Gait speed and prognosis in idiopathic pulmonary fibrosis

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Declaration of originality

The studies described in this thesis were performed between 2015 and 2017 during my PhD candidature at Imperial College London. I confirm that the work in it is my own, and I take full responsibility for the analysis and presentation of the data. This thesis was written wholly by me with the guidance of my supervisors Dr William Man, Dr Matthew Maddocks, Professor Paul Cullinan and Professor Toby Maher.

Dr Jane Canavan (Research Physiologist), Ms. Sarah Jones (Research Physiotherapist), Ms Suhani Patel (Research Physiologist) and Ms. Ruth Barker (Research Physiotherapist) helped with the recruitment of participants and / or collection of data for the studies presented in Chapters 3 and 4 and 6.

The pulmonary rehabilitation teams at the Royal Brompton and Harefield NHS Foundation Trust and Guy's and St. Thomas' NHS Foundation Trust provided the intervention described in Chapters 4 and 6. Team members also identified potential participants and helped with the clinical data collection for these studies.

Mr. Winston Banya provided help with the statistical analysis of the data presented in Chapters 5 and 6.

All sources of information have been referenced within the text. The work in this thesis has not previously been presented for assessment in a higher degree application.

Claire Marie Nolan

29th March 2018

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Abstract

Background: Idiopathic Pulmonary Fibrosis (IPF) is a progressive disease of the lungs with a median life expectancy of three years. Surrogate endpoints that can predict adverse outcomes are required to help develop and evaluate new treatments for IPF, but existing options have limitations. The four metre gait speed (4MGS) test measures usual walking speed, which in older people is a consistently strong predictor of adverse outcomes and has been described as a 'marker of global well-being'.

Aims: To evaluate the reliability, concurrent validity, responsiveness, minimum clinically important difference (MCID) and predictive validity of the 4MGS test in patients with IPF.

Methods and results: 4MGS was reliable (n=46) and showed concurrent validity with established IPF measures in two independent cohorts (n=65 and n=62). Stratification according to slow gait speed phenotype (4MGS <0.80ms^{-1}) identified significant impairments in exercise capacity, dyspnoea, quality of life and prognostic index. The 4MGS test was responsive to pulmonary rehabilitation (n=90) with an MCID of 0.08 to 0.18ms^{-1} calculated using distribution- and anchor-based methods. In a separate cohort of patients newly diagnosed with IPF (n=130), 4MGS was associated with a significantly increased risk of all-cause mortality (hazard ratio (HR) (95% confidence interval (95% CI)): 0.03 (0.01 to 0.25) and non-elective hospitalisation (HR (95% CI): 0.03 (0.01 to 0.18) at one year. Multivariable models that included 4MGS had higher discrimination for predicting adverse outcomes (c-statistic: 0.78-0.81) than established prognostic indices (c-statistic: 0.65-0.73). Improvement in 4MGS following rehabilitation was associated with longer survival but not time to non-elective hospitalisation. A 4MGS change cut-point of ≥0.09ms^{-1} provided the best sensitivity and specificity to identify survival at one year.

Conclusion: The 4MGS test is a reliable, valid and responsive objective measure of physical performance that has prognostic ability and potential utility as a simple assessment tool and surrogate endpoint in IPF.

Awards arising from this thesis

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  Abstract entitled

  - *'Four metre gait speed predicts mortality in idiopathic pulmonary fibrosis'*

- 2018: **American Thoracic Society Pulmonary Rehabilitation Assembly Scholarship**

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  - *'Improvement in gait speed with pulmonary rehabilitation is associated with increased survival in idiopathic pulmonary fibrosis'*
  - *'Physical frailty in idiopathic pulmonary fibrosis'*

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  Abstract entitled 'Improvement in gait speed with pulmonary rehabilitation is associated with increased survival in idiopathic pulmonary fibrosis' selected for oral presentation as part of the best abstracts submitted to the Pulmonary Rehabilitation Assembly

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- **Nolan CM**, Maddocks M, Delogu V et al., *Responsiveness and MCID of the 4MGS in fibrotic interstitial lung disease (thematic poster)* ATS (2017).

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Dedication

To my parents, Mary and Tom, for their life-long support and encouragement.

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Abbreviations list

4MGS: Four metre gait speed

6MWT: Six minute walk test

ABOT: Ambulatory oxygen therapy

ARDS: Acute Respiratory Distress Syndrome

ATAQ-IPF: A Tool to Assess Quality of life in IPF

BMI: Body mass index:

CI: Confidence interval

COPD: Chronic obstructive pulmonary disease

CPI: Composite Physiologic Index

CRQ: Chronic Respiratory Questionnaire

CRQ-IA: Chronic Respiratory Questionnaire interviewer-administered

CRQ-SA: Chronic Respiratory Questionnaire self-administered

DL_{CO}: Diffusing capacity of the lung for carbon monoxide

ECCS: European Community for Coal and Steel

ERS: European Respiratory Society

FEV_1: Forced expiratory volume in one second

FEV_1/FVC: Ratio of forced expiratory volume in one second and forced vital capacity

F-FDG: 2-fluoro-2-deoxy-D-glucose

FVC: Forced vital capacity

GAP index: Gender Age and lung Physiology index

GRCQ: Global Rating of Change Questionnaire

HR: Hazard ratio

HRCT: High resolution computed tomography

ICC: Intra class correlation coefficients

ILD: Interstitial lung disease

IPF: Idiopathic pulmonary fibrosis

ISW: Incremental shuttle walk test

KBILD: King's Brief Interstitial Lung Disease questionnaire

LTOT: Long-term oxygen therapy

MCID: Minimum clinically important difference

MDC_{95}: Minimal detectable change at 95% confidence

METS: Metabolic equivalents

mMRC: Modified MRC Dyspneoa scale / score

MRC Dyspnoea Scale / Score: Medical Research Council Dyspnoea Scale / Score

NICE: National Institute for Health and Care Excellence

NSIP: Non-Specific Interstitial Pneumonia

OR: Odds ratio

PET: Positron Emission Tomography

PR: Pulmonary rehabilitation

PROMs: Patient reported outcome measures

Q: Quartile

QMVC: Quadriceps maximum voluntary contraction

RR: Relative risk

ROC: Receiver Operating Characteristic

SD: Standard deviation

SEM: Standard error of measurement

SF-36: Short-Form 36

SGRQ: St. George's Respiratory Questionnaire

SGRQ-I: St. George's Respiratory Questionnaire – IPF-specific version

SPPB: Short Physical Performance Battery

SUV: Standardised uptake value

UIP: Usual interstitial pneumonia

Chapter 1 : Introduction

1.1. Idiopathic pulmonary fibrosis (IPF)

Idiopathic pulmonary fibrosis is defined as 'a chronic, progressive fibrotic interstitial lung disease (ILD) of unknown origin' and is the most common idiopathic interstitial pneumonia (1). Although the specific cause of IPF is yet to be determined, it has been suggested that the disease occurs as a result of aberrant wound healing following injury to the alveolar epithelium in genetically susceptible individuals (2). The occurrence of IPF is on the rise worldwide, but due to heterogeneous methodologies employed, the complexities of establishing a diagnosis, and inadequate international disease classification codes, there is uncertainty about its true incidence, prevalence and mortality rates (3-8). Current estimates for the incidence of IPF lie between three to nine per 100,000 person years in North America (5, 9) and Europe, with lower rates estimated in East Asia and South America (9). The most recent prevalence estimates in the United State are between 14 to 28 cases per 100,000 population (5, 10) and 59 per 100,000 person years (11), and, in Europe one to 23 cases per 100,000 population (10).

IPF has a heterogeneous disease course with three distinct phenotypes: a stable or slowly progressive course; a rapidly progressive course; or a course with repeated acute exacerbations (12). IPF is more frequently seen in older men, smokers, individuals exposed to workplace dusts e.g. wood, or metal, and in those with a familial history; up to 5% of cases occur in individuals with a first degree relative who has IPF (13-15). Comorbidities commonly associated with IPF include coronary artery disease; venous thromboembolic disease; lung cancer; emphysema; obstructive sleep apnoea; pulmonary hypertension and gastro-oesophageal reflux (16-22). Consequently patients with IPF experience a high symptom burden, with dyspnoea, cough and a progressive decline in physical function that causes anxiety, depression and reduces health-related quality of life (18, 23). Accordingly, non-pharmacological management strategies, such as pulmonary rehabilitation (PR) –

an exercise and education programme for people with chronic lung disease - form an integral component of IPF care (1, 24, 25). Indeed, the National Institute for Health and Care Excellence 'IPF in adults: diagnosis and management' guideline states that all people with IPF should be referred to PR at the time of diagnosis (1).

