physical activity behavioural modification strategies alongside pulmonary rehabilitation induced significantly greater improvements in C-PPAC total, amount and difficulty scores. This could suggest that the combination of both exercise training to enhance exercise capacity and physical activity behavioural modification strategies to stimulate physical activity engagement, is optimal to improve the difficulty domain of the C-PPAC instrument. This is supported by the work of Gimeno-Santos et al. (2015), demonstrating moderate to strong correlations between the C-PPAC difficulty domain and exercise capacity and symptoms, which are outcomes commonly addressed and improved by pulmonary rehabilitation interventions (Spruit, 2014). That said, Arbillaga-Etxarri et al. (2018) implemented an urban training programme combining behavioural strategies with unsupervised outdoor walking in COPD patients and reported significant increases in C-PPAC total, amount and difficulty scores in the urban training group, but not usual care. However, the difference between the urban training and usual care groups was not significant.

7.4.4 HRQoL and Psychological Wellbeing Outcomes

For SF-36 PCS scores, a clinically important improvement was shown in both the tele-coaching (+10) and usual care (+5) group, showing that SF-36 PCS scores demonstrate a natural course of recovery following LTx, likely due to improved pulmonary function, symptoms and ability to perform daily activities (Finlen Copeland et al., 2013; Kugler,

Strueber, Tegtbur, Niedermeyer, & Haverich, 2004). However, the improvement in the tele-coaching group exceeds usual care by clinically important margins, suggesting that tele-coaching can optimise patient's perceived benefits of their physical functioning. The improvement in SF-36 PCS scores aligns with the findings by Schneeberger et al. (2017) who showed clinically meaningful changes following a pulmonary rehabilitation programme, with no differences displayed between the underlying disease entity (COPD or ILD) or transplant type (single or double LTx).

When examining the eight individual SF-36 health domains, only the tele-coaching group demonstrated significant improvements in the 'physical functioning' and 'role physical' domains, suggesting that tele-coaching can help to improve patient's perceptions of their physical functioning and ability to return to work and undertake activities of daily living. Similar to the current study, Langer et al. (2012) reported no significant difference between the exercise training and usual care group in any of the SF-36 domains at 3 months, which was attributed to the large improvements that all patients experienced during the early stages of recovery. However, at 12 months the difference between groups became more pronounced and the exercise training group displayed significantly higher 'physical functioning' and 'role physical' scores, compared to usual care.

In contrast to SF-36 PCS, neither tele-coaching nor usual care enhanced MCS scores over the 3-month intervention period. This reflects findings shown previously by Da Fontoura et al. (2018) following 12 weeks of exercise training. This may be due to several factors such as the uncertainty of organ rejection, adverse effects of immunosuppressive medications and recurring pain following LTx, which may limit further improvements in this domain (Singer & Singer, 2013). On the other hand, a large study (n=5396) reporting normative data for the SF-36 in a Norwegian population, mean scores were 50 and 51 for SF-36 PCS and MCS scores, respectively (Garratt & Stavem, 2017). Comparably, in Chapter 6 the data in UK healthy individuals showed mean SF-36 PCS and MCS scores

of 55 and 59, respectively. Thus, as shown in Chapter 6, SF-36 MCS scores at baseline (hospital discharge) in the tele-coaching (56 points) and usual care (51 points) groups were comparable to normative scores. This is supported by previous research showing that SF-36 MCS scores improve dramatically as a result of LTx itself (Pinson et al., 2000; Rodrigue, Baz, Kanasky, & MacNaughton, 2005), thus allowing little scope for improvement when implementing an intervention following hospital discharge. Whereas impairments after transplant cluster in domains related to physical function (Singer & Singer, 2013).

The findings pertaining to SF-36 MCS scores are also supported by the lack of change in HADs anxiety and depression scores. This was also reflected in the study by Langer et al. (2012) following 12 weeks of exercise training. This may also be due to the low baseline scores indicative of sub-clinical levels of anxiety and depression, allowing little scope for improvement. Indeed, in an exercise training study conducted by Candemir et al. (2019), significant improvements in HADs anxiety and depression scores were shown when baseline scores demonstrated mild to moderate anxiety (10 points) and depression (9 points).

7.4.5 6 Month Follow Up

From the LTx recipients completing the 6-month follow up, it appears that the tele-coaching group maintained improvements in physical activity and HRQoL outcomes obtained throughout the 3-month intervention. This is promising, as following the 3-month intervention, the tele-coaching intervention was removed, and patients were advised to keep the pedometer and monitor and adjust their physical activity levels independently. On the other hand, the usual care group showed clinically important worsening in daily steps, C-PPAC amount scores, SF-36 PCS scores and HADs anxiety scores.

A survey conducted in solid organ transplant recipients found that major facilitators for physical activity engagement included a high level of motivation, social support, recommendation from a physician and knowledge and confidence about exercise (Gustaw et al., 2017). Therefore, tele-coaching can facilitate participation in physical activity by providing tailored support and education to patients, whilst teaching them how to monitor and safely adjust their physical activity levels beyond the initial stages of recovery, as well as overcome any potential barriers that arise. Parallel findings were reported by Langer et al. (2012), showing that 12 weeks of exercise training alongside physical activity counselling following LTx, resulted in higher levels of physical activity at one year compared to usual care. It was suggested that participating in an exercise training programme following hospital discharge contributed to enhanced self-efficacy, increasing patient's confidence to engage in more physical activity. Conversely, in COPD patients, Hoaas, Morseth, Holland, and Zanaboni (2016) investigated whether physical activity levels were maintained following completion of a 2-year tele-rehabilitation intervention consisting of home-based exercise supported by a physiotherapist. At the one year follow up, results showed a significant decline in daily steps and time spent in light physical activity, showing that physical activity levels were not maintained once regular supervision and motivational support were withdrawn. Whereas, Berry et al. (2010) implemented a lifestyle intervention in COPD patients that gradually reduced dependency on staff and structured exercise, towards independent promotion and regulation of physical activity at home, and showed that improvements in physical activity were maintained at 12 months. Thus, highlighting the importance of developing competence and autonomy throughout physical activity interventions, in line with the self-determination theory (Teixeira, Carraça, Markland, Silva, & Ryan, 2012). Additionally, previous evidence has shown that patient-centred and autonomy supportive communication interventions such as motivational interviewing used in the current study, can incite intrinsic motivation and are helpful for achieving long term changes in physical activity (Leunis et al., 2022).

In transplant recipients, data on how behaviour change techniques may stimulate long term physical activity are scarce (Leunis et al., 2022). However, behaviour change techniques that were used within the tele-coaching intervention including action planning, goal setting, self-monitoring, instruction on how to perform the behaviour and prompts/cues have demonstrated effectiveness for adopting and maintaining physical activity in non-transplanted individuals (Samdal, Eide, Barth, Williams, & Meland, 2017). A review examining physical activity behaviour in transplant recipients proposes that habit formation may be facilitated by focusing on incidental physical activity such as active commuting, gardening, household chores and playing with grandkids, as this requires less time commitment and planning so can be easily embedded into a daily routine. Additionally, light activity is associated with less bodily signals and discomforts in transplant recipients, therefore as the tele-coaching intervention focused mainly on walking and increasing step count, its long term continuation may be more likely and can serve as a step up to undertaking higher intensity physical activities (Leunis et al., 2022). It is important to note that although the follow up data is promising, a larger sample size is needed to draw definite conclusions.

Furthermore, it is important to highlight that there are a number of potential confounders that may have impacted the differential evolution of physical activity participation between the tele-coaching and usual care groups. For instance, differences in periods of infection, organ rejection and/or hospitalisation between the tele-coaching and usual care groups may have influenced physical activity participation. In patients with COPD an acute reduction in physical activity has been demonstrated in both severe exacerbations requiring hospitalisation and community treated exacerbations, with sustained physical activity reduction evident at one month following hospitalisation (Demeyer et al., 2018). Evidence in LTx recipients shows that there is a high incidence of respiratory viral infections following lung transplantation and these contribute significantly to patient's respiratory symptomology (Bridevaux et al., 2014), which will

likely have a successive impact on daily physical activity. This is further supported by Wanigatunga et al. (2019) showing that accumulated hospitalisation time was negatively associated with objectively measured sedentary and physical activity time, with these effects magnified if hospitalisation exceeded 4 days in mobility-limited older adults. As previously acknowledged in chapter 2, additional environmental factors such as weather may have also impacted physical activity parameters at the different time points in the study. Thus, future work should look at the prevalence of these factors in the intervention and usual care group, and their influence on the trajectory of physical activity.

7.4.6 Study Limitations

There are several limitations that must be considered in this study. Firstly, this was a small-scale study, therefore, generalisability of the results to clinical practice may be limited. However, the main aim of this study was to explore the feasibility and acceptability of tele-coaching in LTx recipients, thus it was not powered to detect differences in study outcomes between groups. Secondly, acceptability of the intervention was assessed through a project specific questionnaire, which was used previously by Loeckx et al. (2018) in COPD patients. This makes it challenging to make comparisons with other studies implementing digital health interventions, however it provides useful insights into patient acceptability and can be compared to the findings by Loeckx et al. (2018) to explore differences between different patient groups using the same intervention. Finally, randomisation to the tele-coaching and usual care groups was stratified based on functional exercise capacity (6MWD) as this has been demonstrated as a strong predictor of physical activity change (Osadnik et al., 2018), consequently it was not possible to balance groups for all variables (e.g. sex and disease entities) and there was a large diversity of primary disease diagnosis and therefore underlying pathophysiology of physical activity limitation (Vogiatzis, Zakynthinos, & Andrianopoulos, 2012).

7.5 Conclusion

In conclusion, physical activity tele-coaching appears to be a feasible, safe, and acceptable intervention to support patients post LTx. Additionally, there is a degree of natural recovery in some physical activity and HRQoL parameters, however tele-coaching appears to elicit greater improvements in physical activity measures. Furthermore, the behavioural modification strategies implemented as part of the tele-coaching intervention appeared to result in better maintenance of physical activity and HRQoL outcomes three-months after the initial intervention. It would therefore seem appropriate to conduct a fully powered RCT to determine the efficacy of physical activity tele-coaching in LTx recipients. Our data will inform sample size estimation for a full-scale RCT.

Chapter 8: General Discussion

8.1 Thesis outline

The overall aim of this thesis was to investigate the feasibility of a remote physical activity promotion intervention that utilised digital health technology in lung transplant recipients. The aim of Chapter 3 was to systematically review the existing evidence on the effects of exercise training on exercise capacity, quality of life and clinical outcomes in lung transplant candidates and recipients. Chapter 5 aimed to determine the criterion validity and test re-test reliability of a commercially available pedometer, that was employed in the physical activity tele-coaching intervention within the main trial of this thesis to self-monitor physical activity levels. Prior to conducting the main trial, Chapter 6 aimed to understand the degree of limitation in daily physical activity, HRQoL and psychological wellbeing in lung transplant recipients who had just been discharged from hospital following lung transplant surgery, compared to healthy age-matched individuals in the UK. Finally, Chapter 7 investigated the feasibility and acceptability of a physical activity behavioural modification tele-coaching intervention in lung transplant recipients, as well as the short- and longer- term effect of the intervention to optimise physical activity and HRQoL, in comparison to usual care.

8.2 Summary of main findings

The systematic review explored the current literature on exercise training in lung transplant candidates and recipients, as this was highlighted as an important component in the management of lung transplant patients in the latest ATS-ERS guidelines for pulmonary rehabilitation (Spruit, 2014). The review demonstrated that both inpatient and outpatient exercise training appears to be beneficial for patients prior to and following LTx, with most studies displaying an improvement or at least maintenance of functional exercise capacity. More favourable effects were demonstrated in lung transplant recipients, which is not surprising, given that lung transplant candidates have a poorer prognosis, and the focus of exercise training is to maintain physical function and HRQoL.

Additionally, most studies showed a beneficial impact on HRQoL measures, however data on clinical outcomes was sparse. An important conclusion was that the quality of the included studies was limited by the lack of RCTs and absence of a comparator group, thus limiting the ability to distinguish the effect of the intervention from the natural recovery that might be expected following LTx. This has also been emphasised in a recent Cochrane review exploring exercise training for lung transplant recipients, concluding that in terms of exercise capacity and HRQoL the evidence is very uncertain due to imprecise estimates of effects and high risk of bias (Gutierrez-Arias et al., 2021). Therefore, when designing the main clinical trial (Chapter 7) of this thesis, an RCT design was employed in which patients were randomised to either the physical activity tele-coaching intervention in addition to usual care, or usual care alone.

As highlighted consistently throughout this thesis, investigation into daily physical activity levels and interventions to enhance physical activity levels in lung transplant patients is scarce. The case control study conducted in Chapter 6, is the first study to examine physical activity levels in UK LTx recipients in the early stages following LTx. The findings established that lung transplant recipients were significantly inactive in daily life compared to healthy age matched UK individuals, demonstrating significantly lower accelerometry-derived daily steps, movement intensity and time spent in light and moderate to vigorous intensity activity. Additionally, the impairment in daily physical activity levels was accompanied with significant and clinically important reductions in HRQoL parameters, particularly those pertaining to physical functioning. Physical inactivity in lung transplant recipients may result from a combination of factors related to physical capabilities (e.g. deconditioning, co-morbidities or symptoms that may interfere with physical activities and side effects of medications), psychological capabilities (e.g. lack of knowledge on benefits of physical activity or appropriate/safe conduction of physical activities), physical opportunity (e.g. environmental constraints such as lack of access to safe physical activity facilities, costs of facilities and bad weather) and social

opportunity (e.g. lack of support or low expectations from family or physicians) (Leunis et al., 2022). The findings of Chapter 6 support those of previous cohort studies that have examined physical activity levels of lung transplant recipients in both the early and later stages of lung transplant recovery in other regions of the world (Langer et al., 2009; Ulvestad et al., 2020; Wickerson et al., 2015). Therefore, stressing the need to develop and evaluate interventions targeting physical inactivity in this population. Reviews undertaken in the area of rehabilitation in LTx also emphasise the need for sufficiently powered randomised controlled trials on rehabilitation interventions for improving long term outcomes such as daily physical activity, quality of life, survival and co-morbidities, with remotely monitored tele-health interventions such as pedometer-based walking or home exercise interventions proposed as interesting alternatives that warrant further investigation (Langer, 2015, 2021).