Prognosis for patients with IPF is poor with an untreated median survival time between two to five years from diagnosis (26-30). Until recently, IPF was considered untreatable with lung transplantation the only option for selected patients with severe disease (31, 32). Since 2010, the results of five randomised, double blind, placebo-controlled trials have led to the licensing of two anti-fibrotic drugs - pirfenidone and nintendanib - that slow the decline in pulmonary function, specifically forced vital capacity (FVC – the primary endpoint) at one year in study participants with FVC ≥50% (33-36). All studies were underpowered to detect a change in mortality and neither therapy showed a significant impact on survival; however, the pirfenidone trials showed a trend towards a reduced mortality rate (33, 37). Exercise capacity, measured using the six minute walk test (6MWT), was only assessed in two of the pirfenidone trials (and not measured in the nintedanib trial). Neither anti-fibrotic drug has been shown to have a significant benefit upon 6MWT, patient reported outcome measures (PROMs) such as dyspnoea and health related quality of life, or time to exacerbation (33, 35, 36). This may be because these outcome measures were insufficiently sensitive to detect mild changes associated with the therapy. While these studies represent a breakthrough in the management of IPF, the effects of these drugs beyond one year, on acute IPF exacerbations and in patients with more severe disease are unknown. Accordingly, given the poor prognosis of IPF, the development of new or advancement of existing therapies is a priority.

1.2 Endpoints in IPF

An endpoint 'directly measures how a patient feels, functions or survives' and is 'well defined, reliable, measureable, interpretable, and sensitive to the effects of an intervention' (38). A major barrier to the development of new and existing therapies for IPF is the lack of a standardised approach to endpoints in phase II and phase III clinical trials of novel therapies (39). Mortality, either as all-cause, respiratory- or IPF-related, appears to be the most attractive endpoint as it is not rare (given the prognosis in IPF), is well-defined and simple to measure with a low risk of missing data (39). Investigators in the US proposed that all-cause mortality or all-cause, non-elective hospital admission should be the primary endpoint of choice as there are 'currently no validated surrogate endpoints' for patients with IPF (39). In contrast, the European IPF Consensus Group stated mortality is 'a highly unsuitable primary end-point in phase III trials as it is unacceptable to potential study participants and likely to deter pharmaceutical companies from developing new IPF therapies' (40). Furthermore, it should be noted that 12-month mortality in IPF trial participants is about one third that seen in non-selected patients due to a selection bias favouring those with milder disease and fewer co-morbidities (41). From a participant's perspective, a trial protocol which requires a commitment to a long-term intervention, to which he / she is blinded, despite obvious progression of disease is unlikely to be acceptable (32). Additionally, as pirfenidone and nintedanib are now licensed in many countries, albeit at a high cost to the purchaser, it may be considered ethically unacceptable to deny study participants a therapeutic intervention in clinical trials thus making placebo-controlled mortality trials difficult to undertake (32). IPF is a rare and variably progressive disease; therefore recruiting large sample sizes with long follow-up periods make clinical trials neither feasible nor affordable (40). Based on available data it is estimated that a phase III study powered to detect a 25% decrease in mortality would require 2,600 patients, five-years of follow-up and a cost in excess of US$250 million (42). Furthermore, Maher (32) reported that out of 18 late phase pharmacological clinical trials involving patients with IPF published between 2004 and 2013 (34, 37, 43-58), only two used survival as a primary endpoint (43, 44). The majority of the studies excluded patients with advanced disease because secondary complications such as non-IPF

respiratory conditions (e.g. pneumonia), cardiovascular diseases and secondary pulmonary hypertension could result in death irrespective of disease stability or progression (32). Consequently, there is much interest in surrogate endpoints which could potentially reduce the sample size requirements, follow up, duration and costs of clinical trials in IPF (59).

1.3 Surrogate endpoints of mortality in IPF

The United States of America's National Institute for Health defines a surrogate endpoint as an 'indirect measure intended to substitute for a clinically meaningful endpoint' where 'the effect of an intervention on a clinically meaningful endpoint must be reliably predicted by the effect of the intervention on the surrogate endpoint' (60). Similarly, the Food and Drug Association's definition is 'a laboratory measurement or physical sign that is used in therapeutic trials as a substitute for a clinically meaningful end point… and is expected to predict the effect of the therapy' (61). Surrogate endpoints have an important role in clinical trials as well as in clinical practice. For example, total cholesterol is a viable measure and surrogate endpoint for coronary atherosclerosis (62). Conversely, while they may accelerate clinical trials and improve cost-effectiveness, reliance on surrogate endpoints that have not been validated may at best provide incorrect clinical information and at worst incur patient harm (63).

1.3.1 Physiology as a surrogate endpoint

1.3.1.1 Disease progression: forced vital capacity (FVC)

FVC, the maximum volume of air a person can forcefully exhale from the lungs, has been used for many decades as the standard spirometric measure of IPF as it is reliable, reproducible and responsive to disease progression (64, 65). There is a strong relationship between FVC % predicted and measures of dyspnoea (modified Medical Research Council (MRC) Dyspnoea scale) (66) as well as disease severity (high resolution computed tomography (HRCT) scans of the chest) (66). However,

only weak relationships exist between change in FVC % predicted and change in diffusing capacity of the lung for carbon monoxide (DL_{CO}) % predicted (64) and health-related quality of life (St. George's Respiratory Questionnaire (SGRQ)) (64). The estimate for the minimum clinically important difference (MCID) of FVC % predicted is between 2% and 6% (64).

Change in FVC % predicted measured serially over time is associated with disease progression and mortality, and is commonly used as a primary endpoint in clinical trials (64). A >10% absolute decline in FVC % predicted over six months indicates a significant decline in pulmonary function signifying disease progression (67) and is associated with increased risk of further IPF progression (68, 69), acute exacerbation (68), a higher rate of health-care resource usage (68) and increased mortality (figure 1.1) (67-73). Furthermore, patients with a stable FVC % predicted (decline <5%) have longer survival (hazard ratio (95% confidence interval) (HR (95% CI): 2.80 (1.54 to 5.06)) and longer progression-free survival (HR (95% CI): 2.24 (1.63 to 3.08)) than those with a decline between 5% and 10% (71). However, in healthy individuals, FVC measurements repeated over long intervals (e.g. one year apart) vary from 5% to 9%, which is pertinent considering the aforementioned definition of IPF disease progression (74). Furthermore, this pulmonary function measure has been shown to be stable in a proportion of patients with IPF prior to death either because of missing values or because an acute exacerbation or pulmonary hypertension, rather than declining lung capacity, is the ultimate cause of death (32). Change in FVC over six months has been approved by the Food and Drug Administration as a primary outcome for IPF clinical trials (75). Although, FVC is frequently used as an endpoint in clinical trials missing values occur because a proportion of study participants are unable to perform serial measurements due to development of cough, worsening dyspnoea or inter-current infection (32). For example, Raghu *et al* reported that at one year follow up, almost 20% of patients with IPF on pirfenidone were not able to perform FVC measurements (76). Owing to these limitations, FVC is not an ideal surrogate outcome measure of mortality or morbidity (72, 75).

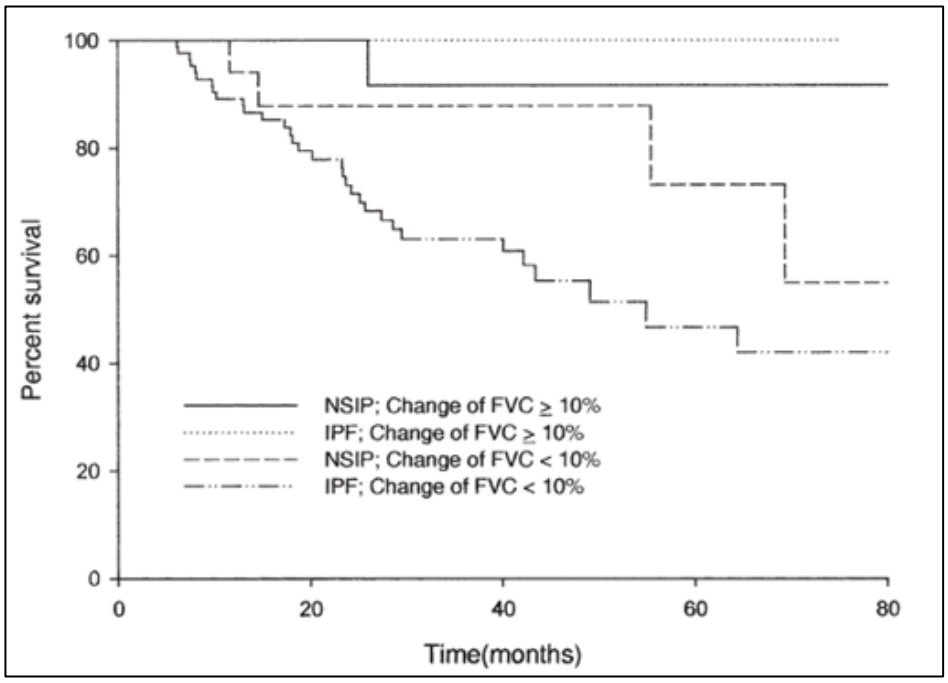

Figure 1.1: The relationship between change in FVC % predicted over six months and mortality (67).