Accordingly, the clinical trial implemented in Chapter 7 primarily aimed to assess the feasibility of a physical activity behavioural modification tele-coaching intervention in lung transplant recipients, but also obtain preliminary data on the short- and longer-term effects of the intervention on important outcomes such as daily physical activity, HRQoL, anxiety and depression and survival. Prior to conducting the clinical trial, Chapter 5 assessed the criterion validity and test re-test reliability of the pedometer that was employed as the motivational feedback tool within the tele-coaching intervention. The findings showed that the pedometer was valid for measuring step counts in healthy individuals and patients with chronic respiratory disease, at walking speeds of 3.0 to 4.0 km/h, however the accuracy was more limited at slower walking speeds (< 2.5km/h).

The findings from Chapter 7 concluded that physical activity tele-coaching in lung transplant recipients was deemed to be a feasible, well accepted, and safe intervention in lung transplant recipients. Whilst the study was not powered to detect differences in physical activity, HRQoL and anxiety and depression outcomes, compared to usual care,

tele-coaching elicited improvements in physical activity and HRQoL outcomes that exceeded clinically important margins. Furthermore, those assigned to the tele-coaching group were able to maintain improvements in these outcomes at 6 months, whereas the usual care group showed clinically important declines in daily steps, HRQoL physical component scores and anxiety scores. Thus, the semi-automated design of the tele-coaching intervention facilitated patients' self-management, whilst providing the additional benefit of coach input to enhance patient confidence and allow them to maintain their physical activity levels independently.

8.3 Feasibility of implementing a physical activity tele-coaching intervention in LTx recipients

In Chapter 7, a set of criteria were used to determine the feasibility of physical activity tele-coaching consisting of a pedometer and smartphone application in lung transplant recipients. These criteria consisted of 1) feasibility to recruit participants, 2) retention of participants, 3) feasibility of randomisation processes, 4) intervention acceptability, and 5) intervention usage (Haines, 2020; Hawkins et al., 2019; Ward et al., 2018). Overall, the intervention was deemed feasible and therefore the findings from this study can be used to inform the design and implementation of a full-scale RCT.

The findings on the feasibility of recruitment emphasise the significant impact of COVID-19, as LTx was suspended during the midst of the pandemic (Hardman et al., 2021). Despite the limitation in the number of patients undergoing LTx, uptake of the study was high at 91%. Following it's suspension, the lung transplant service at Freeman Hospital was reconfigured by streamlining patient pathways and utilising tele-conferencing to ensure safe resumption of the service (Umair et al., 2021). As a result, patients became accustomed to using tele-health modalities for transplant education, psychological evaluation, social worker reviews and surgical/anaesthetic consent, thus the physical activity tele-coaching trial aligned well with this model of care and the majority of the trial

was undertaken remotely. Although the COVID-19 pandemic reduced the number of lung transplants performed at Freeman Hospital by ~70%, the number of transplants performed prior to the pandemic was 33 in 2016 to 2017 and 46 from 2017 to 2018 (NHS Blood and Transplant, 2019). Therefore, if progressing the trial to a full scale RCT, adopting a multi-centre approach may be beneficial to facilitate recruitment. Compared to single-centre studies, multi-centre research offers a larger sample size, greater generalisability and ability to share resources across centres. However, it is important to put in place rigorous study protocols to ensure uniform data collection across the multiple sites. From the systematic review conducted in Chapter 3, there were no rehabilitation studies in lung transplant candidates or recipients that were undertaken in the UK, therefore progressing this trial to a multi-centre RCT could offer further opportunities for networking and collaboration amongst UK transplant centres. The retention rate of the feasibility study was also high, with an even drop out demonstrated between the two groups, further supporting the acceptability of the study procedures and randomisation process, as patients were still willing to participate in the study if assigned to the usual care group.

The findings of Chapter 7 show that the physical activity tele-coaching intervention was well accepted by lung transplant recipients. However, a limitation of this study is that patient acceptability was only assessed using a project-specific questionnaire, which yielded predominantly quantitative data. Therefore, if conducting this study on a larger scale, employing a mixed methods design (both quantitative and qualitative methods) would be preferable to answer the research questions more comprehensively and allow the strengths and weaknesses of each approach to complement each other. For instance, two common qualitative methods for assessing the acceptability of an intervention in a target population are focus groups and interviews. Implementing these methods would result in a greater understanding of factors that may facilitate or impede the implementation of an intervention (Tariq & Woodman, 2013). As stated in literature,

one major consideration when implementing a mixed methods design is that it is demanding in terms of time and methodological skillset, and therefore requires a team of researchers who are experienced in both methodologies (Regnault, Willgoss, & Barbic, 2018).

In Chapter 7, the feasibility of tele-coaching from the healthcare professional/coach perspective was partly assessed by examining the number of contacts that were required per patient, along with the duration and nature of each contact. The findings showed that tele-coaching offers a minimal contact intervention that can be delivered to patients at home, with less resource requirement than interventions such as pulmonary rehabilitation. If progressed to a larger national study, an economic evaluation could be undertaken to identify and quantify the additional costs of delivering the intervention. Furthermore, the cost effectiveness of the intervention could be assessed using quality-adjusted life-years (QALYs) analysis, which combine the quantity and quality of life following healthcare interventions. For instance, previous research has looked at QALYs for interventions such as pulmonary rehabilitation (Griffiths, Phillips, Davies, Burr, & Campbell, 2001) and cognitive behavioural therapy (Heslop-Marshall et al., 2018), with both showing a high likelihood of generating QALYs at a negative or relatively low cost.

Whilst the feasibility of the intervention by coaches was partly assessed by examining contact time per patient, this could be explored further in a future study by conducting focus groups and interviews with the coaches delivering the intervention. Due to the small scale of the current feasibility study this could not be undertaken, as the intervention was delivered by one coach only. In addition, the views of clinicians involved in the clinical care of lung transplant recipients and their perceptions of conducting the intervention in clinical practice could be explored. In the mixed-methods study by Loeckx et al. (2018) exploring physical activity tele-coaching in COPD patients, focus groups were conducted with coaches delivering the intervention at the multiple sites and all

coaches expressed that the intervention would be a useful addition to usual care. When considering future use, coaches described that some patients felt the smartphone app lacked variation and the home exercise booklet did not result in higher step counts, which could have led to its low usage (Loeckx et al., 2018). A suggestion made by a patient in the project-tailored questionnaire in the current study, is that the intervention could be developed to work with existing apps such as Fitbit. The research into apps such as Fitbit to promote healthy lifestyle behaviours has grown rapidly over recent years. A systematic review and meta-analysis of 37 studies found that Fitbit based interventions significantly increased daily step counts when compared to a control group (mean difference 951 steps/day, 95% CI 475.89-1425.18; P<.001), in a population combined of healthy individuals and patients with a range of health conditions (Ringeval, Wagner, Denford, Paré, & Kitsiou, 2020). Furthermore, a benefit of using popular commercially available activity monitors such as the Fitbit, Garmin and Apple watch is that they have already been validated in various populations, similar to that conducted in Chapter 5 of this thesis (Evenson, Goto, & Furberg, 2015; Fuller et al., 2020).

In a study exploring desired features for digital health tools in solid organ transplant recipients, patients expressed a desire for a tool that would consolidate multiple features such as physiological monitoring (e.g. oxygen saturation and heart rate), nutrition advice, water intake and medication reminders (Mathur et al., 2021). Thus, some of these features could be implemented with more sophisticated health applications that exist on the market. The incorporation of multiple features including exercise sessions, spirometry, monitoring of oxygen saturation, heart and symptoms, psychological support, dietary and self-management advice has been previously implemented in a tele-rehabilitation study in COPD, demonstrating equal effectiveness to hospital-based outpatient pulmonary rehabilitation in reducing exacerbations and hospitalisations (Vasilopoulou et al., 2017). Due to the diversity of transplant recipients and levels of digital literacy, flexibility in being able to choose “add-on” items within a digital health tool

was a desire previously communicated by solid organ recipients (Mathur et al., 2021). A benefit of the smartphone application used in the current thesis was that most patients found it easy to use, suggesting the application is feasible to use in lung transplant recipients of varying demographics. Both the study by Mathur et al. (2021) in transplant recipients and the tele-coaching study by Loeckx et al. (2018) in COPD patients, highlighted the need for flexibility to deal with non-linear health trajectories and other factors such as the weather, which have been shown to impact physical activity (Alahmari et al., 2015; Pitta et al., 2006). In the current study, hospital admissions throughout the intervention period were common, due to reasons such as acute rejection and other complications related to LTx, which required treatment or alteration to immunosuppressant regimes. Whilst the intervention was able to adjust goals based on the preceding week's activity, if developing the intervention further, then incorporating a feature to allow patients to record instances such as hospital admissions would be helpful and may further reduce contact time between the patient and healthcare professional. This is also an important point for designing a full scale RCT, as often patients spent periods of the 3-month intervention in hospital, therefore allowing flexibility within the trial should be considered. This may include allowing pausing of the intervention if the patient is in hospital and unable to monitor their physical activity, as well as allowing a wider window for follow up assessments (e.g. +/- 2 weeks of pre-specified date).

Overall, the feasibility study demonstrated high actual usage and compliance with the intervention components (pedometer and step goals). Previous research into the use of mobile technology for health self-monitoring in lung transplant recipients demonstrated that usage of the intervention decreased over time, with higher usage associated with older age, lower psychological distress, and better physical functioning (Jiang, Sereika, Dabbs, Handler, & Schlenk, 2016). In this feasibility trial, participants were no longer required to upload activity after the 3-month intervention but were advised to continue monitoring their steps independently with the pedometer. The data from the 6 month

follow up demonstrates that improvements in physical activity and HRQoL were maintained in the tele-coaching group, however it may be interesting to assess actual patient usage of the pedometer at further follow up assessments. Additionally, over the course of the study four pedometers were lost or broken and were subsequently replaced, which was largely attributed to the waist application of the pedometer. Therefore, if used in clinical practice or a full scale RCT, a wrist worn pedometer may be preferable.

8.4 Effect of tele-coaching on daily physical activity and HRQoL in LTx recipients

The primary aim of the clinical trial in Chapter 7 was to determine the feasibility and acceptability of the physical activity tele-coaching intervention in lung transplant recipients, but the study also obtained preliminary data on the short (3 month) and longer (6 month) term impact on physical activity, HRQoL and anxiety and depression outcomes following 3 months of tele-coaching group compared to usual care. Whilst the study was not powered to detect significant differences between groups, the improvement in daily steps in the tele-coaching group exceeded the usual care group by clinically important margins over the 3-month intervention period. Furthermore, only the tele-coaching group demonstrated significant increases in movement intensity and time spent in at least light activity over 3 months, suggesting that tele-coaching may be favourable for improving physical activity outcomes. Similarly, for HRQoL the improvement in SF-36 PCS scores in the tele-coaching group exceeded the usual care group by clinically important margins, thus the intervention optimised patient's perceptions of their physical functioning. Although these findings are promising, an RCT with full statistical power to detect differences between the tele-coaching and usual care groups should be undertaken to confirm these preliminary findings.

Using the effect size for the difference between the tele-coaching and usual care group in daily steps and movement intensity at 3 months from Chapter 7, power calculations (alpha = 0.05) using 80%, 90% and 95% statistical were undertaken. These calculations included a 10% attrition rate, which is based on the findings from the feasibility trial as 90% of patients were retained to 3 months. For 80% power, a total sample size of 46 and 44 patients were required for daily steps and movement intensity, respectively. Whereas for 95% power, the required total sample size was estimated at 76 and 70 patients for daily steps and movement intensity, respectively. The results of the sample size calculations undertaken are presented in Table 8-1.

Table 8-1: Results of sample size calculation based on physical activity data from Chapter 7

Statistical Power	Daily Steps Effect Size = 0.166	Movement Intensity (VMU) Effect Size = 0.176
80%	46 (23 per group)	44 (22 per group)
90%	62 (31 per group)	58 (29 per group)
95%	76 (38 per group)	70 (35 per group)

If the number of lung transplants performed at Freeman Hospital returns to the figures reported prior to the COVID-19 pandemic (~40 lung transplants per year) and recruitment rates reflect those of the feasibility study (76% of screened patients recruited), then approximate recruitment rate would be 30 patients per year. Therefore, to obtain a statistical power of 90% in daily steps, it would be estimated that recruiting the required sample size (62 patients) would take approximately two years. If aiming to recruit the required sample size in one year, then collaborating with another lung transplant site who have similar annual figures for the number of LTx performed (e.g. Royal Papworth Hospital: ~45 lung transplants per year) could be a viable option (NHS Blood and Transplant, 2020).

An important finding from Chapter 7 is that both groups demonstrated clinically important improvements in a number of variables over the intervention period, including daily steps, SF-36 PCS scores and C-PPAC total and amount scores. This emphasises the natural recovery that occurs following LTx and the caution that should be taken when interpreting the results of single-arm studies. This raises further doubt on a number of the positive findings reported in the studies of the systematic review in Chapter 3, due to the absence of a usual care group in most studies, highlighting the need for more rigorously conducted RCT's in the area of rehabilitation and physical activity promotion in lung transplant recipients.

The findings from the follow up data (6 months) demonstrate that the tele-coaching group maintains improvements gained in physical activity and HRQoL outcomes during the intervention period. In contrast, the usual care group showed clinically important declines in daily steps, SF-36 PCS scores and HADs anxiety scores. A previous study in lung transplant recipients revealed that treatment adherence was better in the early stages after LTx, with support from the transplant medical team, family and friends described as a crucial factor for optimising long-term outcomes (Teichman, Burker, Weiner, & Egan, 2000). This also seems to be the case for physical activity, as the usual care group were able to improve their physical activity levels initially over 3 months, perhaps due to renewed physical capabilities, but without behavioural modification strategies these could not be maintained. On the other hand, the behavioural modification strategies incorporated in the tele-coaching intervention, facilitated patient self-management by teaching patients how to self-monitor and adjust their physical activity levels. The timing of the intervention was an important design feature as patients were recruited when they transitioned from the security of the hospital to their own home environment, which is a period where patients may be more likely to discontinue their physiotherapy routine (Blumenthal et al., 2020). Therefore, patients may have been more receptive to behavioural interventions during this window (McBride, Emmons, & Lipkus, 2003).

A limitation of the clinical trial in Chapter 7 is that due to restrictions introduced by the COVID-19 pandemic and the requirement to conduct the study remotely, it was not possible to assess important outcomes such as exercise capacity and peripheral muscle function. Previous data in lung transplant recipients shows that after hospitalisation quadriceps muscle force decreases by ~20%, compared to pre-transplant levels (Langer et al., 2012; Maury et al., 2008). The implementation of exercise training has been shown to recover skeletal muscle force in the months following LTx, however a degree of skeletal muscle weakness is still observed (Langer et al., 2012; Maury et al., 2008). It is currently unknown whether physical activity tele-coaching would recover quadriceps muscle force, without the implementation of specific resistance exercises at higher training intensities. In addition to exercise capacity and quadriceps muscle force, other outcomes that warrant further investigation in future studies include metabolic risk factors (e.g. abdominal obesity, insulin resistance, blood pressure and cholesterol), body composition, physical function (e.g. Short Performance Physical Battery to assess gait, balance and lower extremity performance) and fatigue (e.g. FSS, FACIT questionnaires), as these have all been highlighted as important factors that are prevalent post-lung transplantation (Forsberg, Kisch, Lennerling, & Jakobsson, 2018; Schaenman et al., 2021).

From exploring the literature and clinical trials database, it is encouraging to see that there have been several protocols for RCT's published in the field of rehabilitation and physical activity promotion for lung transplant recipients. An ongoing study that will complement the clinical trial of this thesis, is a project investigating the effectiveness of a multi-component physical activity tele-coaching intervention (ClinicalTrials.gov Identifier: NCT04122768). This study differs to the current trial as it will compare the multi-component tele-coaching intervention with a light coaching intervention, rather than usual care. Furthermore, the study will implement the intervention in the later stages of

lung transplant recovery (6 months to 4 years post LTx) to determine the feasibility and effectiveness of the tele-coaching intervention in the long-term post operative phase.

Another study protocol that has been published by Blumenthal et al. (2020) is for an RCT investigating the impact of a remote intervention combining coping skills training with aerobic exercise (CSTEX), compared to a usual care and education control group. The coping skills training (CST) component of the intervention will train patients to use coping skills for stress reduction (e.g. relaxation, imagery, cognitive restructuring) and promote key transplant-specific health behaviours (e.g. monitoring of pulmonary function, medical adherence etc.). The EX-component of the intervention will progressively increase patients exercise and promote daily physical activity using motivational interviewing techniques and a Fitbit activity monitor. If successful, the CSTEX intervention can be delivered remotely to enhance quality of life and improve clinical outcomes in lung transplant recipients.

Finally, the most recent protocol published by Rozenberg et al. (2022) plans to assess the feasibility of a 12-week home-based aerobic and resistance training programme in lung transplant recipients, as well as assess estimates of intervention efficacy on metabolic risk factors, exercise self-efficacy and HRQoL. Thus, like the current study, this study intends to inform the design of a full scale RCT into a home-based rehabilitation intervention that will utilise tele-health modalities, as well as provide a greater understanding on behavioural strategies aimed at increasing physical activity in lung transplant recipients at risk of post-transplant metabolic syndrome. Overall, these planned or ongoing studies along with the findings of Chapter 7, will help to address the gaps in the literature, by developing and evaluating interventions that can be delivered remotely in clinical practice to enhance important outcomes for lung transplant recipients such as physical activity, quality of life and post-transplant morbidities.

8.5 Conclusions

When combined, the findings of this thesis emphasise that lung transplant recipients are significantly inactive in daily life and exhibit limitations in HRQoL, which collectively could lead to poorer outcomes following LTx. Physical activity tele-coaching incorporating behavioural modification strategies is a feasible and well-accepted intervention in lung transplant recipients, that offers a less resource intensive intervention to optimise functional and clinical outcomes.

8.6 Future directions

Collectively, the findings and lessons learnt from this feasibility trial can inform the process (e.g. recruitment, retention and adherence), resource requirements (e.g. staff time and consumables) and management (e.g. data collection and analysis) of a fully powered RCT, to draw definitive conclusions on the efficacy of physical activity tele-coaching to optimise short and longer term health and clinical outcomes in LTx recipients, compared to usual clinical care. This should also include additional outcomes to the current study such as exercise capacity, quadriceps muscle force and development of co-morbidities.

If the preliminary findings from this thesis are supported by a fully powered RCT, physical activity tele-coaching poses an attractive intervention to implement within UK clinical services to support patients post-LTx, particularly in the absence of routine face-to-face rehabilitation services for these patients. Future trials could also explore the feasibility and efficacy of a more comprehensive intervention combining physical activity tele-coaching with a tele-rehabilitation programme (incorporating exercise training and physiological monitoring), to determine whether this can elicit superior clinical and functional outcomes following LTx.

List of Appendices

Physical Activity Promotion in Lung Transplant Recipients

Emily Hume
PhD Viva Defence
University of Northumbria at Newcastle
Faculty of Health and Life Sciences

Aims

To investigate the feasibility and acceptability of a physical activity tele-coaching intervention in lung transplant recipients.

To investigate the short- and longer term efficacy of the intervention to optimise physical activity and HRQoL compared to usual care.

What are the gaps in the area..

- Despite the benefits of lung transplantation, physical activity levels remain low and limitations in physical functioning often persist.
- Following hospital discharge, rehabilitation services are not delivered routinely for lung transplant recipients in the UK.
- Research into rehabilitation interventions in lung transplant recipients is predominantly limited to small single arm studies, which lack a comparator group.
- There is a scarcity of research into interventions to enhance physical activity levels in lung transplant patients.

Systematic Review

- Both inpatient and outpatient exercise training appears to be beneficial for patients before and after lung transplantation .
- Exercise capacity and HRQoL were most commonly assessed using the 6MWT and SF-36 questionnaire, respectively.
- Most studies showed improvements in exercise capacity and HRQoL measures.
- Evidence was **significantly limited by the lack of RCTs**, making it challenging to differentiate the true effectiveness of exercise training from the natural recovery that often occurs following lung transplantation .

Case Control Study

- Lung transplant recipients in the UK demonstrate significantly lower daily physical activity (daily steps, movement intensity, time spent in light and moderate to vigorous intensity activity) compared to healthy individuals in the UK.

- Lung transplant recipients exhibited significantly lower HRQoL scores compared to healthy individuals, particularly in domains pertaining to physical functioning.

- These findings highlight the need to develop and evaluate interventions to enhance physical activity and HRQoL in lung transplant recipients, to facilitate recovery and long term outcomes following lung transplantation.

Validation of Pedometer

- The iChoice pedometer was shown to be accurate in chronic respiratory patients during a 6MWT at an average walking speed of 3.5 km/h.

- iChoice pedometer showed good accuracy during controlled treadmill walking at speeds of 3.0, 3.5 and 4.0 km/h in healthy individuals, however more caution should be taken at slower walking speeds (<3.0km/h).

- Good test ret-test reliability at all walking speeds (2.5 to 4.0 km/h).

Rationale for clinical intervention

Literature Review

- **Lack of research** into interventions to improve **physical activity** in lung transplant recipients
- Digital health and interventions incorporating behavioural modification strategies have shown promise in patients with chronic respiratory disease and pose interesting alternatives to exercise training in lung transplant recipients

Systematic review

Exercise training appears to be beneficial for lung transplant candidates and recipients.

However evidence is **limited by the lack of RCTs** and usual care arm.

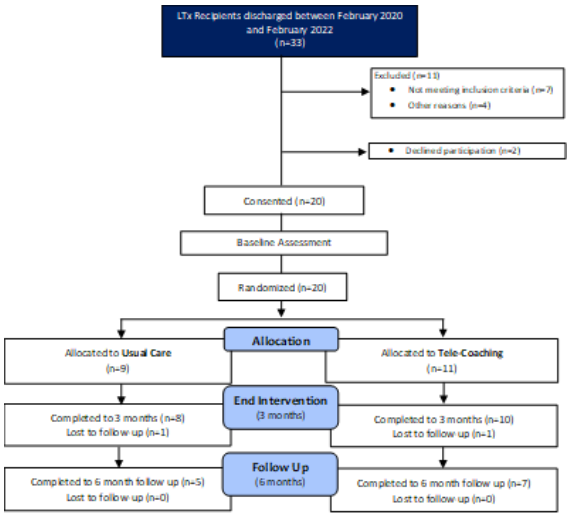
Case control

Lung transplant recipients are **significantly inactive** compared to healthy individuals in the UK, accompanied with **significantly lower HRQoL.**

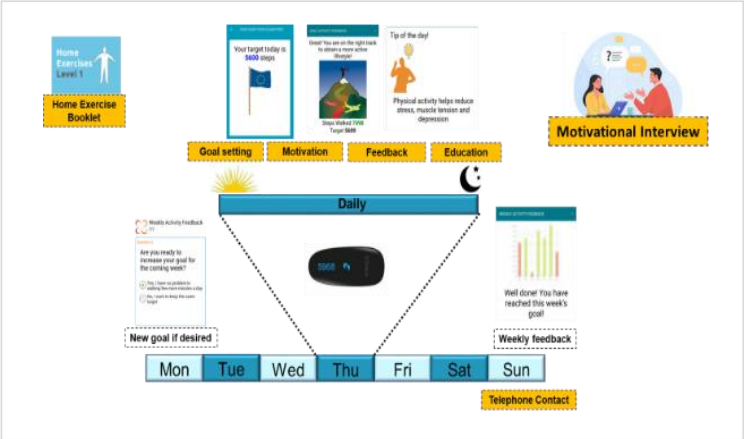
Clinical intervention

Feasibility of physical activity tele coaching intervention.

Efficacy of intervention to enhance physical activity and HRQoL compared to usual care.



Overview of Intervention Components



Main outcomes of intervention

Feasibility:

- Physical activity tele -coaching was **feasible** and **well accepted** by lung transplant recipients.
  - *Recruitment impacted by COVID -19, however uptake was high.*
  - *Good retention to 3 months*
  - *All patients willing to be randomised*
  - *Positive patient feedback from acceptability questionnaire*
  - *High usage of the pedometer over 3 months*

Efficacy:

- The usual care group demonstrated a degree of natural recovery in physical activity and HRQoL parameters, however tele-coaching appears to elicit greater improvements in physical activity measures and the physical component of HRQoL.

- The implementation of physical activity tele-coaching incorporating behavioural modification strategies resulted in better maintenance of daily steps, SF-36 physical component and anxiety scores at 6 months, compared to usual care.

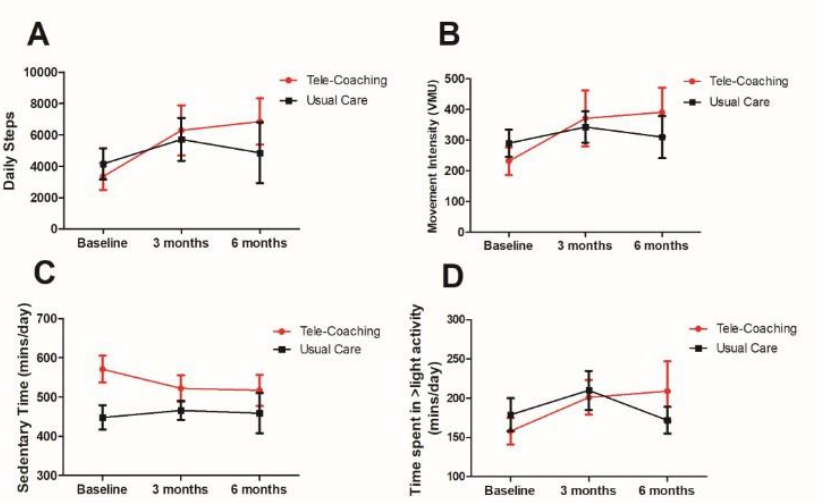

Original Paper

Chronic Respiratory Disease

Feasibility and acceptability of a physical activity behavioural modification tele-coaching intervention in lung transplant recipients

Emily Hume[1], Hazel Muse[2], Kirstie Wallace[2], Mick Wilkinson[1], Karen Heslop Marshall[2], Arun Nair[2], Stephen Clark[1,2] and Ioannis Vogiatzis[1]

Efficacy of tele-coaching intervention



Take home messages..

Northumbria University NEWCASTLE

- Lung transplant recipients are significantly inactive in daily life and exhibit limitations in HRQoL, which collectively could lead to poorer outcomes following lung transplantation.
- Physical activity tele-coaching incorporating behavioural modification strategies is a feasible and well-accepted intervention in lung transplant recipients, that offers a less resource intensive intervention to optimise physical activity, HRQoL and facilitate functional recovery following lung transplantation .
- The findings from this feasibility trial can inform a full scale RCT with adequate statistical power, to determine the true efficacy of physical activity tele-coaching compared to usual care.

Appendix 4a: Chapter 7 NHS Ethics Study Protocol

Study Title: Efficacy of physical activity tele-coaching to optimise daily physical activity levels in lung transplant recipients

Summary:

Lung transplantation is an established treatment for patients with end-stage lung disease. During the last two decades, considerable advances in organ preservation, surgical techniques, immunosuppression and antibiotic therapy have contributed to an improvement in postoperative survival. With increasing survival rates after lung transplantation, more attention has been directed towards the importance of improving exercise capacity, independent functioning and quality of life in these patients. However, despite near-normal lung function, exercise intolerance and reductions in quality of life often persist after transplantation. Based on objective accelerometry measurements, lung transplant recipients are markedly inactive in daily life compared to their healthy age-matched counterparts. Locomotor muscle weakness following extended hospital and intensive care unit stay, immunosuppressant medications, and the psychological effects of transplantation contribute to persisting physical inactivity.

Physical activity is a complex health behaviour that is modified by behavioural change interventions. Such interventions may combine the use of wearable monitors (i.e. step counters) with goal setting to increase daily physical activity. In patients with chronic obstructive pulmonary disease (COPD) use of a semi-automated tele-coaching intervention, consisting of a step-counter and a smartphone application, in combination with behavioural strategies (identification of barriers, goal setting, self-efficacy, motivation, self-monitoring and feedback) increases both daily physical activity levels and quality of life. Therefore, application of tele-coaching to lung transplant recipients, may improve surgery outcomes, functional capacity, and engagement with community-based pulmonary rehabilitation program, thereby reducing the risk of developing complications following transplantation.