Reprinted with permission of the American Thoracic Society. Copyright © 2017 American Thoracic Society. Cite: Jegal Y, Kim DS, Shim TS, Lim C-M, Do Lee S, Koh Y, Kim WS, Kim WD, Lee JS, Travis WD. 2005. Physiology is a stronger predictor of survival than pathology in fibrotic interstitial pneumonia. American journal of respiratory and critical care medicine; 171: 639-644. The American Journal of Respiratory and Critical Care Medicine is an official journal of the American Thoracic Society (Appendix 1).

Abbreviations: FVC: Forced Vital Capacity; IPF: Idiopathic Pulmonary Fibrosis; NSIP: Non-Specific Interstitial Pneumonia.

1.3.1.2 Diffusing capacity of the lung for carbon monoxide (DL_{CO}) as a surrogate endpoint

DL_{CO} reflects the diffusion properties of the lung as well as changes in the pulmonary vasculature and therefore reduces in the presence in pulmonary hypertension (32, 77). In 15 patients with IPF who performed a cardiopulmonary exercise test, DL_{CO} corrected for alveolar volume correlated with ventilation-perfusion mismatch, oxygen diffusion limitation and an increase in pulmonary vascular resistance, thus indicating the degree of gas-exchange impairment during exercise (78). Baseline and change in DL_{CO} is associated with survival. In a univariable analysis of 74 patients with IPF over four years, worse survival was associated with a number of factors including a lower DL_{CO} % predicted (HR (95% CI): 0.69 (0.53 to 0.89) (79). Similarly, Collard *et al* reported that baseline and change over six

months (adjusted for baseline values) in DL_{CO} % predicted were predictive of mortality in 75 patients (HR: 0.96 and 0.94 respectively, both p<0.01) (72). Recently, after consideration of spirometric variables, 6MWT, composite endpoints, age, gender and long-term oxygen initiation, baseline DL_{CO} was the best prognostic marker for mortality and progression-free survival in a service audit of 167 patients with IPF (69). In contrast, Latsi *et al* showed that trends of DL_{CO} % predicted and other pulmonary function variables over six months in 85 patients had no prognostic value after adjusting for change in DL_{CO} % predicted in the preceding six months (no data provided) (80). However, when measured over 12 months, a significant decline in DL_{CO} % predicted (>15% from baseline) was associated with reduced time to death compared with those with stable / improved DL_{CO} % predicted (<15% decline) (log rank test: p<0.0005) (80).

Despite the positive attributes of DL_{CO}, its use as an endpoint is compromised by the inherent variability of the test due to the difficulty in ensuring standardisation and quality control across centres (2). Accordingly, in clinical trials DL_{CO} is generally used as part of a composite index e.g. the Composite Physiologic Index (CPI) or the Gender Age and lung Physiology (GAP) index rather than an independent primary or surrogate endpoint (2).

1.3.1.3 Composite Indices as Surrogate Endpoints

Composite indices are an amalgamation of two or more separate outcome measures that form a single index that is usually calculated from an equation or scoring system (81). The benefits of using these as endpoints may include a smaller sample size and shorter trial duration (81). Composite indices should be clinically relevant and the intervention under investigation should ideally affect each separate outcome within the endpoint equally (81). Commonly used composite indices in IPF trials include the CPI, GAP index and mortality risk scoring system.

1.3.1.3a Composite Physiologic Index (CPI)

The CPI is a measure of disease severity calculated using pulmonary function variables (82). It indicates the extent of fibrosis on a HRCT scan and accounts for the presence of emphysema (82). It was initially developed to improve the precision of disease monitoring and to allow accurate stratification in clinical trials (40). It is calculated using the following equation (82) with lower values indicating less severe disease and higher values more severe disease:

$$CPI = 91 - (0.65\ x\ DLCO\%) - (0.53\ x\ FVC\%) + (0.34\ x\ FEV1\%)$$

The CPI shares moderate to strong relationships with disease extent on HRCT in patients with IPF only (40) and in those with combined pulmonary fibrosis and emphysema (CPFE) (83). Conversely, there is a weak association between the CPI and the extent of emphysema on HRCT in patients with CPFE (83). It also correlates significantly with DL_{CO} (82) (although this variable is a component of the CPI), and dyspnoea (modified MRC Dyspnoea scale) (83).

Wells *et al* showed that the CPI predicts survival more accurately than pulmonary function indices alone among 36 patients with IPF diagnosed using clinical and HRCT criteria or histological methods (HR (95% CI): 0.09 (0.04 to 0.14)) (82). This was confirmed by another study (n=104) that demonstrated that the CPI was the strongest determinant of mortality compared to pulmonary function indices alone (80). However, only mortality within three years, but not after this time-point, was strongly associated with CPI, FVC % predicted and DL_{CO} % predicted (80). In contrast, Schmidt *et al* reported that both baseline CPI and pulmonary function variables were predictive of mortality in 396 study participants and that the CPI may be the best predictor in patients with IPF without emphysema (84). In a service audit of 167 patients with IPF, the CPI was predictive of disease progression and performed better than the GAP staging system but not as well as DL_{CO} and long-term

oxygen initiation (69). An increase in five points in the CPI from baseline to 12 months predicted mortality and was defined as a clinically meaningful change (84).

1.3.1.3b Gender, Age and lung Physiology (GAP) index and staging system

The GAP index and staging system is a prognostic staging tool comprising commonly measured anthropometric and physiological variables: gender, age, FVC % predicted and DL_{CO} % predicted (85). It was developed to inform prognosis and management decisions such as end of life planning and timing of lung transplantation as well as a screening tool to estimate risk (85). The GAP index (range 0 to 8 with higher scores indicating worse status) is calculated from the four variables above and informs the GAP staging system (stage I, II, III) which estimates the of the risk of one, two and three year mortality in each category (85).

Two studies have demonstrated that the GAP index and staging system could predict risk of one, two and three year mortality in 228 patients with IPF (85) and 1,012 patients with ILD (n=307 IPF) (86). Chinchilli *et al* also noted that in 474 patients on an IPF registry, a one point increase in the GAP index could predict time to death or transplant (hazard ratio (HR): 1.56 – confidence interval (CI) not provided) (87).

1.3.1.3c Mortality risk scoring system

Du Bois *et al* developed this tool to facilitate clinical decision making and clinical trial design (70). It comprises four predictors (age, number of respiratory-related hospitalisations in the previous 24 weeks, FVC % predicted and change in FVC % predicted over 24 weeks) each of which is assigned a value that is summed (range 0 to 61 with higher scores indicating worse status) (70). This total score is compared with a risk scoring system that provides an estimate of the expected risk of one year

mortality (70). The predictive ability for one year mortality of the risk scoring system is consistent with observed data: 9.9% versus 9.7% (c-statistic: 0.75) (70).

The principle problem with using the CPI, GAP index and mortality risk scoring system as surrogate endpoints of mortality is that their value is based on the characteristics of their component parts. The limitations of FVC and DL_{CO} were described in section 1.3.1. Components of the mortality risk scoring system are based on measuring data over 24 weeks. Thus it is not possible to use this system at 'baseline' because it is scored using data collected prior to this time-point. Consequently, these composite indices may not be suitable to act as surrogate endpoints.

1.3.1.4 Functional exercise capacity: the six minute walk test (6MWT)

The 6MWT measures the maximum distance a patient can walk on a flat surface during a six minute period (88). It is a well-established measure of functional exercise capacity in IPF (89-91). It is also thought to reflect, in a quantitative manner, the performance of activities of daily living (92). The 6MWT has good inter-observer (93) and test-retest reliability (91) and is responsive to deterioration over time (89, 91, 94) as well as intervention, namely PR (95). The MCID estimate is between 25 to 33 metres for patients with chronic respiratory disease (including IPF) (96) and 22 to 45 metres for patients with IPF specifically (89, 91, 95, 97).