Alongside physical activity promotion, incorporation of behavioural modification strategies are important in terms of reversing physical inactivity in patients with chronic lung diseases. These strategies address behavioural barriers such as low self-motivation and self-efficacy, and constitute an important component in the self-management of chronic diseases to improve long term engagement in activities of daily living.

The trial will assess the clinical efficacy of physical activity tele-coaching to enhance daily physical activity levels within a population at high risk for post-surgical complications. The intervention combines usual care with tele-coaching. Tele-coaching is designed to embed behavioural change and remote coaching to adhere to simple daily physical activity tasks. Cognitive behavioural therapy will be applied to all patients prior to hospital discharge to alleviate distress, and help them develop more adaptive cognitions, behaviours and active lifestyle choices.

This single-centre feasibility, randomised controlled trial will compare tele-coaching added to Usual Care and Usual Care in lung transplant recipients following discharge from hospital. We will record their activity levels (daily steps), functional capacity, aspects of health-related quality of life, engagement with pulmonary rehabilitation, frequency or re-hospitalisations and survival.

Background:

It has been observed that despite an almost complete restoration of lung function after transplant surgery, limitations in exercise capacity in the range of 40-60% of predicted normal values are commonly observed, even up to 1 year following the transplant (Mathur et al., 2004). These persisting limitations are predominantly owed to skeletal muscle abnormalities including muscle atrophy, weakness and increased fatigability, secondary to prolonged deconditioning (Reinsma et al., 2006).

In lung transplant recipients higher levels of physical activity have been associated with preserved muscle strength, higher exercise capacity and fewer self-reported limitations in physical functioning, indicating that increasing physical activity levels could enhance functional recovery after lung transplantation (Langer et al., 2009). Pulmonary rehabilitation (PR) constitutes an important component in the management of chronic lung disease and has proven effective at improving physical activity levels, functional capacity and quality of life (QOL) in patients post lung transplant (Langer et al., 2012). Despite the well documented benefits of traditional PR, these programs are underutilized by patients due to factors such as travel and transportation issues, lack of family support and perception of minimal benefit (Vogiatzis, Rochester, Spruit, Troosters, & Clini, 2016).

Accordingly, the efficacy of alternative physical activity modalities should be explored to overcome problems with provision and uptake of PR by lung transplant recipients. Remotely monitored (telehealth) home-based exercise or pedometer-based walking interventions constitute feasible alternatives to supervised outpatient rehabilitation interventions following the transplant phase and warrant further investigation (Langer, 2015). In stable patients with COPD use of a semi-automated tele-coaching intervention, consisting of a step-counter and a smartphone application, in combination with behavioural strategies (goal setting, contracting, feedback, consequences, and/or cues) increases daily physical activity levels (Demeyer et al., 2017). Therefore, tele-coaching may offer the possibility of decreasing the burden on clinicians, whilst providing a standardized intervention that can be used by lung transplant patients that find it difficult to attend pulmonary rehabilitation.

In lung transplant patients, the incorporation of physical activity as a consistent lifestyle behaviour may be hindered by factors such as reduced exercise tolerance, low motivation and self-efficacy. Behavioural modification strategies can be used to enhance the motivation of patients to address behavioural changes and adopt a physically active lifestyle (Dalle Grave, Calugi, Centis, El Ghoch, & Marchesini, 2011). A number of techniques can be used including education on the benefits of exercising, creating a “pros and cons” list, goal setting, self-monitoring, pacing activities and rating achievement/pleasure of activities, which all help to overcome barriers and improve confidence to regularly engage in daily physical activities. Therefore, application of these strategies prior to tele-coaching in lung transplant recipients may facilitate clinically meaningful improvement in physical activity levels and accelerate post-surgery recovery.

Research question:
Whether adding tele-coaching to usual care following lung transplantation is superior to usual care in terms of change in physical activity levels (daily steps), health related quality of life, anxiety and depression scores, hospitalisations and survival.

Aims:
The primary aim is to evaluate the additive value of tele-coaching to usual care compared with usual care alone by assessing the change in physical activity levels (steps/day) following 3 months of tele-coaching post-hospital discharge for lung transplant surgery.

Secondary aims include health related quality of life, anxiety and depression, adherence to TC, hospitalisations and survival.

Objectives:

1. Assess recruitment and retention of participants and their willingness to be randomised.
2. Examine patient adherence to the tele-coaching intervention.
3. Explore participants' reasons for participation, barriers and facilitators to physical activity and acceptability of the intervention programme and trial procedures.
4. Assess the acceptability and perceived utility of tele-coaching among patients and clinicians.
5. Explore barriers and facilitators to delivering / using tele-coaching

Project plan

Research design

A single-centre feasibility, parallel two group, randomised controlled trial, to evaluate the outcomes and mechanisms of tele-coaching added to usual care following lung transplantation compared to usual care. Patients will be randomised in a 1:1 ratio following stratification for functional capacity (6MWT) immediately prior to or soon after hospital discharge.

Study population

We will recruit 40 lung transplant patients.

Patients will be recruited from those referred and accepted for lung transplantation at the Freeman hospital. Potentially eligible patients will be identified by the cardiothoracic transplant team working within the Trust, who will provide initial information about the trial. Delegated investigators will confirm eligibility and discuss full details of the trial. Patients will be given time to consider participation in the trial before written informed consent is obtained. All patients who have been consented to participate will undergo a preliminary screening visit. Randomization will be performed after lung transplantation following a review of the study inclusion and exclusion criteria in participants who have been stepped down from intensive care unit.

Key inclusion criteria:

1) Patients who are accepted for single or double lung transplant with a primary diagnosis of ILD, COPD, Cystic Fibrosis, Bronchiectasis and Pulmonary Vascular Disease.
2) Able to provide informed consent
3) Aged 18 and above.
4) Patients who are able to speak and read English

Key exclusion criteria:

1) Severe post-transplant critical illness neuromyopathy.
2) Bilateral diaphragmatic weakness
3) Presence of any other significant disease or disorder which, in the opinion of the investigators, may either put the participant at risk because of participation in the study, or may influence the result of the study, or the participant's ability to participate in the study.

Planned interventions

Tele-coaching: 3 months of tele-coaching (TC) following hospital discharge from lung transplantation (consisting of a step-counter and a smartphone application) provided via a telehealth platform. TC includes: 1) A one-to-one interview exploring motivational factors, potential physical barriers, preferred and non-preferred activities and strategies to become more active. Patients develop a plan to increase physical activity with the interviewer, based on preferred and achievable activities; 2) A step counter providing direct feedback; 3) Smart phone with tele-coaching application, that provides the semi-automated tele-coaching module, using data collected by the step counter, automatically

transmitted to the smart phone via Bluetooth and simultaneously to the Linkcare web-based platform via 3/4G or Wifi. Patients' targets are automatically revised every 7 days, based on performance in the preceding week. The goal can be altered if required; 4) Booklet containing home exercises, which are available in 3 difficulties and consist of general strengthening and stretching exercises; 5) Weekly messages with activity proposals; 6) Telephone contacts triggered in the case of failure to transmit data or progress (Figure 2). Patients will be asked to wear the step counter during waking hours and to interact with the application on a daily basis. Patients will be required to open and review automated tasks that appear on the smartphone's display. Every evening, patients will be guided by an automated application task to send their step data to their smartphone (through Bluetooth) using an application previously downloaded on their smartphone. The application provides patients with daily goals, which are set for a week. Daily encouraging feedback messages will be displayed on the smartphone with texts and pictograms.

Whilst on the waiting list and during hospital stay post-surgery patients will be familiarised with the operation of the step counter and will be taught how to monitor their daily activity levels (daily/steps), how to transfer data from the step counter to the smart phone and to the platform and how to follow ques to adjust their daily step goals.

Behavioural modification strategies: During inpatient hospital stay or soon after discharge ALL patients will undergo 2-3 sessions of behavioural modification strategies to encourage and motivate patients to become more physically active. Strategies that will be used include; education on the benefits of exercise, creating a "pros and cons" list, goal setting, self-monitoring and rating achievement/pleasure of physical activities.

Control (Usual Care): This includes physical mobilization whilst in hospital at the high dependency unit. Following discharge usual care includes advice to maintain an active lifestyle.

Study outcomes

The primary outcome is to compare the efficacy of TC+UC to UC by assessing the change in physical activity (daily steps assessed by a validated in chronic lung disease patients' triaxial activity monitor: actigraph GT3X) at 3 months.

Secondary outcomes:

- Change in physical activity at 6 and 12 months
- Change in Hospital anxiety and depression score at 3, 6 and 12 months
- Change in health-related quality of life assessed by the SF-36 questionnaire at 3, 6 and 12 months
- Survival to 12 months post transplantation.
- Time to first hospitalisation and emergency department visit.
- Adherence to tele coaching assessed by the number of completed application tasks and presence of step count data.
- Acceptability of tele-coaching intervention

Assessment Procedures:

A set of outcome variables outlined below will be assessed at time points throughout the course of the study (outlined in figure 3 and table 1).

Daily Physical Activity:

Daily steps will be assessed over 7 days using a triaxial activity monitor (Actigraph GT3X; Actigraph LLC, Pensacola, FL, USA) validated in COPD, with at least 3 acceptable week days data, excluding days with less than 8 hours of wear time (Demeyer et al., 2017).

Functional Capacity:

The six-minute walk test (6MWT) will be performed according to the instructions of the American Thoracic Society, in order to assess the functional capacity of patients (i.e. the maximum distance walked by each patient on a 30-meter hospital corridor in 6 minutes). Patients will be instructed to walk from end to end at their own pace, whilst attempting to cover as much distance as possible in the allotted 6 minutes ("ATS Statement," 2002).

Health-related Quality of Life:

The Medical Outcomes 36-item Short-Form Health Survey (SF-36) will be used to assess health-related quality of life (HRQL). Additionally, anxiety and depression symptoms will be assessed using the Hospital Anxiety and Depression Score (HADS) questionnaire.

Patient Acceptability:

Acceptability of the tele-coaching intervention will be assessed using a self-administered, project tailored, validated questionnaire (Loeckx et al., 2018).

Statistical analysis

Statistical analyses will be supported by standard statistical software (e.g. SPSS, SAS) as required. The Shapiro-Wilk test will be used to check normal distribution of the data. A two-way ANCOVA will be employed to detect statistically significant differences in the following variables across the different time points between the two groups, whilst controlling for baseline differences in physical activity levels (daily steps): daily steps, 6-minute walk distance, SF-36 score and HADs score. This will be followed by appropriate post-hoc analysis. Descriptive statistics will be used to report survival to 52 weeks. Time to first hospitalisation and emergency department visit for each group will be evaluated by Kaplan-Meier survival curves and log-rank tests. The level of significance is set at $P<0.05$.

Safety Reporting

Any AE or SAE during the trial period will be recorded in the participant AE log.
Only events deemed by the investigator to be related to the study procedures will be reported. Expected events (such as hospital admissions related to a participant's lung transplant surgery) are not considered SAEs.

A Serious Adverse Event (SAE) is an untoward occurrence that:
a) results in death
b) is life-threatening
c) requires hospitalisation or prolongation of existing hospitalisation (non-related to a participant's lung transplant surgery)
d) results in persistent or significant disability or incapacity
e) consists of a congenital anomaly or birth defect
f) is otherwise considered medically significant by the investigator.

If it is deemed that the SAE is related to the study procedures, a report will be submitted to the REC using the Non-CTIMP safety report to REC form. These will be sent within 15 days of the CI becoming aware of the event.

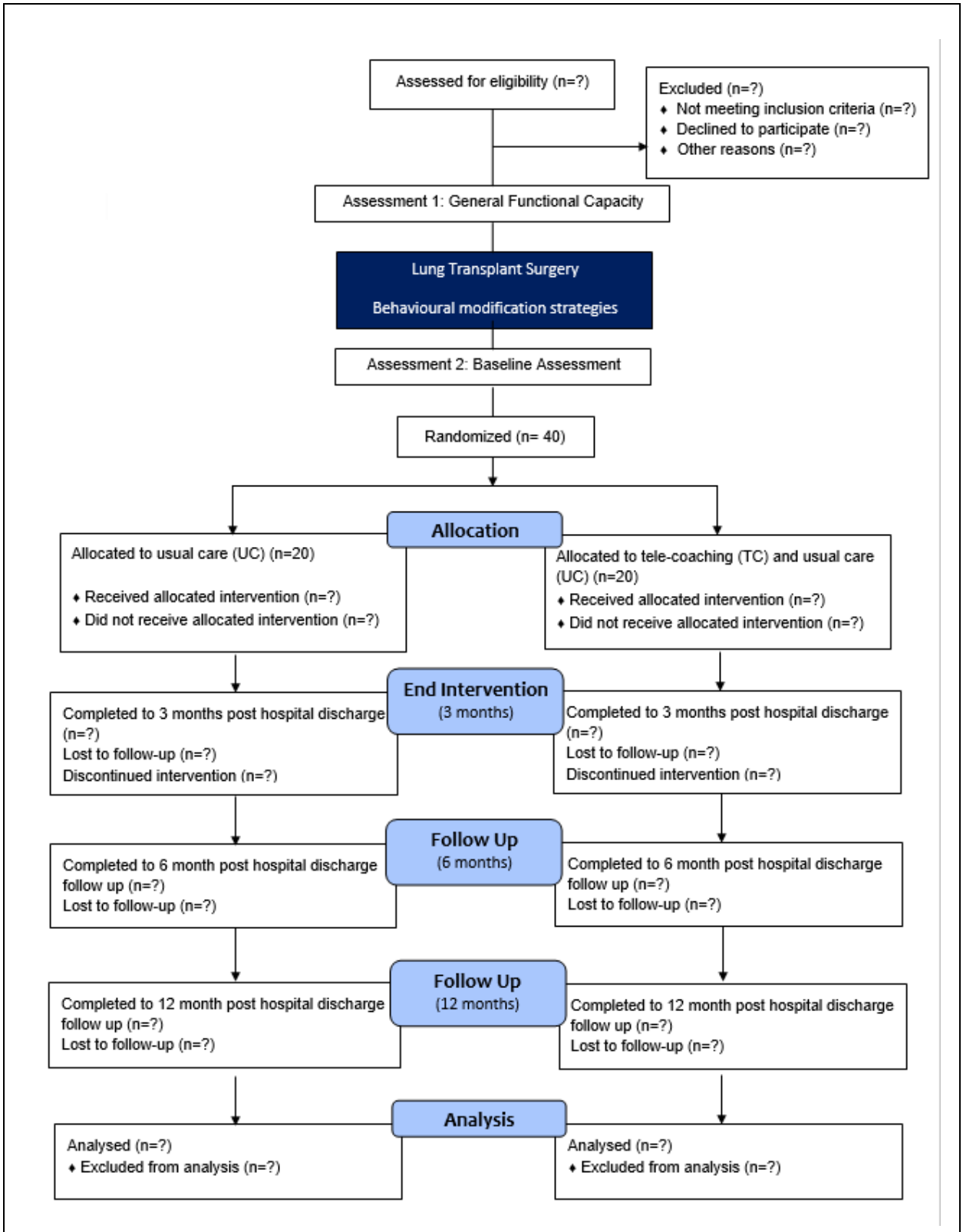


***Figure 1**: Consort Diagram – Patient allocation to the intervention arm combining tele-coaching (TC) and usual care (UC) compared to usual care (UC) over a 12 month period.*