The relationship between baseline 6MWT and pulmonary function variables such as FVC % predicted and DL_{CO} % predicted is significant but weak (89, 91) and this is comparable to the relationships observed between change in 6MWT and change in pulmonary function variables (89). There is a significant relationship between peak oxygen consumption during the 6MWT and cardiopulmonary exercise testing (93). For these reasons, the 6MWT is used in clinical trials in IPF, typically as a secondary endpoint (33, 37, 43).

There is evidence of a positive association between both baseline 6MWT and desaturation during the 6MWT in patients with IPF and mortality. A baseline 6MWT distance of <212 (98) or <250 metres (94) is associated with mortality, and in IPF patients listed for lung transplantation <207 metres is associated with a four-fold increase in mortality (99). Similarly, a >50m decline in 6MWT over 24 weeks is associated with a three-fold (94) and four-fold (91) increase in incidence of mortality. In contrast, Flaherty *et al* (100) reported that baseline 6MWT was unable to predict mortality but noted that desaturation during the 6MWT was associated with increased mortality. Similarly, a separate study stated that desaturation ≤88% during the test was associated with a four-fold increase in mortality (101).

In some studies investigating the validity and predictive capacity of the 6MWT in IPF, patients with more severe disease (FVC <55% predicted, DL_{CO} <35% predicted and 6MWT <150m) have been excluded (91, 94). Consequently, it is unknown if 6MWT can predict mortality or is indeed a valid measure of exercise capacity in patients with severe disease. There are also practical difficulties in undertaking a 6MWT, such as the requirement of an unobstructed straight 30 metre flat course, trained personnel, ensuring patient motivation and standardising protocols between centres. A substantial learning effect of this test has been documented with 17% longer walking distances recorded when a second test is performed the next day (102); thus sufficient time to perform two tests, with adequate rest in between, is required. These characteristics may limit its utility, particularly in the home and primary care setting. Also, in a disease characterized by diffusion impairment, performance of the test at different altitudes may introduce a confounding factor into multi-centre trials (32). Like FVC, missing 6MWT values in clinical trials are also common in IPF due to inability or reluctance of patients to perform sequential tests because of disease progression. These limitations significantly impact the utility of the 6MWT as a primary outcome measure in IPF studies.

1.3.2 Patient reported outcome measures (PROMs) as surrogate endpoints

PROMs aim to 'directly report the status of a patient's health condition without the interpretation of a patient's response by a clinician or anybody else' (39). They can measure the impact of symptoms or a specific disease on the person as well as broader constructs such as health-related quality of life (32). For a disease like IPF which is rapidly progressive and has a large symptom burden, PROMs are particularly relevant as they can highlight the impact of the disease and in clinical trials may capture treatment effects not detected by other outcome measures (103).

The PROMs most commonly used to measure health-related quality of life in IPF include a mixture of generic, respiratory and IPF-specific tools. The Short-Form 36 (SF-36) measures generic health status and has been validated in IPF (104). It comprises eight domains and has a total of 36 items, taking five minutes to complete. Compared to healthy controls, patients with IPF had worse health status scores and the domains on the SF-36 showed a varied relationship with pulmonary function (FVC % predicted: r=-0.04 to 0.43; forced expiratory volume in one second (FEV_1) % predicted: r=0.09 to 0.45) and dyspnoea (Baseline Dyspnoea Index: r=-0.08 to 0.78) (104). Internal consistency for the SF-36 domains was satisfactory and the MCID was estimated between 2 to 4 points (105).

The SGRQ was initially developed and validated in patients with chronic obstructive pulmonary disease (COPD) (106), but both the original version and an IPF-specific version (SGRQ-I) have been validated in patients with IPF. The original SGRQ contains three domains (symptoms, activity, impact) and a total score with 50 items in total and takes 10 minutes to complete. It displayed excellent internal consistency in the activity and impact domains as well as the total score (105, 107), and moderate results in the symptom domain (107). There are moderately strong relationships between the activity domain and total score with FVC (107) and the total score with total lung capacity % predicted (108). The SGRQ shares a moderate to strong relationship with other measures

of health-related quality of life (mostly measures of dyspnoea) and exercise capacity (6MWT) (107). The MCID estimates range from five to eight points (105) and in a study of 87 patients with IPF the SGRQ did not predict survival (109). The IPF-specific version of the SGRQ contains 34 items from the original questionnaire that were found to be most relevant to patients with IPF (110). When compared to the original SGRQ, the SGRQ-I had good internal consistency, a weak relationship with pulmonary function variables (FVC % predicted and DL_{CO} % predicted), and a weak to strong relationship with other measures of health-related quality of life (SF-36) (110). There was no relationship with the 6MWT (110).

The King's Brief Interstitial Lung Disease (KBILD) questionnaire (KBILD) is an ILD-specific measure of health status developed in response to a paucity of instruments for this group of patients (111). It is a 15-item questionnaire comprising three domains (psychological, breathlessness and activities, chest symptoms) and a total score. It takes five to seven minutes to complete and has been shown to be valid (moderate relationship with FVC % predicted and physical component of the Short Form 36, strong relationship with SGRQ (111, 112)), reproducible (112) as well as responsive to PR (113, 114) and longitudinal change (115) in patients with ILD, including those with IPF. The KBILD can be scored using a Rasch analysis or impact factor scoring system which both yield similar results (112). Using the Rasch analysis method, the MCID estimate for the total score is five point increase in response to longitudinal change (116). Similarly, the using the impact factor scoring system, the MCID estimate of the total score is four points in response to PR (114).

A Tool to Assess Quality of life in IPF (ATAQ-IPF) was developed in America to provide an IPF-specific measure of health-related quality of life (117). It is a 74-item questionnaire that takes 10 to 12 minutes to complete. It is reproducible, moderately correlated with DL_{CO} % predicted but has no relationship with FVC % predicted or the 6MWT (117). The questionnaire was modified for British patients with IPF (ATAQ-IPF cross-country analysis) and was found to be reliable and had moderate

to strong correlations with measures of dyspnoea (Dyspnoea-12; modified MRC Dyspnoea Scale) (118).

Although, a number of PROMs that measure health-related quality of life in patients with IPF have been validated, their longitudinal validity, responsiveness and predictive capacity remain unknown in the majority of cases. Nonetheless, PROMs are likely to become established as important secondary endpoints in future IPF trials (32) to ensure the perspectives of patients with IPF are considered (119) and because research funding organisations have started to place a stronger emphasis on meaningful impact for patients (32).

1.3.3 Imaging as a surrogate endpoint

1.3.3.1 High resolution computed tomography (HRCT) of the chest

HRCT of the chest is one of the tests required for the diagnosis of IPF (1) as it provides an evaluation of the extent of lung disease (82) (figure 1.2). In clinical trials it is typically used to determine eligibility for inclusion in a study (33, 36, 37, 120) and as an outcome measure to assess the impact of an intervention (121-124). Multiple methods of scoring HRCT scans exist but the majority are scored visually for alveolar and interstitial abnormalities (121, 123, 124).

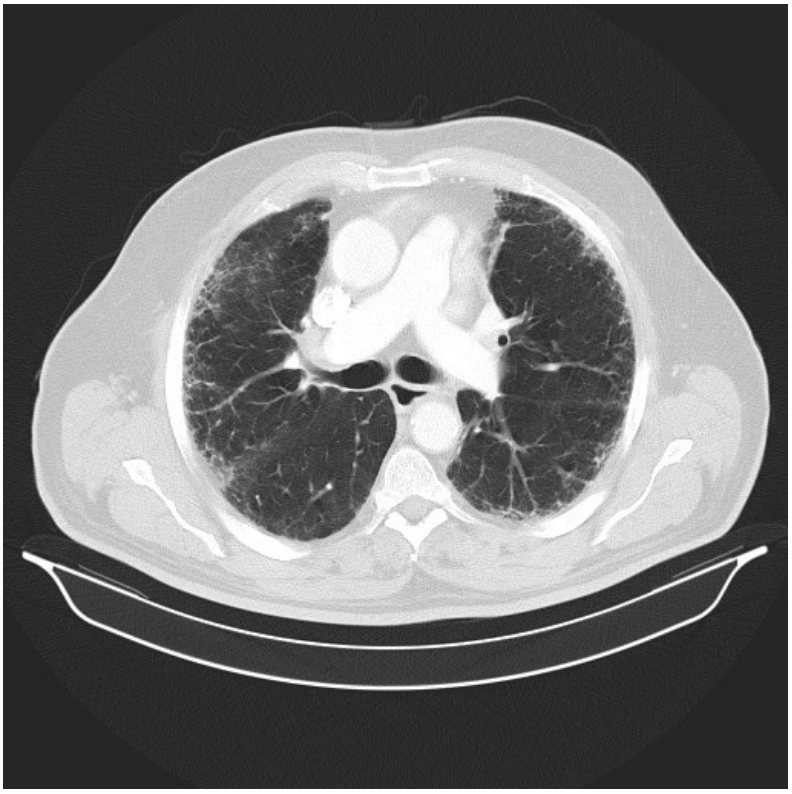

Figure 1.2: HRCT of the chest from a study participant.

A study participant provided written consent for this image to be used in this thesis.

Abbreviations: HRCT: High resolution computed tomography.

HRCT scores correlate with measures of disease severity: there is a significant relationship between the extent of fibrosis and ground glass on HRCT with the pathology fibrosis score and histologic inflammation score respectively (121). Xaubert *et al* showed that HRCT lung fibrosis and ground glass scores in 39 patients with IPF were weakly but significantly correlated with FVC and DL_{CO} and that there was a moderate strength relationship between the fibrosis score over six months with change in FVC and DL_{CO} (124). Similarly, in a phase II trial of 54 patients, Raghu *et al* reported a moderate relationship between computerised determination of changes in HRCT 'quantity of abnormal interstitial lung disease' and FVC % predicted over 24 weeks in response to an anti-connective tissue growth factor antibody FG-3019 (122).

The use of HRCT as an endpoint in clinical trials is hindered by its poor ability to detect subtle changes, inter-assessor variability in scoring, and subjective scoring methodologies (32, 125). The latter point is being addressed by the aforementioned computerised scoring system (122) but this technique requires longitudinal validation (32).

1.3.3.2 Positron Emission Tomography (PET)

PET offers an in vivo, non-invasive, highly sensitive method of assessing disease activity in patients with cancer (126) as it provides metabolic and morphologic information allowing enhanced specificity and accuracy for nodal staging (127). This diagnostic ability has also been used to stage mediastinal nodes in patients with non-small cell lung carcinoma and IPF using 2-fluoro-2-deoxy-D-glucose (F-FDG) PET (127).

In an extension of this role a number of studies have evaluated the F-FDG PET in patients with IPF without cancer. Groves *et al* reported that in 36 patients with ILD (IPF: n=18) the maximum standardised uptake value (SUV) of F-FDG PET had a significant relationship with measures of health-related quality of life (global health score: r=0.50, p=0.004) and pulmonary function (FVC % predicted: r=0.41, p=0.014; DL_{CO} % predicted: r=0.37, p=0.042) (128). Similarly, in a smaller study of eight patients with IPF, corrected mean SUV also correlated with FVC % predicted (r=-0.60, p=0.024) and DL_{CO} % predicted (r=-0.70, p=0.01) (129). Maximum SUV and SUV corrected for tissue fraction effect of F-FDG PET displayed satisfactory inter-observer and test-retest reliability in 13 patients with IPF and the authors postulated it could have a role as an endpoint in clinical trials (130). F-FDG PET also has predictive capacity as median progression-free survival was better for patients with a positive retention index SUV (27.9 versus 13.3 months, p=0.0002) and, when this score was coded as a binary variable, it was a significant predictor of mortality (HR (95% CI): 7.31 (2.64 to 20.3)) (131).

PET displays potential for use as an endpoint but the large radiation burden associated with this test precludes it from routine use in late phase clinical trials (32). However, it may have a role in early phase trials for proof of concept or mechanistic purposes (32).

1.3.4 Physical activity as a surrogate endpoint

Physical activity is is defined as 'any bodily movement produced by the skeletal muscles which results in increased energy expenditure' (132). In another chronic respiratory disease, chronic obstructive pulmonary disease, physical inactivity is associated with increased risk of mortality and exacerbations, greater decline in lung function, and impaired quality of life (133). However, little is known about physical activity in patients with IPF. Leuchte *et al* used an unvalidated physical activity questionnaire to explore the clinical correlates of physical activity levels in 156 IPF patients (134). They reported that lower physical activity levels were associated with increasing disease severity ($p<0.05$) and lower levels of exercise capacity ($p<0.05$) (r-values were not reported) (134). Two small randomised controlled trials (Vainshelboim *et al*: n=34, Gaunaurd *et al*: n=21) compared the impact of a three month pulmonary rehabilitation (PR) programme on physical activity levels, measured using the International Physical Activity Questionnaire, to no intervention in patients with IPF (135, 136). Both studies reported significant improvments in physical activity levels in the PR groups, compared to the control group at three months but the duration of benefit remains unknown (135, 136). The results of these studies should be interpreted with caution because of the small sample sizes and the method of physical activity measurement. Accelerometry is the gold standard method of measuring physical activity with tools should as questionnaires subject to measurement error owing to recall and reporting bias (137). Owing to the paucity of studies examining the prevlance, clinical correlates and predictive ability of physical activity in IPF, this outcome measure does not yet have a role as a surrogate endpoint in this patient group.

Considering the limitations of the currently available outcome measures, there is a need for a reliable, valid and practical surrogate endpoint that is responsive and sensitive to mild changes and that can predict mortality and morbidity in patients with IPF, for use in both research and clinical activities. Furthermore, new surrogate endpoints should have stronger predictive validity than the most widely used endpoint (change in FVC) and be measured at a single time point, rather than over time.

1.4 Gait speed

Usual gait speed, typically measured over four metres, is a measure of functional performance (138). It was originally a component of a three-part measure of functional perfromance called the Short Physical Performance Battery (SPPB) which was developed in the early 1990s (139). However, because usual gait speed was shown to be as sensitive as the SPPB in predicting adverse outcomes it has been used as single item tool since the turn of the century (139). Walking ability relies on many factors and the integration of multiple systems (140). Musculoskeletal, neurological, cardio-respiratory and mental health function, the presence of co-morbidities as well as the environment can influence walking ability and speed (141). Reduced gait speed or the inability to walk suggests dysfunction in these factors and or systems, due to ageing or acute or chronic medical conditions. Consequently, gait speed has been described as a 'clinical indicator of multi-system well-being' or the 'sixth vital sign' (138, 141). Tests of gait speed are different to other field walking tests such as the 6MWT or incremental shuttle walk test as they are a reflection of a person's functional ability i.e. what people 'do do' in contrast to the aforementioned field walking tests which measure exercise capacity i.e. what people 'can do' (142).

1.4.1 Gait speed in gerontology

The majority of studies that have examined gait speed have been undertaken in community-dwelling older adults (typically aged ≥65 years). Large epidemiological studies of this group have shown that usual gait speed, typically measured over four metres, reflects physical and functional performance, health status and is a strong and consistent predictor of adverse outcomes such as mortality, hospitalisation, disability and cognitive decline (139, 143-145). It is also a surrogate marker of frailty and sarcopaenia, and has been proposed as a functional test for clinical trials in frail older adults (146), a statement supported by the results of a systematic review by the International Academy of Nutrition and Ageing which reported that gait speed, as a single item tool, was at least as sensitive as composite tools in predicting outcomes over time and could be used as an outcome measure or as an inclusion or exclusion criterion in clinical trials (147). They concluded that a cut-off of <0.80 ms^{-1} could be used to predict poor outcomes and a gait speed >1.00 ms^{-1} was associated with improved survival and a reduced risk of ill-health (147). Furthermore, gait speed has already been used as the primary outcome measure in phase III multi-centre trial of extended release oral dalfampridine in 239 patients with multiple sclerosis (148). Participants were randomised to receive 9 weeks of the investigative medicinal product (10mg, twice per day) or a placebo. Significant improvements in mean (95% confidence interval) gait speed were demonstrated by the intervention (0.16 (0.13 to 0.18)ms^{-1}) but not the control group (0.05 (0.03 to 0.07)ms^{-1}) ($p<0.05$) (148).

The psychometric properties of gait speed have been evaluated in community-dwelling older adults as well as in those with Alzheimer's disease, post-hip fracture, brain tumours, neuromuscular diseases (children) and neurological conditions (traumatic brain injury, Parkinson's disease, stroke, multiple sclerosis, spinal cord injury).

1.4.1.1 Reliability

The reliability of gait speed has been demonstrated in studies involving elderly people, stroke survivors, those with cognitive impairment, Parkinson's disease and following hip fracture. Only three studies have examined inter-observer reliability, but high intra class correlation coefficients (ICCs) ranging from 0.88 to 0.96 were observed (149-151). Satisfactory test-retest reliability results (ICCs: 0.81 to 0.97) over a variety of speeds (usual or fast-paced) and time differences between testing (same day to two weeks apart) as well as different timing methods (manual or automated gait mat system) have been reported (149, 151-157).