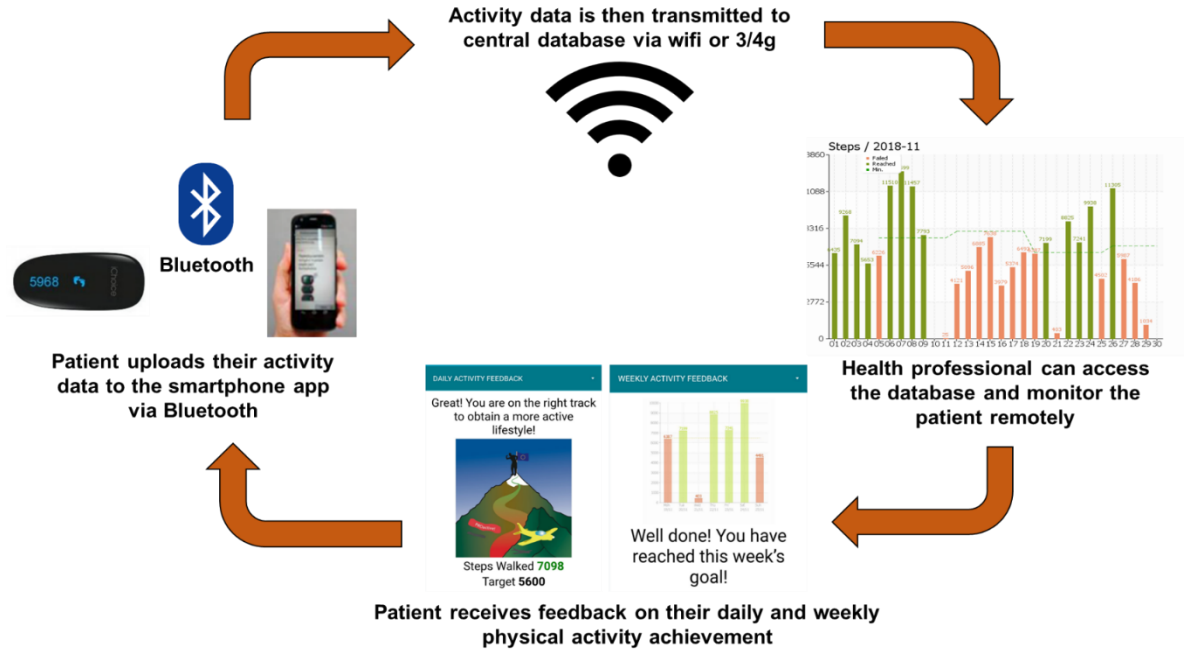


***Figure 2**: Conceptual representation of the tele-coaching intervention including step counter, a mobile phone application and the Linkcare tele-health platform.*

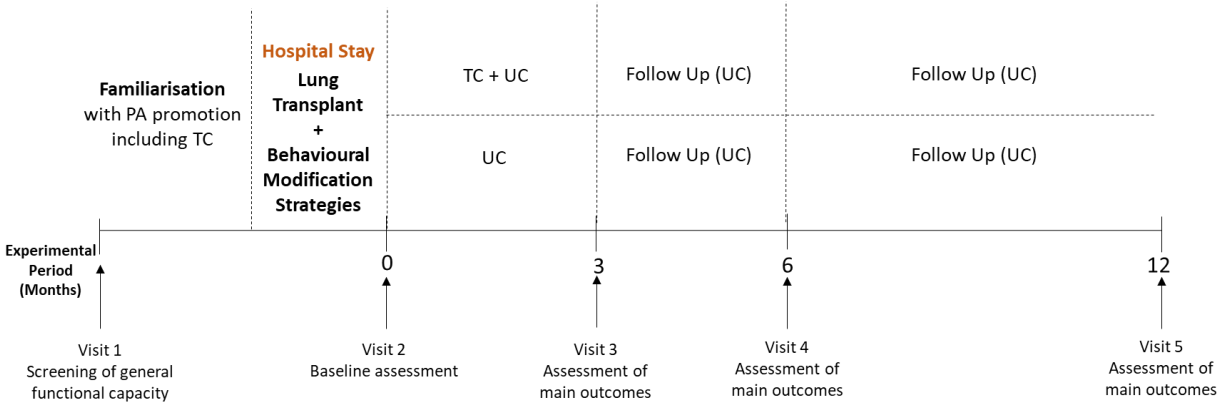


***Figure 3**: Study design outlining the time points where physical activity measurements will take place. PA: physical activity; TC: tele-coaching; UC: usual care.*

Table 1: Schedule of events

Event	V1 Baseline (Pre-Transplant or Post-transplant)	V2 Randomisation (Post-Transplant)	V3 3 months Post-randomisation	V4 6 months Post-randomisation	V5 12 months Post-randomisation
Inclusion/exclusion criteria	X	X			
Informed Consent	X	X			
Randomisation		X			
Medical History	X	X			
Train Participant in use of equipment	X	X			
Interview discussing favourite activities and acceptability		X	X		
Physical activity assessment	X	X	X	X	X
6 minute walk test (As per standard of care)	X	X			
Hospital anxiety and depression questionnaire	X	X	X	X	X
SF-36 questionnaire	X	X	X	X	X
SAE/AE Review		X	X	X	X
Validated questionnaires assessing patient acceptability and actual usage of the activity monitor			X		

References:

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2. Reinsma GD, ten Hacken NH, Grevink RG, van der Bij W, Koeter GH, van Weert E. Limiting factors of exercise performance 1 year after lung transplantation. The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation. 2006;25(11):1310-6.
3. Langer D, Gosselink R, Pitta F, Burtin C, Verleden G, Dupont L, et al. Physical activity in daily life 1 year after lung transplantation. The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation. 2009;28(6):572-8.
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6. Langer D. Rehabilitation in Patients before and after Lung Transplantation. Respiration; international review of thoracic diseases. 2015;89(5):353-62.
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8. Dalle Grave R, Calugi S, Centis E, El Ghoch M, Marchesini G. Cognitive-Behavioral Strategies to Increase the Adherence to Exercise in the Management of Obesity. Journal of Obesity. 2011;2011.
9. ATS Statement. American Journal of Respiratory and Critical Care Medicine. 2002;166(1):111-7.
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Appendix 4b: Chapter 7 Participant Information Sheet

The Newcastle upon Tyne Hospitals NHS
NHS Foundation Trust

The Freeman Hospital
Freeman Road
Newcastle upon Tyne
NE7 7DN

Northumbria University
NEWCASTLE

Faculty of Health and Life Sciences
Northumberland Building
Newcastle upon
Tyne
NE1 8ST

Participant Information Sheet
- Trial -

Title of Project: **Efficacy of physical activity tele-coaching to optimise daily physical activity levels in lung transplant recipients**

Researchers: Miss Emily Hume, *PhD Researcher*
Mrs Hazel Muse, *Cardiothoracic Transplant Co-ordinator*
Mr Stephen Clark, *Consultant Cardiac & Transplant Surgeon*
Professor Ioannis Vogiatzis, *Professor of Rehabilitation Sciences*
Dr Karen Heslop-Marshall, *Respiratory Nurse & CBT Specialist*
Dr Arun Nair, *Consultant in Respiratory Medicine and Lung Transplantation*

Introduction

You are being invited to take part in a research study entitled "Efficacy of physical activity tele-coaching to optimise daily physical activity levels in lung transplant recipients". Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of this study?

When discharged from hospital following lung transplant surgery, it is common to have reduced daily physical activity levels and muscle strength, due to the time spent inactive in hospital. This can adversely affect recovery of physical function, thereby compromising quality of life and psychological wellbeing. Therefore, it is important to regularly engage in physical activities that are enjoyable, to speed up recovery and restore health.

Tele-coaching is an intervention where coaching support is provided remotely to you at home using a step counter and an application that can be downloaded to your smartphone. In stable patients with lung disease, tele-coaching has been shown to improve engagement in physical activity and promote an active lifestyle. To date no study has looked at the effectiveness of tele-coaching in people that undergo lung transplant surgery.

Therefore, the purpose of this study is to assess whether tele-coaching can progressively and consistently increase your physical activity levels through remote coaching, and whether improved physical activity levels are associated with better health outcomes.

Why have I been chosen?

You have been chosen to take part in the study as you were referred for lung transplantation at Freeman Hospital. You are also able to provide written consent.

Do I have to take part?

There is no obligation to take part. If you choose to take part, you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part in this study, you are still free to withdraw at any time and without giving reason. Withdrawing from the study will not affect the healthcare that you receive or your legal rights.

Where will the study take place?

The study will take place in the Institute of Transplantation at Freeman Hospital, Newcastle upon Tyne Health Care Trust.

What will happen to me if I take part?

If interested in the study, a member of the research team will ask you to provide written consent. Once you have given consent, you will undergo some basic assessment measures including:

- A walk test where you will be asked to walk as far as you can in 6 minutes.
- Questionnaires which will assess your health-related quality of life and levels of anxiety and depression.
- Physical activity assessment where you will be asked to wear a small activity monitor around your waist for 7 days.

Before your transplant:

Whilst on the transplant waiting list, you will be provided with a step counter for 12 weeks and taught how to monitor and gradually increase your daily steps, to help you remain fit whilst waiting for lung transplant. We will help you download an application to your smartphone so that you can easily monitor your daily steps during this time.

Hospital stay:

During your hospital stay or soon after discharge following surgery, you will receive 2-3 behavioural modification sessions focused on increasing your motivation and confidence to regularly engage in physical activities.

After your transplant:

Following your lung transplant surgery, you will be randomly allocated to one of two groups; tele-coaching in addition to usual care **OR** usual care. The group you are allocated to will be selected using a computer programme providing a 50% chance of being assigned to tele-coaching plus usual care and 50% chance of being assigned to usual care. Neither the researcher, nor you will be able to decide which group you are assigned to.

Everyone in the study will receive usual care which includes physical mobilisation whilst in hospital at the high dependency unit. Following discharge usual care includes advice

to maintain an active lifestyle. Additionally, whilst in hospital or soon after discharge everyone will receive behavioural modification sessions and have physical activity levels and fitness assessed over the course of the study.

We will follow your progress for 12 months from the day that you are discharged from hospital. The aforementioned assessment measures (physical activity and questionnaires) will be repeated just before you are discharged from hospital or soon afterwards and at 3, 6 and 12 months following this, which we will try to coincide with your scheduled appointments at Freeman Hospital.

What will the Tele-Coaching intervention involve?

The tele-coaching intervention will consist of:

1) A one-to-one session where we will discuss your favourite activities, motivation issues and strategies to help you become more physically active.
2) A small monitor (step counter) that you will be asked to wear, which links to an application that is easily installed on to your smartphone.
3) A smartphone app which will provide you with feedback on your daily steps and provide individualised weekly goals, coaching and activity proposals to help you become more physically active.
4) A booklet containing exercises (general strengthening and stretching exercises) that you can use at home.

On a daily basis you will be guided by the app to send your step data wirelessly (through Bluetooth) to your smartphone so that the research team can follow your progress and advise you accordingly. If you have problems uploading your data, struggle to progress or experience technical problems, a member of the research team will contact you to discuss any issues with physical tasks, as well as provide feedback and encouragement to improve physical fitness.

If you are assigned to the tele-coaching group, the researcher will spend time with you and your family/friends to ensure that the app is installed correctly onto your smartphone and that you are happy with how to use the app and step counter. ***If you do not have your own smartphone or your smartphone is not compatible, then a smartphone will be provided to you by the research team.***

What are behavioural modification sessions?

These will include 2-3 one-to-one sessions where a number of techniques will be used to try and help you to increase your physical activity levels. These techniques include education on the benefits of exercise, goal setting, self-monitoring, pacing activities and rating achievement/pleasure of activities.

What are the possible disadvantages and risks of taking part?

If in the tele-coaching group, you may experience some muscle discomfort as you will be encouraged to do more activity than usual, however this will be progressive and is expected to recover very quickly.

What are the possible benefits of taking part?
Once you have undergone lung transplantation you will receive 2-3 behavioural modification sessions during hospital stay or soon afterwards, which should help you to overcome barriers to being active, so that you feel more confident and motivated to undertake physical activities. If you are assigned to the tele-coaching intervention you will be able to monitor your daily steps and receive feedback to try and improve each week.

The results of the study will help us to determine whether tele-coaching is beneficial to lung transplant recipients and therefore may help inform future practice for patients undergoing lung transplantation. Additionally, the information will be used to inform future studies and funding applications.

What will happen if I don't carry on with the study?

You are free to withdraw from the study at any time.

Will my taking part in this study be kept confidential?
During the study, we will collect information about your health and well-being. Your personal information such as your name and date of birth will be kept confidential and only available to the research team. The information you give will only be used in a way that cannot be traced back to you, and any personal information will be stored securely. With your permission, we will write to your GP to let him/her know that you are taking part in the study.

What will happen to the results of the research study?

The results of this study are likely to be published in scientific journals and discussed at scientific medical meetings so that others can learn from our findings. When we draw conclusions from the results of all participants, we will hold a patient forum to inform patients and their relatives on the outcomes of the study. No personally identifiable information will be published.

Who do I contact if I have a complaint?

If you wish to complain, or have any concerns about the study, please ask to speak to the Cardiothoracic Transplant Co-ordinator, Hazel Muse who will do her best to answer your questions. If you are still unhappy, you can complain formally using the normal NHS complaints channels.