1.4.1.2 Concurrent validity

Gait speed demonstrates concurrent validity with other measures of physical and functional performance as well as measures of lower limb muscle strength. Strong to moderate correlations between gait speed and 6MWT, time taken to rapidly ascend four steps (lower extremity power) and the Short Physical Performance Battery (SPPB) were observed in 108 patients post-hip fracture (158). Similar results were evident in patients with a spinal cord injury with strong correlations between gait speed and the 6MWT; Timed-Up-and-Go test and the Berg Balance Scale (159-161), whereas in older adults, weak correlations have been shown with chair rise time (162). Usual gait speed measured over eight and six metres respectively shared moderate correlations with quadriceps strength in stroke survivors (163) and a small cohort of elderly people (164).

Studies have also evaluated the validity of gait speed using measures of health-related quality of life. In 1,388 hospitalised, acutely unwell, elderly veterans, every 0.10 ms^{-1} reduction in baseline gait speed was associated with worse health status (SF-36), conversely every 0.10 ms^{-1} increase in gait speed was associated with enhanced status (165). Yanagita *et al* reported that in 2,586 elderly Japanese-American men, gait speed measured over ten feet was significantly slower in those with depressive symptoms measured using the Centre for Epidemiologic Studies Depression Scale (166).

Comparably, in a study involving 3,670 patients with multiple sclerosis, those who reported that the disease had affected their gait speed reported poor health status measured using the Short Form-12 physical component scale (r=-0.69) and the Euro-Qol Visual Analogue Scale (r=-0.51) (167).

1.4.1.3 Predictive validity

Large epidemiological studies have demonstrated that gait speed is associated with subsequent mortality, morbidity, disability and cognitive decline. In a pooled analysis of nine cohort studies of 34,485 community-dwelling older adults followed up for up to 21 years, gait speed was significantly associated with survival (HR (95% CI): 0.88 (0.87 to 0.90) per 0.10 ms^{-1} decrease in gait speed) and was most informative after 75 years of age (144) (figure 1.3). A gait speed ≥1.00 ms^{-1} predicted survival better than gender and age alone (144). Similarly, slow gait speed (<1.00 ms^{-1}) has also been associated with shorter term survival at 4.9, 6.9 and 8.4 years (168-170). In a study of 7,250 community-dwelling non-disabled older French women, gait speed, measured over six metres, independently identified a gradient of mortality risk. The adjusted hazard ratio (95% CI) for women unable to perform the gait speed test was 4.15 (1.87 to 9.19) compared to those whose gait speed was ≥0.78 ms^{-1} (171).

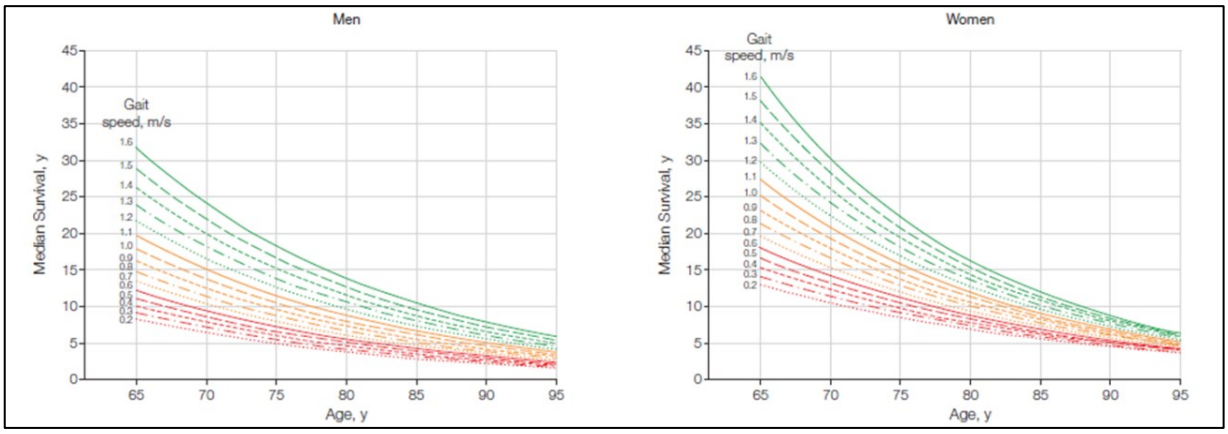

Figure 1.3: Predicted median life expectancy by age and gait speed (144).

Reprinted with permission of the American Medical Association (Appendix 1).

A number of studies have demonstrated that improvements in gait speed are associated with improved survival (172, 173), and conversely, that reductions in gait speed are associated with increased mortality risk (173-175). Hardy *et al* reported that improvements in four metre gait speed (4MGS) over one year in 439 community-dwelling elders predicted reduced mortality over eight years (HR (95% CI): 0.42 (0.29 to 0.61) per 0.10 ms^{-1} increase in gait speed) (172). Sabia *et al* reported that patients (n=2049 community-dwelling elders) who improved their fast gait speed measured over six metres had a longer time to death (HR (95% CI): 0.80 (0.71 to 0.90) per 0.10 ms^{-1} increase in gait speed) (173). In contrast, when change in fast gait speed was classified as a categorical variable, a 'substantial decline' of <-0.17 ms^{-1} was associated with a greater risk of mortality compared to a reference group (-0.14 to -0.06 ms^{-1}) (no data provided) (173). Similarly, White *et al* used cut-points, to demonstrate that compared to a small reduction in usual walking speed (measured over 20 metres) in one year (-0.02 ms^{-1}), a large reduction (-0.03 ms^{-1}) was associated with a greater risk of all-cause death after adjusting for confounding variables (HR (95% CI): 1.9 (1.3 to 2.8) (175). Perera *et al* reported that a 0.10 ms^{-1} reduction in 4MGS over one year was associated with increased risk of mortality at five years in 439 older patients (HR (95% CI) 2.23 (1.44 to 3.46)) (174).

Gait speed has been investigated as a predictor of hospitalisation and institutionalisation. The unadjusted hazard ratio (95% CI) for hospitalisation at 12 months in patients with a baseline gait speed <1.0 ms^{-1} was 1.38 (1.13 to 1.68) (169) and the odds ratio for institutionalisation at three years for elderly Chinese adults was 1.03 to 1.09 (176). Gait speed can also predict length of hospital stay and discharge location post-stroke and in elderly adults. Using the two-minute walk test, stroke survivors with gait speeds <0.15 ms^{-1} had significantly longer hospital admission duration and predicted discharge disposition correctly in 78% of cases irrespective of age and Functional Independence Measure score (177). Comparably, elderly people admitted to a geriatric hospital unit

with gait speeds <0.40 ms^{-1} had significantly longer inpatient hospital admissions and reduced odds of a home discharge compared to those with gait speeds of at least 0.60 ms^{-1} (178).

In a study of 1,122 community-dwelling elderly adults who performed activities of daily living independently, walking half a mile and climbing stairs, a slow baseline gait speed was associated with a significant increase in the frequency of activities of daily living- and mobility-related disability four years later (139). Similar data were reported by the Health, Aging and Body Composition Study which showed that gait speed predicted lower limb impairment (difficulty in climbing ten steps or walking a quarter of a mile) with a hazard ratio (95% CI) of 1.53 (1.35 to 1.74) in a study involving 3,000 well-functioning elderly adults monitored for up to 6.9 years (169). In 3,156 disability-free adults followed for a median 8.4 years, the hazard ratio (95% CI) for future disability was 0.88 (0.80 to 0.96) with a gait speed >1.00 ms^{-1} and increased mortality rates were observed in those with a gait speed <1.00 ms^{-1} (168). In a study involving 1,388 acutely unwell older male veterans, Purser *et al* demonstrated that increases in gait speed measured at hospital admission and at one year were associated with improved health status; physical function; fewer disabilities as well as lower healthcare utilisation and costs at one year (165). Gill *et al* undertook a study involving 586 adults living in retirement villages and measured fast gait speed back and forth over a three metre course, one year apart (179). The results showed that compared to no decline in fast gait speed, a large decline was associated with dependence with activities of daily living at one year (OR (95% CI): 5.3 (3.0 to 9.3)) but not three years (0.9 (0.5 to 1.8)) (179).

Gait speed can also predict the onset of cognitive decline, Alzheimer's disease and dementia. In a prospective study of 2,288 persons, aged 65 years or older and without dementia, faster gait speed over a 10 metre course was associated with a lower risk of dementia and Alzheimer's disease (180). There is a paucity of data on the relationship between gait speed and falls, however the authors of the aforementioned study of 7,250 community-dwelling non-disabled older French women reported

a relative risk of 1.4 between the lowest quartile of gait speed and femoral neck fracture due to a fall (171).