You can contact the Patient Advice Liaison Service (PALS) who are completely independent:

Freephone: 0800 0320202 Email: northoftynepals@nhct.nhs.uk

Who is organising and funding the research?

The research is organised by Northumbria University and The Freeman Hospital, Newcastle Upon Tyne NHS Health Care Trust. The research is funded by Northumbria University, The Freeman Heart & Lung Transplant Association and The Transplant Association.

Northumbria University is the sponsor for this study based in the United Kingdom. We will be using information from you in order to undertake this study and will act as the data

controller for this study. This means that we are responsible for looking after your information and using it properly. Northumbria University will keep identifiable information about you for three years after the study has finished.

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally identifiable information possible. You can find out more about how we use your information at https://www.northumbria.ac.uk/about-us/leadership-governance/vice-chancellors-office/legal-services-team/gdpr/gdpr---privacy-notices/

Newcastle upon Tyne Healthcare Trust will collect information from you records for this research study in accordance with our instructions. Newcastle upon Tyne Healthcare Trust will use your name and contact details to contact you about the research study, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study. Individuals from Northumbria University and regulatory organisations may look at your medical and research records to check the accuracy of the research study. Newcastle upon Tyne Healthcare Trust will pass these details to Northumbria University along with the information collected from you. The only people in Northumbria University who will have access to information that identifies you will be people who need to contact you to conduct the study (members of the research team) or audit the data collection process. The people who analyse the information will not be able to identify you and will not be able to find out your name or contact details. Newcastle upon Tyne Healthcare Trust will keep identifiable information about you from this study for three years after the study has finished.

Who has reviewed the study?

Northumbria University Ethics Committee and the NHS Research Ethics Committee.

Contact for further information

Emily Hume
PhD Researcher
Northumbria University
Email: emily.c.hume@northumbria.ac.uk
Phone: 07827973856

Hazel Muse
Transplant Co-ordinator
Freeman Hospital
Email: hmuse@nhs.net
Phone: +44(0)191 244 8377

Appendix 4c: Chapter 7 Informed Consent Form

The Newcastle upon Tyne Hospitals NHS
NHS Foundation Trust
The Freeman Hospital
Freeman Road
Newcastle upon Tyne
NE7 7DN

Northumbria University
NEWCASTLE
Faculty of Health and Life Sciences
Northumberland Building
Newcastle upon
Tyne
NE1 8ST

Informed Consent Form
- Trial -

Project Title: **Efficacy of physical activity tele-coaching to optimise daily physical activity levels in lung transplant recipients**

Principle Investigator: Emily Hume

	please initial where applicable
I have carefully read and understood the Participant Information Sheet.	☐
I have had an opportunity to ask questions and discuss this study and I have received satisfactory answers.	☐
I understand I am free to withdraw from the study at any time, without having to give a reason for withdrawing, without my medical care or legal rights being affected and without prejudice. The information I have provided will still be used up to when I withdraw, but with my personal information removed so I cannot be identified, unless I state otherwise.	☐
I agree for the researcher to inform my General Practitioner of my participation in this study.	☐
I understand that relevant sections of my medical notes and data collected during the study may be looked at by members of the research team from Northumbria University, the NHS organisation and by regulatory authorities, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	☐
I understand that the information will be used in future reports, articles and presentations by the research team, however this will **not** include my personal information.	☐
I agree to take part in this study.	☐

Name of Participant	Date	Signature
Name of Person taking consent	Date	Signature

Appendix 4d: Chapter 7 GP Letter Template

GP

Newcastle Upon Tyne Hospitals NHS Foundation Trust

Freeman Hospital

PATIENT DETAILS

Freeman Road

Newcastle upon Tyne

NE7 7DN

DATE

Dear General Practitioner,

Your patient, named …… has agreed to take part in a research project entitled:

Efficacy of physical activity tele-coaching to optimise daily physical activity levels in lung transplant recipients

Ethical approval has been obtained. Reference: REC…….

We are looking into the effect of adding 3 months of semi-automated physical activity tele-coaching to usual care in patients that undergo lung transplantation. Patients will be randomly assigned to either the tele-coaching intervention plus usual care OR usual care following their lung transplant surgery. All patients in the study that undergo lung transplantation will recieve behavioural modification sessions focused on improving knowledge, motivation and confidence to increase physical activity levels. The trial will be conducted at Freeman Hospital and all aspects of the trial will be arranged by the research team and cardiothoracic transplant team.

The study will involve 5 assessment visits which we will try to coincide with the patient routine appointments at Freeman Hospital. The first visit will take place whilst on the waiting list and will involve some basic assessments including a 6-minute walk test, Hospital Anxiety and Depression Questionnaire (HADS) and Short Form (36) Health Survey (SF-36). Additionally, the patient will be given an accelerometer to assess baseline physical activity levels prior to surgery. These assessment measures will then be repeated prior to hospital discharge following transplantation, and at scheduled follow-up appointments at 3, 6 and 12 months following discharge.

Please contact us if you would like any further information about the study.

Kind regards,

Stephen Clark

Consultant Cardiothoracic Surgeon

Appendix 4e: REC Approval Letter

NHS
Health Research Authority
North East – Tyne & Wear South Research Ethics Committee

NHSBT Newcastle Blood Donor Centre
Holland Drive
Newcastle upon Tyne
NE2 4NQ

Telephone: 0207 1048084

Please note: This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

29 May 2019

Professor Ioannis Vogiatzis
Northumberland Building
Northumbria University
Newcastle upon Tyne
NE1 8ST

Dear Professor Vogiatzis

Study title:	**Efficacy of physical activity tele-coaching to optimise daily physical activity levels in lung transplant recipients**
REC reference:	**19/NE/0119**
Protocol number:	**1.0**
IRAS project ID:	**257479**

Thank you for your letter of 23 May 2019, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to make a request to postpone publication, please contact hra.studyregistration@nhs.net outlining the reasons for your request.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a **Favourable** ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for HRA and HCRW Approval (England and Wales)/ NHS permission for research is available in the Integrated Research Application System, at www.hra.nhs.uk or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact hra.studyregistration@nhs.net. The expectation is that all clinical trials will be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from the HRA. Guidance on where to register is provided on the HRA website.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS sites

The application did not include any non-NHS sites. If you decide to include a non-NHS site for this study, then you will need to contact the HRA regarding the procedure for assessment.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Insurance]		16 July 2018
GP/consultant information sheets or letters [GP Letter]	2.0	23 May 2019
Interview schedules or topic guides for participants	1.0	04 April 2019
IRAS Application Form [IRAS_Form_12042019]		12 April 2019
Other [Responses to REC]	1.0	23 May 2019
Other [Responses to HRA assessment]	1.0	23 May 2019
Participant consent form [Informed Consent Form]	1.0	13 February 2019
Participant information sheet (PIS) [PIS]	2.0	23 May 2019
Research protocol or project proposal [Study Protocol]	2.0	23 May 2019
Summary CV for Chief Investigator (CI) [Summary CV - Ioannis Vogiatzis]		05 March 2019
Summary CV for student [Research CV - Emily Hume]		05 March 2019
Validated questionnaire		

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study.

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

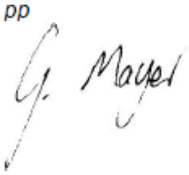
HRA Learning

We are pleased to welcome researchers and research staff to our HRA Learning Events and online learning opportunities– see details at: https://www.hra.nhs.uk/planning-and-improving-research/learning/

19/NE/0119	Please quote this number on all correspondence

With the Committee's best wishes for the success of this project.

Yours sincerely
pp



Mr Ian Campbell
Chair

Email:nrescommittee.northeast-tyneandwearsouth@nhs.net

Enclosures: 'After ethical review – guidance for researchers' SL-AR2

Copy to: Mrs Laura Hutchinson – Research Dept, University of Northumbria

Miss Emily Hume – PhD Researcher, University of Northumbria

Appendix 4f: HRA Approval Letter

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

Professor Ioannis Vogiatzis
Northumberland Building
Northumbria University
NE1 8ST

Email: hra.approval@nhs.net
Research-permissions@wales.nhs.uk

29 May 2019

Dear Professor Vogiatzis

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**Efficacy of physical activity tele-coaching to optimise daily physical activity levels in lung transplant recipients**
IRAS project ID:	**257479**
Protocol number:	**1.0**
REC reference:	**19/NE/0119**
Sponsor	**University of Northumbria at Newcastle**

I am pleased to confirm that HRA and Health and Care Research Wales (HCRW) Approval has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

Please now work with participating NHS organisations to confirm capacity and capability, in line with the instructions provided in the "Information to support study set up" section towards the end of this letter.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?
HRA and HCRW Approval does not apply to NHS/HSC organisations within Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report (including this letter) have been sent to the coordinating centre of each participating nation. The relevant national coordinating function/s will contact you as appropriate.

Please see IRAS Help for information on working with NHS/HSC organisations in Northern Ireland and Scotland.

How should I work with participating non-NHS organisations?
HRA and HCRW Approval does not apply to non-NHS organisations. You should work with your non-NHS organisations to obtain local agreement in accordance with their procedures.

What are my notification responsibilities during the study?

The document "*After Ethical Review – guidance for sponsors and investigators*", issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

Who should I contact for further information?
Please do not hesitate to contact me for assistance with this application. My contact details are below.

Your IRAS project ID is **257479**. Please quote this on all correspondence.

Yours sincerely,

Isobel Lyle
HRA Approvals Manager
Health Research Authority
NHSBT Newcastle Blood Donor Centre | Holland Drive | HRA Newcastle | NE2 4NQ
T. 0207 972 2496
E. isobel.lyle@nhs.net
W. www.hra.nhs.uk

Copy to: *Mrs Laura Hutchinson*

List of Documents

The final document set assessed and approved by HRA and HCRW Approval is listed below.

Document	*Version*	*Date*
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Insurance]		16 July 2018
GP/consultant information sheets or letters [GP Letter]	2.0	23 May 2019
HRA Schedule of Events [HRA assessed]	1.0	10 April 2019
HRA Statement of Activities [HRA assessed]	2.0	10 April 2019
Interview schedules or topic guides for participants	1.0	04 April 2019
IRAS Application Form [IRAS_Form_12042019]		12 April 2019
Other [Responses to REC]	1.0	23 May 2019
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Research protocol or project proposal [Study Protocol]	2.0	23 May 2019
Summary CV for Chief Investigator (CI) [Summary CV - Ioannis Vogiatzis]		05 March 2019
Summary CV for student [Research CV - Emily Hume]		05 March 2019
Validated questionnaire		

IRAS project ID	257479

Information to support study set up

The below provides all parties with information to support the arranging and confirming of capacity and capability with participating NHS organisations in England and Wales. This is intended to be an accurate reflection of the study at the time of issue of this letter.

Types of participating NHS organisation	Expectations related to confirmation of capacity and capability	Agreement to be used	Funding arrangements	Oversight expectations	HR Good Practice Resource Pack expectations
There is one site type for this study which will undertake all site activities. The Sponsor will conduct a Site Initiation Visit	Research activities should not commence at participating NHS organisations in England or Wales prior to their formal confirmation of capacity and capability to deliver the study.	A statement of activities has been submitted and the sponsor is not requesting and does not expect any other site agreement to be used.	The Sponsor has confirmed that no funds/resources/equipment, etc. are being provided to this organisation.	A local Principal Investigator is required and a named PI is in place.	Where arrangements are not already in place, research staff not employed by the NHS host organisation undertaking any of the research activities listed in the research application would be expected to obtain an honorary research contract from one NHS organisation (if university employed), followed by Letters of Access for subsequent organisations. This would be on the basis of a Research Passport (if university employed) or an NHS to NHS confirmation of pre-engagement checks letter (if NHS employed). These should confirm
					enhanced DBS checks, including appropriate barred list checks, and occupational health clearance

Other information to aid study set-up and delivery

This details any other information that may be helpful to sponsors and participating NHS organisations in England and Wales in study set-up.
The applicant has indicated that they do not intend to apply for inclusion on the NIHR CRN Portfolio

Appendix 4g: NHS Research Passport – Letter of Access

The Newcastle upon Tyne Hospitals
NHS Foundation Trust

Human Resources
Regent Point (Level 1)
Regent Farm Road
Gosforth
Newcastle upon Tyne
NE3 3HD

Tel: (0191) 233 6161

Our Ref: LOA/SM

9th June 2021

Sent by email only to: Emily.c.hume@northumbria.ac.uk
Miss Emily Hume

Dear Miss Hume

Letter of Access – Research Project No. 9258, 9672 and 8968

I confirm that approval has been given to an extension of your current **Letter of Access** which was due to expire on **31st August 2020**. Your new expiry date is **1st March 2022.**

Except where amended by this letter, your terms and conditions of employment are as detailed in your Principal Statement of Main Terms & Conditions of Employment.

If you have any queries, please contact me on 0191 28 26171.

Yours sincerely

S McArthur

Sarah McArthur
Human Resources Assistant

cc:

HR Representative	Paul.agnew@northumbria.ac.uk
NHS Representative	Karen.heslop3@nhs.net
Applicant Supervisor	Ioannis.vogiatzis@northumbria.ac.uk
R&D Representative	Nuth.researchpassports@nhs.net

1 of 1

Appendix 4h: Case report form for assessment visits (example of Visit 1 template)

9258 - Physical Activity Tele-coaching in Lung Transplant Recipients

Visit 1 - Baseline

Consent Checklist	Version Number: 1.0	Version Date: 28.03.19
Description	**Information**	**Confirmation** *(Initial & Date)*
Participant identifier:		
Date of provision of study Patient Information Sheet:		
Details of PIS provided	Title of PIS supplied: Version No.: Date of version:	
Details of consent received: *(As annotated on the Informed Consent Form)*	Date received: Person receiving consent:	
Details of ICF Provided	Title of ICF supplied: Version No.: Date of version:	
Has the subject been given the opportunity to read the PIS, ask questions and have them satisfactorily answered	☐ yes ☐ no	
A copy of the ICF was provided to the participant by: *(If posted, annotate confirmation of this and date of posting)*	Signature: Printed Name: Date:	

NB: Copy of PIS and Completed ICF should be stored in medical notes

Eligibility Checklist	Version Number: 1.0	Version Date: 28.03.19	
Date of eligibility assessment:			
Participant Identifier:			
Inclusion criteria		Met *(tick as appropriate)*	Not met *(tick as appropriate)*
1. Patients who are accepted for single or double lung transplant with a primary diagnosis of ILD, COPD, Cystic Fibrosis, Bronchiectasis and Pulmonary Vascular Disease			
2. Able to provide informed consent			
3. Aged 18 and above.			
4. Patients who are able to speak and read English			
Exclusion criteria:		Met *(tick as appropriate)*	Not met *(tick as appropriate)*
5. Severe post-transplant critical illness neuromyopathy			
6. Bilateral diaphragmatic weakness			
7. Presence of any other significant disease or disorder which, in the opinion of the investigators, may either put the participant at risk because of participation in the study, or may influence the result of the study, or the participant's ability to participate in the study			
This patient meets the inclusion criteria and none of the exclusion criteria and is therefore eligible for entry into the Lung Transplant Tele-Coaching study		Signature: Printed Name: Date:	

NB: Source data confirming any of the eligibility criterions should be stored in the patient notes

9258 - Physical Activity Tele-coaching in Lung Transplant Recipients

Visit 1 - Baseline

Participant Identifier:		
Date of Visit:		
Activity completed	*Yes* *(tick as appropriate)*	No *(tick as appropriate)*
Physical activity assessment		
Participant trained in use of equipment		
6 minute walk test (As per standard of care)		
Questionnaires completed?	*Yes* *(tick as appropriate)*	No *(tick as appropriate)*
Hospital anxiety and depression questionnaire		
SF-36 questionnaire		
Patient acceptability questionnaire		
Additional Notes:		
Completed by	Signature: Printed Name: Date:	

Appendix 4i: Chapter 5 and 6 Recruitment Poster

Participants WANTED

Healthy males and females aged 18-75.

To assess levels of **daily physical activity** and **muscular function**

Why?

We are looking to assess daily physical activity levels and muscle function in healthy individuals to compare with patients who have chronic lung disease.

What's involved?

2 visits to the laboratory (approx. 1 hr each), at least 7 days apart

- 7 day assessment of your daily physical activity levels
- Treadmill walking to assess pedometer accuracy and reliability
- Lung function assessment
- Muscle function assessments

What Next?

Northumbria University NEWCASTLE

For more information or if you are interested in taking part, please contact:
matthew.armstrong@northumbria.ac.uk or emily.c.hume@northumbria.ac.uk
0191 243 7018

This study has received ethical approval from Northumbria University (ref: 16428)

Appendix 4j: Chapter 5 and 6 Participant Information Sheet

Normative daily physical activity levels in healthy individuals living in the UK

PARTICIPANT INFORMATION SHEET

You have been invited to take part in a research study. Before you decide whether to participate, it is important for you to understand why the research is being carried out and what it will involve.

Please take time to read the information carefully, discuss it with others and ask any questions you may have.

1. What is the purpose of the study?

Physical activity can provide immediate and long-term health benefits for everyone. The World Health Organisation recommends that adults should aim to achieve 150 minutes of moderate or 75 minutes of vigorous activity per week. Reaching these guidelines can lead to improvements in many aspects of health including fitness, psychological well-being and reduce the risk of developing chronic conditions such as type 2 diabetes and cancer.

In patients with chronic lung disease, low levels of physical activity are common due to impaired muscle function and symptoms such as breathlessness and fatigue. This can adversely affect physical functioning, which can impact psychological wellbeing and quality of life. Given the multiple health benefits of improved physical activity, it is important to study levels of activity in this patient population. However, comparison of physical activity levels between patients with chronic lung disease and healthy individuals are lacking.

Therefore, this study aims to compare levels of physical activity and muscle function in healthy individuals with patients who have chronic lung disease. Alongside the assessment of daily physical activity and muscle function, the study will investigate the accuracy and reliability of a low cost, high street pedometer.

2. Who can take part?

You have been chosen because you are a healthy individual aged between 18-75 years. Before you can be enrolled onto this research study you must be able to meet the study

inclusion criteria which will be outlined by a member of the research team during enrolment/screening over telephone.

3. Do I have to take part?

No, there is no obligation to take part. If you decide to take part, you will be asked to sign a consent form. You are free at any time to withdraw from the study, and do not have to give a reason. If you decide to withdraw from the study, we will use the information we have gathered up to that point, but we will not include your personal information unless you give us permission to do so.

4. What would taking part involve?

If you chose to take part, you will need to attend Northumbria University on two separate occasions. Each visit should last no longer than 60 minutes. Before starting the study, a member of the research team will ask you to provide informed consent. You will also be asked to provide consent for video recording your lower limbs during treadmill walking, so that the number of steps you undertake can be visually counted.

During visit 1, we will collect some demographic information from you and ask you to fill in a short physical activity questionnaire. You will then undergo a lung function assessment which will involve breathing out into a tube as hard as you can several times, with recovery periods between each effort. A member of the research team will then check that you meet the study inclusion/exclusion criteria. Following this, you will perform an 8-minute walking protocol on a treadmill, which will involve walking for 2 minutes with no incline at 4 different speeds (2.5, 3, 3.5 and 4 km/h). Whilst walking you will be required to attach a pedometer to your waist and wrist, as well as an activity tracker around your waist. Throughout the walking protocol, a video camera will record the number of steps that you take, so that this number can be compared to the pedometer and activity tracker.

At the end of visit 1, you will be given the activity tracker to take home with you to measure your daily physical activity. This should be worn around your waist for 7 days during waking hours.

Following 7 days of wearing the activity tracker, you will be asked to return to the university. During visit 2, the walking protocol performed in visit 1 will be repeated again followed by measures of muscle function. These will include:

- A 30-second sit-to-stand test which will involve you standing and sitting from a chair as many times as you can in 30 seconds.
- A hand grip strength test which will involve you squeezing a device with your hand as hard as you can.
- A leg strength test where you will be sat on a chair with your ankle attached to a cuff and will be asked to push your leg out as hard as you can.

5. Are there any expense of payments involved?

Unfortunately, there are no payments involved for taking part in this research study and we are unable to reimburse you for any travel expenses incurred.

6. What are the possible benefits, disadvantages, risks or discomfort of taking part?

The findings of this study will help to understand how physical activity levels in chronic lung disease patients compare to those seen in healthy individuals in the UK. As well as this, we will gauge a better understanding of the accuracy and reliability of a pedometer for reporting daily steps.

You may feel a slight level of fatigue in your legs following the muscle function tests and treadmill walking exercise, however none of the speeds in our walking protocol are greater than every day walking speeds. No risk or discomfort will be felt while wearing either the pedometer or accelerometer.

7. How will my information be kept confidential? How will my data be stored?

All data collected in this study will be fully anonymised using numerical coding to maintain confidentiality. Only the researcher will have access to any identifiable information which will be kept separate from any data that can identify you. All data will be stored on a password protected computer in accordance with university guidelines and the Data Protection Act (2018). At no point will your personal information or data be revealed unless forced to do so by the courts.

8. What if I change my mind about taking part during the study? Can I withdraw?

If you do decide to take part, you are still free to withdraw at any time with no reason required. Inform the researcher as soon as possible (contact details provided below) and they will facilitate your withdrawal and discuss how you would like your data to be treated. We would like to use all your data collected up to this point to help with analysis, however if you would prefer your data not be used you may request it to be removed from the study. If you do complete the study, it may not be possible to withdraw your individual data after a month as the results may have already been published. However, as all data are anonymous, your individual data will not be identifiable in any way.

9. What will happen to the results of the study?

The results will be used in the formation of a PhD thesis that will be examined as part of a postgraduate degree. Occasionally, some results might be reported in a scientific journal or presented at a research conference, however the data will always remain anonymous unless specific consent is obtained beforehand. Findings may also be shared with other organisations/institutions that have been involved with the study. A summary of the study's findings can be provided to you if you request them from the research team.

10. Who is funding the study?

This study has not received any funding.

11. What happens if I have a complaint?

If you are unhappy about the way you have been approached or treated before, during or after your participation, the researcher should be contacted. However, if you feel this is not appropriate you should contact the Chair of ethics for Sport, Exercise and Rehabilitation: Dr Nick Neave, Email: nick.neave@northumbria.ac.uk

12. Who has reviewed this study?

This study has received full ethical approval from the organisation Northumbria University, Department of Sport, Exercise and Rehabilitation postgraduate ethics committee. If you require confirmation of this please contact the chair of ethics committee using the details below, please state the full title of this project and the chief investigator.

Dr Nick Neave
Faculty Director of Ethics and Chair of Faculty Research Ethics Committee
Northumbria University
Northumberland Road
Newcastle-upon-Tyne
NE1 8ST
nick.neave@northumbria.ac.uk

Contact Information

For further information please contact:

Emily Hume or Matthew Armstrong (Study Co-ordinators):

Email: emily.c.hume@northumbria.ac.uk or matthew.armstrong@northumbria.ac.uk

Professor Ioannis Vogiatzis (Chief Investigator)

Email: Ioannis.vogiatzis@northumbria.ac.uk

Department of Sport, Exercise and Rehabilitation, Northumbria University, Newcastle Upon Tyne

Appendix 4k: Chapter 5 and 6 Informed Consent Form

Northumbria University NEWCASTLE

Normative daily physical activity levels in healthy individuals living in the UK

Informed Consent Form

	please initial where applicable
I have carefully read and understood the Participant Information Sheet.	☐
I have had an opportunity to ask questions and discuss this study and I have received satisfactory answers.	☐
I understand that my participation is voluntary and I am free to withdraw from the study at any time, without having to give a reason for withdrawing. The information I have provided will still be used up to when I withdraw, but with my personal information removed so I cannot be identified, unless I state otherwise.	☐
I understand that the information will be used in future reports, articles and presentations by the research team, however this will **not** include my personal information.	☐
I understand that if I would like to receive feedback on the overall results of the study I must contact the researcher at: emily.c.hume@northumbria.ac.uk	☐
I agree to take part in the above study	☐

Name of Participant	Date	Signature

Name of Person taking consent	Date	Signature

Appendix 4l: Accelerometer instructions for participants

Activity Monitor - Participant Instructions

As part of this study, we wish to gather data on your physical activity. To do this we have provided you with an activity monitor which you should wear for **seven consecutive days**. The date and time you should remove the monitor will be completed by the researcher below:

Start wearing sensor:

Date: _____

Time: _____

Remove sensor:

Date: _____

Time: _____

Monitor Information

- There are no switches/buttons on the mobility monitor; it will remain 'on' for the full seven days.
- You do not need to press anything on the belt, just wear it from when you get up in the morning and then remove for bed. Also remove the belt when showering, bathing or swimming etc.

Attaching the Activity Monitor

- Wear the belt around your waist, with the red monitor positioned on your dominant hip (see photo below).

- The monitor can be worn directly on the skin or over a thin layer of clothes.

Returning the Mobility Monitor

After the seven days, please place the activity monitor in the provided pre-paid envelope and post back to us. Any problems or questions please contact**:** **Emily Hume: 07827973856 or** **emily.c.hume@northumbria.ac.uk**

Appendix 4m: SF-36 Questionnaire

RAND HEALTH

RAND > RAND Health > Surveys > RAND Medical Outcomes Study > 36-Item Short Form Survey (SF-36) >

36-Item Short Form Survey Instrument (SF-36)

RAND 36-Item Health Survey 1.0 Questionnaire Items

Choose one option for each questionnaire item.

1. In general, would you say your health is:

- 1 - Excellent
- 2 - Very good
- 3 - Good
- 4 - Fair
- 5 - Poor

---

2. **Compared to one year ago**, how would you rate your health in general **now**?

- 1 - Much better now than one year ago
- 2 - Somewhat better now than one year ago
- 3 - About the same
- 4 - Somewhat worse now than one year ago
- 5 - Much worse now than one year ago

The following items are about activities you might do during a typical day. Does **your health now limit you** in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
3. **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports	○ 1	○ 2	○ 3
4. **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	○ 1	○ 2	○ 3
5. Lifting or carrying groceries	○ 1	○ 2	○ 3
6. Climbing **several** flights of stairs	○ 1	○ 2	○ 3
7. Climbing **one** flight of stairs	○ 1	○ 2	○ 3
8. Bending, kneeling, or stooping	○ 1	○ 2	○ 3
9. Walking **more than a mile**	○ 1	○ 2	○ 3
10. Walking **several blocks**	○ 1	○ 2	○ 3
11. Walking **one block**	○ 1	○ 2	○ 3
12. Bathing or dressing yourself	○ 1	○ 2	○ 3

During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of your physical health**?

	Yes	No
13. Cut down the **amount of time** you spent on work or other activities	○ 1	○ 2
14. **Accomplished less** than you would like	○ 1	○ 2
15. Were limited in the **kind** of work or other activities	○ 1	○ 2
16. Had **difficulty** performing the work or other activities (for example, it took extra effort)	○ 1	○ 2

During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious)?

	Yes	No
17. Cut down the **amount of time** you spent on work or other activities	○ 1	○ 2
18. **Accomplished less** than you would like	○ 1	○ 2
19. Didn't do work or other activities as **carefully** as usual	○ 1	○ 2

20. During the **past 4 weeks**, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

- ○ 1 - Not at all
- ○ 2 - Slightly
- ○ 3 - Moderately
- ○ 4 - Quite a bit
- ○ 5 - Extremely

21. How much **bodily** pain have you had during the **past 4 weeks**?

- 1 - None
- 2 - Very mild
- 3 - Mild
- 4 - Moderate
- 5 - Severe
- 6 - Very severe

---

22. During the **past 4 weeks**, how much did **pain** interfere with your normal work (including both work outside the home and housework)?

- 1 - Not at all
- 2 - A little bit
- 3 - Moderately
- 4 - Quite a bit
- 5 - Extremely

These questions are about how you feel and how things have been with you **during the past 4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the **past 4 weeks**...

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
23. Did you feel full of pep?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
24. Have you been a very nervous person?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
25. Have you felt so down in the dumps that nothing could cheer you up?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
26. Have you felt calm and peaceful?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
27. Did you have a lot of energy?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
28. Have you felt downhearted and blue?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
29. Did you feel worn out?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
30. Have you been a happy person?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
31. Did you feel tired?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6

32. During the **past 4 weeks**, how much of the time has **your physical health or emotional problems** interfered with your social activities (like visiting with friends, relatives, etc.)?

- ○ 1 - All of the time
- ○ 2 - Most of the time
- ○ 3 - Some of the time
- ○ 4 - A little of the time
- ○ 5 - None of the time

How TRUE or FALSE is **each** of the following statements for you.