1.4.1.4 Responsiveness and minimum clinically important difference (MCID)

The principal use of gait speed in intervention studies is as a functional outcome measure and its capacity to detect change has been demonstrated in community-dwelling older adults, neurological conditions (stroke, spinal cord injury, traumatic brain injury) and post-hip fracture. In stroke survivors, an improvement in usual gait speed of 0.21 ms^{-1} from day 20 to 60 post-acute stroke has been reported (181) with an increase of 0.10 ms^{-1} suggested as the MCID after a 12 week stroke rehabilitation programme (182). The mean improvement in gait speed from hospital admission to discharge amongst elderly people undergoing rehabilitation after a hospital admission was 0.20 ms^{-1} (183). Preferred gait speed over 10 metres in patients with incomplete spinal cord injury improved by 0.40 ms^{-1} and 1.12 ms^{-1} at one and six months after initial injury (161). Alley *et al* observed a mean increase in gait speed in patients post-hip fracture of 0.11 to 0.12 ms^{-1} at one year despite reporting no change in walking or stair-climbing ability (184). Gait speed can also detect deterioration as Onder *et al* reported a 5.2% slowing of gait speed over one year in moderately to severely disabled women (185). Estimates for the MCID of gait speed in these populations range from 0.05 to 0.16 ms^{-1} (160, 181, 182, 186).

1.4.2 Gait speed in Chronic Respiratory Disease

The majority of studies that have investigated gait speed in chronic respiratory disease have involved patients with COPD, with one study including patients with severe chronic respiratory disease and another, survivors of Acute Respiratory Distress Syndrome (ARDS). Two studies compared gait speed - measured by calculating average speed during the 6MWT (187) and on a five metre walking course

(188) - of patients with COPD (n=511 and 21 respectively) and matched healthy controls (n=113 and 21 respectively) and found that those with COPD had significantly slower walking speeds.

ICCs for inter-observer reliability of the four metre gait speed test (4MGS – usual walking speed measured over four metres), the most commonly used test, in 58 COPD patients and 32 ARDS survivors were 0.99 (189) and 0.97 respectively (190) with similar results for test-retest reliability. In tests performed over four metres, the ICCs reported in a study involving 70 COPD patients walking at both their usual and maximal walking speeds and timed using an infrared system as well as a stop-watch were all 0.95 (191). The ICCs, for usual waking speed, of 0.97 and 0.88 to 0.99 were reported in 86 COPD patients (189) and 306 ARDS survivors (190) respectively. Similar results were reported for a 10 metre (ICC 0.97 usual and maximal speed) (191) and 30 metre course (ICC 0.87 self-selected speed, 0.93 maximal speed) (192) in COPD patients.

The 4MGS test displays concurrent validity as it correlates significantly with field walking tests such as the incremental shuttle walk test (ISW) (r=0.78) (189) and 6MWT (usual speed: r=0.77, maximal speed: r=0.80) in patients with COPD (193), severe chronic lung disease (r=0.70) (194) and ARDS survivors (r=0.37 to 0.62) (190). Maximal gait speed but not usual gait speed measured over 30 metres also correlated strongly with the 6MWT in COPD patients (192).

A significant, weak to moderate strength relationship was observed between 4MGS and measures of dyspnoea (MRC Dyspnoea score (r=-0.55) (189); modified MRC Dyspnoea score (r=-0.44) (194)) and disease specific health-related quality of life (SGRQ) in patients with COPD (r=-0.44) (add Kon RV Ref) and severe chronic lung disease (r=0.27 to 0.42) (Add ref DePew) as well as generic health status (SF-36 physical function domain (r=0.54 to 0.64)) in ARDS survivors (190). 4MGS shared significant correlations with objectively measured physical activity in patients with severe chronic lung disease

(time spent in moderate intensity physical activity (4 to 6 metabolic equivalents (METS)): r=0.41, time spent in vigorous intensity physical activity (>6 METS): r=0.32) (194). Significant but weak correlations were also evident with measures of disease severity (FEV_1 % predicted) in patients with COPD (r=0.10) (189) and mental health status (Hospital Anxiety and Depression Scale, SF-36 mental health domain) in ARDS survivors (190). Similarly, Ilgin *et al* reported significant correlations between gait speed and pulmonary function tests and the SGRQ which were stronger in those with more severe disease, although gait speed measurement was derived from the 6MWT (187). Kon *et al* also demonstrated that patients with a slow gait speed (<0.80 ms^{-1}) had worse health-related quality of life, exercise capacity and dyspnoea compared to faster walkers (≥0.80 ms^{-1}) (189).

The 4MGS test is responsive to intervention (PR) and changes over time (12 months) in patients with COPD (195) and ARDS survivors (six to 60 months) (190). The MCID for improvement following PR and change over time in patients with COPD was 0.11 ms^{-1} (195) and for change over time in ARDS survivors, 0.03 to 0.06 ms^{-1} (190).

Gait speed also has predictive validity. In COPD patients, Karpman *et al* identified that a gait speed of 0.90 ms^{-1} and 0.80 ms^{-1} measured using the 4MGS test predicts a 6MWT of ≤350 metres (c-statistic (95% CI): 0.87 (0.80 to 0.92)) and ≤200 metres (c-statistic (95% CI): 0.98 (0.94 to 0.99)) respectively (193). The 4MGS test measured at hospital discharge in patients with COPD can also predict risk of 90 day hospital readmission (196) (figure 1.4) as well as future hospitalisation and health-related quality of life in ARDS survivors (190).

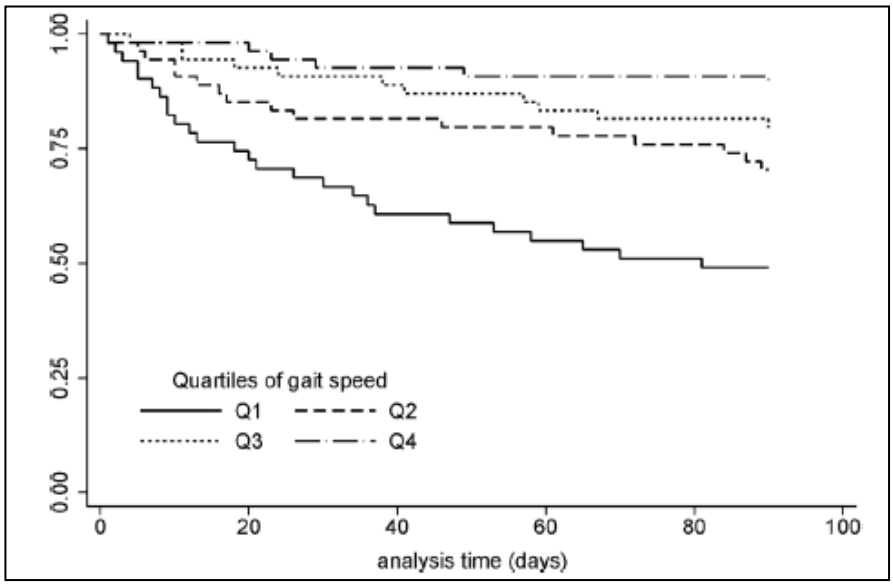

Figure 1.4: Kaplan–Meier curve demonstrating time to 90-day all-cause, non-elective readmission in COPD patients according to 4MGS quartile (Q1: slowest gait speed; Q4: fastest gait speed) (196). Printed with permission from the BMJ Publishing Group Ltd (Appendix 1).

Abbreviations: 4MGS: Four Metre Gait Speed; COPD: Chronic Obstructive Pulmonary Disease; Q: Quartile.

1.4.3 Gait speed in ILD

There are few data on the 4MGS test in patients with IPF or ILD. One of the studies discussed in the previous section analysed the 4MGS test in 70 patients with severe chronic lung disease of whom 39% had ILD and of these 74% (n=20) had IPF (194). They demonstrated a strong correlation between 4MGS and 6MWT and a weak, significant correlation with MRC Dyspnoea score and physical activity variables (time spent in 4 to 6 METS and >6METS) in the whole group but sub-group information was not reported (194). Mendes *et al* measured the SPPB (a component of which comprises usual gait speed measurement over eight feet (2.4 metres)) in 26 patients with advanced ILD listed for lung transplantation, and demonstrated lower total scores compared with 12 age-matched controls (197). Absolute gait speed values were not reported, but there was no significant between-group difference in gait speed scores and the relationship between gait speed and measures of muscle function or functional status (6MWT and Timed Up and Go test) were not

presented (197). In a study involving 52 ILD patients (38% IPF), no significant between-group difference in gait speed, measured using the 4MGS test, was noted between the whole group and patients with IPF (198). Furthermore, there was a weak but significant relationship between gait speed and measures of dyspnoea in the ILD patients (Baseline Dyspnoea Index: r=-0.36; University of California San Diego Shortness of Breath Questionnaire: r=0.37) (198). The same research group also showed figuratively that the 4MGS test was responsive to a six to nine week outpatient PR programme in 54 ILD patients (41% IPF) but no significant difference was noted between assessment prior to PR and six months later (figure 1.5) (86). Numeric data on the change in gait speed were not reported, neither was the MCID.