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
33. I seem to get sick a little easier than other people	○ 1	○ 2	○ 3	○ 4	○ 5
34. I am as healthy as anybody I know	○ 1	○ 2	○ 3	○ 4	○ 5
35. I expect my health to get worse	○ 1	○ 2	○ 3	○ 4	○ 5
36. My health is excellent	○ 1	○ 2	○ 3	○ 4	○ 5

Appendix 4n: Hospital Anxiety and Depression Scale

Hospital Anxiety and Depression Scale (HADS)

Patients are asked to choose one response from the four given for each interview. They should give an immediate response and be dissuaded from thinking too long about their answers. The questions relating to anxiety are marked "A", and to depression "D". The score for each answer is given in the right column. Instruct the patient to answer how it currently describes their feelings.

A	**I feel tense or 'wound up':**	
	Most of the time	3
	A lot of the time	2
	From time to time, occasionally	1
	Not at all	0

D	**I still enjoy the things I used to enjoy:**	
	Definitely as much	0
	Not quite so much	1
	Only a little	2
	Hardly at all	3

A	**I get a sort of frightened feeling as if something awful is about to happen:**	
	Very definitely and quite badly	3
	Yes, but not too badly	2
	A little, but it doesn't worry me	1
	Not at all	0

D	**I can laugh and see the funny side of things:**	
	As much as I always could	0
	Not quite so much now	1
	Definitely not so much now	2
	Not at all	3

A	**Worrying thoughts go through my mind:**	
	A great deal of the time	3
	A lot of the time	2
	From time to time, but not too often	1
	Only occasionally	0

D	**I feel cheerful:**	
	Not at all	3
	Not often	2
	Sometimes	1
	Most of the time	0

A	I can sit at ease and feel relaxed:	
	Definitely	0
	Usually	1
	Not Often	2
	Not at all	3

D	I feel as if I am slowed down:	
	Nearly all the time	3
	Very often	2
	Sometimes	1
	Not at all	0

A	I get a sort of frightened feeling like 'butterflies' in the stomach:	
	Not at all	0
	Occasionally	1
	Quite Often	2
	Very Often	3

D	I have lost interest in my appearance:	
	Definitely	3
	I don't take as much care as I should	2
	I may not take quite as much care	1
	I take just as much care as ever	0

A	I feel restless as I have to be on the move:	
	Very much indeed	3
	Quite a lot	2
	Not very much	1
	Not at all	0

D	I look forward with enjoyment to things:	
	As much as I ever did	0
	Rather less than I used to	1
	Definitely less than I used to	2
	Hardly at all	3

A	I get sudden feelings of panic:	
	Very often indeed	3
	Quite often	2
	Not very often	1
	Not at all	0

D	I can enjoy a good book or radio or TV program:	
	Often	0
	Sometimes	1
	Not often	2
	Very seldom	3

Appendix 4o: C-PPAC Instrument

Clinical Visit Of Proactive Physical Activity In COPD (C-PPAC)

INSTRUCTIONS TO PATIENTS:

Patients with chronic lung disease like you often report that they have problems during physical activity. By physical activity, we mean all activities that require movement of your body. Examples are household activities, walking, going to work, or getting dressed. However, please consider all activities you do, and not only these examples. We would like to know how you experienced your physical activity IN THE PAST 7 DAYS.

Please select the box next to the response that best applies to you IN THE PAST 7 DAYS.

There are no wrong answers. We very much value your response.

	Difficulty score	Amount score
In the past 7 days, how much walking did you do outside?		
☐ None at all		0
☐ A little bit (about 10 minutes every day)		1
☐ Some (about 30 minutes every day)		2
☐ A lot (about 1 hour every day)		3
☐ A great deal (more than 1 hour every day)		3
In the past 7 days, how many chores did you do outside the house? Some examples are gardening, taking the rubbish out, or doing small errands.		
☐ None at all		0
☐ A few		1
☐ Some		2
☐ A lot		3
☐ A large amount		4
In the past 7 days, how much difficulty did you have getting dressed?		
☐ None at all	4	
☐ A little bit	3	
☐ Some	2	
☐ A lot	1	
☐ A great deal	0	
In the past 7 days, how much difficulty did you have getting out and about?		
☐ None at all	4	
☐ A little bit	3	
☐ Some	2	
☐ A lot	1	
☐ A great deal	0	

In the past 7 days, how often did you avoid doing activities because of your lung problems?

- ☐ Not at all 4
- ☐ Rarely 3
- ☐ Sometimes 2
- ☐ Frequently 1
- ☐ All the time 0

In the past 7 days, how breathless were you in general during your activities?

- ☐ Not at all 4
- ☐ A little bit 3
- ☐ Moderately 2
- ☐ Very 1
- ☐ Extremely 0

In the past 7 days, how often did you lack physical strength to do things because of your lung problems?

- ☐ Not at all 4
- ☐ Rarely 3
- ☐ Sometimes 2
- ☐ Frequently 1
- ☐ All the time 0

In the past 7 days, how tired were you in general during your activities?

- ☐ Not at all 4
- ☐ A little bit 3
- ☐ Moderately 2
- ☐ Very 1
- ☐ Extremely 0

In the past 7 days, how often did you have to take breaks during your physical activities?

- ☐ Not at all 4
- ☐ Rarely 3
- ☐ Sometimes 2
- ☐ Frequently 1
- ☐ All the time 0

In the past 7 days, how breathless were you when walkin on level ground indoors and outdoors?

- ☐ Not at all 4
- ☐ A little bit 3
- ☐ Moderately 2
- ☐ Very 1

☐	Extremely	0

In the past 7 days, how much time did you need to recover from your physical activities?

☐	None at all	4
☐	A little bit	3
☐	Some	2
☐	A lot	1
☐	A great deal	0

In the past 7 days, did you need to consider your lung problems when you planned your activities because of your lung problems? Examples are a trip out, an appointment or expecting visitors.

☐	No	4
☐	A little bit	3
☐	Sometimes	2
☐	A lot	1
☐	A great deal	0

EPS (weekly median)

Weekly steps score

	Measured by Actigraph	Measured by Dynaport	
☐ 0	<1000	<1500	0
☐ 1	1000-2000	1500-2500	1
☐ 2	2000-4000	2500-4500	2
☐ 3	4000-6000	4500-6500	3
☐ 4	>6000	>6500	4

Weekly VMU score

	Measured by Actigraph	Measured by Dynaport	
☐ 0	<100	<60	0
☐ 1	100-200	60-130	1
☐ 2	200-300	130-210	2
☐ 3	300-500	210-370	3
☐ 4	>500	>370	4

Amount scores (sum above):

Difficulty scores (sum above):		
Total scores (sum above):		

Appendix 7a: Project specific patient acceptability questionnaire

Patient satisfaction form

During the last 3 months you have participated in the physical activity coaching program. This included a tele-coaching system developed for this specific intervention. By taking part in this study you are now well placed to evaluate this coaching program. Your experiences during the intervention can help us to further improve this coaching program in the future.

Therefore, we would like to have your opinion about the intervention and we kindly ask you to take some time to complete this patient satisfaction form. Your input is highly appreciated!

How much did you enjoy taking part in this activity program?

- ☐ I liked it a lot
- ☐ I liked it
- ☐ Neutral
- ☐ I did not like it
- ☐ No opinion

Did the intervention help you to increase your physical activity levels?

- ☐ Yes, it helped me it a lot
- ☐ Yes, a little bit
- ☐ Not noticeable
- ☐ No, not at all
- ☐ No, it discouraged me

How did you experience the weekly increases proposed during the intervention?

- ☐ Much too low
- ☐ A little bit too low
- ☐ Reasonable
- ☐ A little bit too high
- ☐ Much too high

How was it for you to work with the smartphone intervention?

- ☐ Very easy
- ☐ Easy
- ☐ Not easy, but I managed
- ☐ Difficult
- ☐ Very difficult

What was for you the most important part of the intervention?

- ☐ The step counter
- ☐ The application on the smartphone
- ☐ The telephone contacts with the study team
- ☐ The home exercise booklet
- ☐ Other (Please specify) ……..

How useful did you find the following parts of the intervention for increasing your physical activity? (please circle a number)

1) The **step counter**

0 1 2 3 4 5 6 7 8 9 10

Not useful at all **Very useful**

2) **Daily activity goal** displayed on your smartphone each day

0 1 2 3 4 5 6 7 8 9 10

Not useful at all **Very useful**

3) **Activity feedback** in the evening (display of text about your achievement together with picture)

0 1 2 3 4 5 6 7 8 9 10

Not useful at all **Very useful**

4) **Graph** displaying your achievements (steps) of the week

0 1 2 3 4 5 6 7 8 9 10

Not useful at all **Very useful**

5) **Tip of the day**

0 1 2 3 4 5 6 7 8 9 10

Not useful at all **Very useful**

6) **Phone calls** with the study team?

0 1 2 3 4 5 6 7 8 9 10

Not useful at all **Very useful**

7) **Home exercise booklet**

0 1 2 3 4 5 6 7 8 9 10

Not useful at all **Very useful**

How often (in general) did you perform the following actions?

	Several times per day	Once per day	Sometimes, but not everyday	Once or twice per week	Never
Look at your step counter	☐	☐	☐	☐	☐
Do any home exercises	☐	☐	☐	☐	☐

How would you rate the graphics used in the Linkcare application?

- ☐ Very helpful and intuitive/supportive
- ☐ Helpful and intuitive/supportive
- ☐ Neutral
- ☐ Poor, not intuitive/supportive
- ☐ Very poor, not intuitive/supportive at all

Comment:

……

……

……

……

How would you rate the interaction between you and the app?

- ☐ Very quick
- ☐ Quick
- ☐ Neutral
- ☐ Slow
- ☐ Very slow

Which part of the intervention would you be willing to use further in the future?

- ☐ Nothing
- ☐ The step counter
- ☐ The step counter and mobile phone providing feedback messages
- ☐ The step counter, mobile phone and the contact with the study team
- ☐ The whole intervention

Would you like to add a comment?

……

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Thank you for your time!

Appendix 7b: Individual changes in daily steps and movement intensity

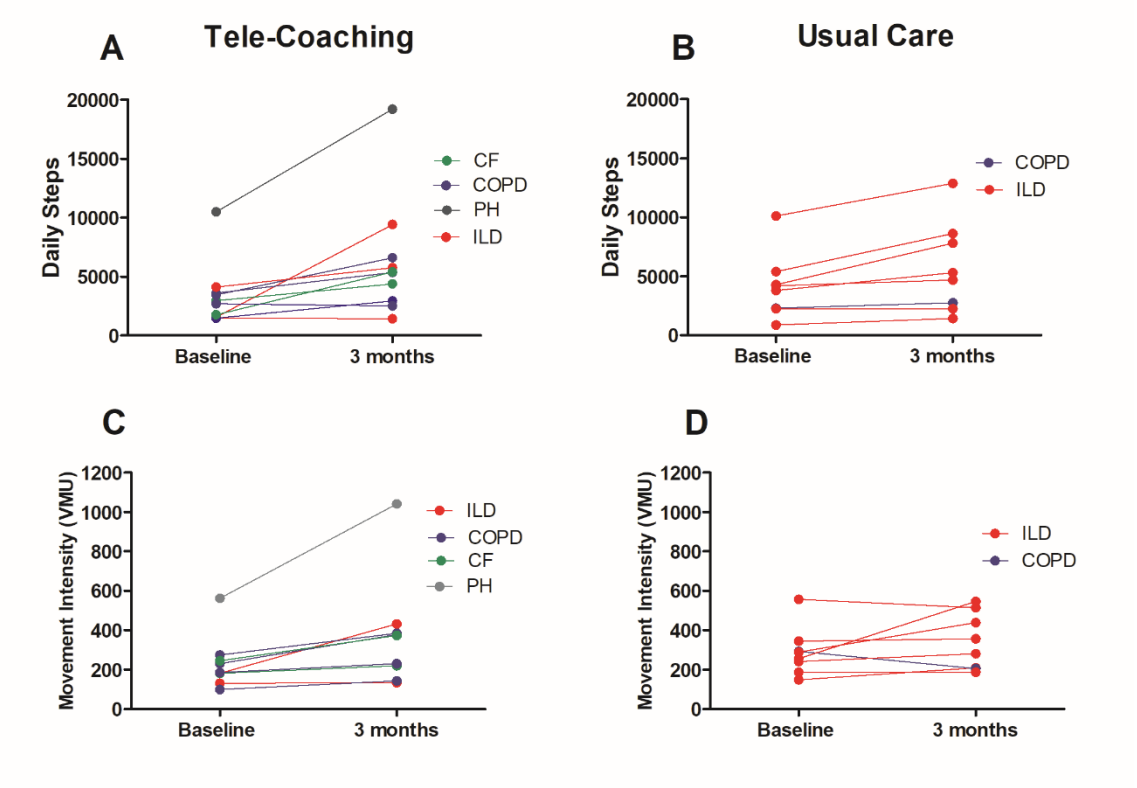

Figure 9-1: Individual changes in steps/day and movement intensity in the tele-coaching (A&C) and usual care (B&D) groups from baseline to 3 months.

Appendix 7c: SF-36 Scores for all domains

Table 9-1: SF-36 individual domain scores in the tele-coaching and usual care group at Baseline and 3 months.

Outcome	Group	Baseline (T1) (n=10)	3 months (T2) (n=8)
SF-36 Individual Domains			
Physical Functioning	TC	43 ± 26	61 ± 24*
	UC	49 ± 18	63 ± 28
Role Physical	TC	22 ± 35	61 ± 42*
	UC	28 ± 34	41 ± 46
Role Emotional	TC	81 ± 31	81 ± 34
	UC	58 ± 43	62 ± 42
Vitality	TC	58 ± 19	61 ± 32
	UC	53 ± 19	61 ± 24
Mental Health	TC	80 ± 18	80 ± 20
	UC	84 ± 14	82 ± 20
Social Functioning	TC	61 ± 37	69 ± 38
	UC	48 ± 27	63 ± 36
Bodily Pain	TC	54 ± 29	72 ± 26
	UC	50 ± 19	54 ± 24
General Health	TC	51 ± 30	53 ± 23
	UC	56 ± 20	62 ± 22

*Values are mean ± SD. * = statistically significant change from baseline (P<0.05)*

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