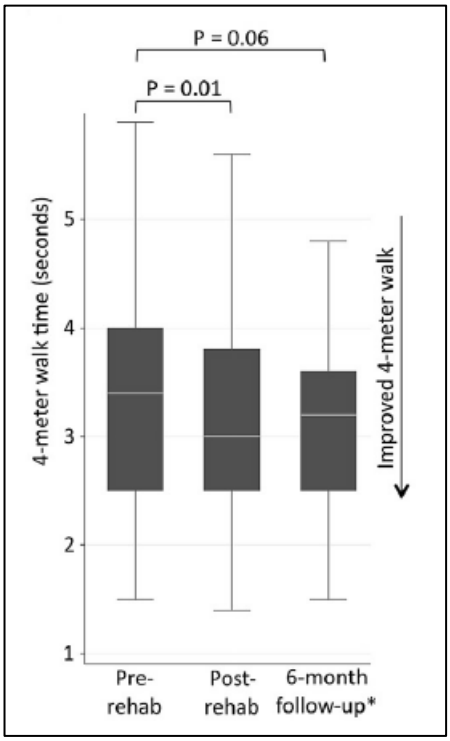

Figure 1.5: Change in four metre walk time following PR and six months after initiation of PR in patients with ILD (86).

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Abbreviations: ILD: Interstitial Lung Disease; PR: Pulmonary Rehabilitation; Rehab: Pulmonary Rehabilitation.

1.4.5 Methodological considerations for measuring gait speed

Gait speed measurement may be influenced by test protocol including the course length, starting position, method of timing, operator measurement error and instructions about the pace of walking. Gait speed tests have been performed over course lengths ranging from 2.4 to 15 metres (154, 199-203) or calculated from walking tests of fixed distances (200 metres (204) or 400 metres (205), and over a six minute duration (187)). However, the four metre distance has emerged as the most popular, balancing feasibility (measured in most clinical settings, including 90% of households (206)), with a distance sufficiently long to ensure measurement accuracy (139, 206). Consistent with this, the test-retest reliability for 4MGS is better than for gait speed over a two metre course, and as good as that reported over six metres (151, 203).

There is debate regarding whether gait speed assessment should involve a standing or rolling start, and whether timing should be automated with laser gates or recorded with a manually operated stopwatch. Proponents of a rolling start argue that this protocol allows the patient time to accelerate to usual gait speed (207). However, a pragmatic argument against this is that such a protocol would require two metre acceleration and deceleration zones in addition to the four metre course, making the overall course of eight-metres less feasible in many settings. A previous systematic review of gait speed assessment in clinical trials has shown that a greater number of studies used a standing start and recommended for continuity reasons and interpretability across studies, that future work should use a standing start (200).

The majority of the gait speed literature, and indeed the predictive capacity of gait speed, is based on the assessment of habitual or usual, rather than fast, walking speed (144). Recent studies in patients with COPD in the out-patient clinic setting have also shown excellent intra-class correlation coefficients (ICC) (>0.95) for test-retest reliability regardless of the course length (four versus ten metres), use of a standing or rolling start and manual or automated method of timing (191).

1.5 Hypothesis and aims

Mortality is considered by many groups to be an inappropriate primary endpoint in IPF clinical trials and problems exist with currently used surrogate outcome measures. I hypothesize that the 4MGS test, a practical measure of usual walking speed, is reliable and valid and has value as a surrogate endpoint or a means of stratifying patients with IPF.

The aims of this thesis are to determine:

- The reliability and validity of 4MGS in patients with IPF.
- The phenotypic characteristics of patients according to the slow gait speed phenotype (4MGS <0.80 ms^{-1}).
- The responsiveness of 4MGS in patients with IPF undergoing pulmonary rehabilitation.
- The MCID of 4MGS in patients with IPF.
- Whether 4MGS can predict subsequent all-cause mortality and all-cause, non-elective hospital admissions in patients with a new diagnosis of IPF compared with existing surrogate endpoints.
- Whether change in 4MGS with pulmonary rehabilitation can predict subsequent survival and all-cause, non-elective hospital admissions in patients with IPF.

Chapter 2 : Methods, materials and measures

This thesis involves four studies:

- Study 1: The reliability and validity of four metre gait speed (4MGS) and the phenotypic characteristics of the slow gait speed phenotype in patients with idiopathic pulmonary fibrosis (IPF).
- Study 2: The responsiveness of 4MGS in patients with IPF and estimation of the minimum clinically important difference (MCID).
- Study 3: 4MGS, mortality and non-elective hospital admission in patients with newly diagnosed IPF.
- Study 4: Change in 4MGS with pulmonary rehabilitation (PR) and the association with survival and non-elective hospital admission in IPF.

2.1 Ethical approval

The studies were approved by the London Riverside National Research Ethics Service Committee (14/LO/2247, 14/LO/2248, 15/LO/0015). All patients provided written informed consent prior to entering a study. Participation in one study did not preclude entry into other studies.

2.2 Study participants

Participants were patients diagnosed with IPF by a multi-disciplinary team of specialist interstitial lung disease (ILD) respiratory physicians, radiologists and pathologists according to international guidelines (7). These guidelines state that an IPF diagnosis requires the exclusion of other ILDs and a usual interstitial pneumonia (UIP) pattern on a high resolution computed tomography (HRCT) chest scan in patients who have not had a surgical lung biopsy, or, a specific combination of a HRCT chest scan and surgical lung biopsy pattern in those who have had a surgical lung biopsy (e.g. UIP pattern

on HRCT chest and a UIP, probable UIP, possible UIP or non-classifiable fibrosis pattern on surgical lung biopsy) (7).

In Chapter 3 (Study 1), I describe the reliability and validity of 4MGS, and the phenotypic characteristics of slow gait speed. Study participants were prospectively recruited from outpatient respiratory, PR and ambulatory oxygen assessment clinics at the Royal Brompton and Harefield NHS Foundation Trust, UK.

In Chapter 4 (Study 2), the responsiveness of the 4MGS test to PR is reported in patients with IPF, whilst Chapter 6 (Study 4) describes the association between improvement in 4MGS following PR with survival and non-elective hospital admission in this cohort. For these chapters, patients were prospectively recruited from PR units at the Royal Brompton and Harefield Hospital NHS Foundation Trust, UK and St. Thomas' Hospital at Guy's and St. Thomas' NHS Foundation Trust, UK.

Chapter 5 (Study 3) determines the prognostic value of 4MGS in newly diagnosed patients with IPF by evaluating the association between baseline 4MGS and mortality and non-elective hospital admission. Patients were prospectively recruited from outpatient respiratory clinics at the Royal Brompton and Harefield Hospital NHS Foundation Trust, UK.

A table showing the number of participants recruited to more than one study is shown in Appendix 2.

The inclusion and exclusion criteria for each individual study are described in the respective results chapters.

2.3 Study design

Schematic diagrams of study design, recruitment dates and detailed statistical analyses are contained within the related results chapters.

2.4 Outcome measures

Some or all of the measures described below have been used in the four studies as illustrated in Table 2.1.

Table 2.1: Outcome measures used in each study.

Outcome	**Study 1: Reliability**	**Study 1: Validity**	**Study 1: Phenotype**	**Study 2**	**Study 3**	**Study 4**
Pulmonary function tests	√	√	√		√	
Spirometry only				√		√
HRCT of the lungs		√	√			
MRC Dyspnoea scale	√	√	√	√	√	√
Anthropometry	√	√	√	√	√	√
Six minute walk test		√	√		√	
Incremental shuttle walk test				√		√
4MGS	√	√	√	√	√	√
QMVC				√		√
Handgrip strength				√		√
KBILD questionnaire		√	√	√	√	√
CRQ questionnaire				√		√
Pulmonary rehabilitation				√		√
Composite scores of mortality in IPF	√	√	√		√	
Mortality and hospitalisation data					√	√

Abbreviations: 4MGS: Four Metre Gait Speed; CRQ: Chronic Respiratory Questionnaire; HRCT: High Resolution Computed Tomography; IPF: Idiopathic Pulmonary Fibrosis; KBILD: King's Brief Interstitial Lung Disease questionnaire; MRC: Medical Research Council Dyspnoea scale; QMVC: Quadriceps Maximum Voluntary Contraction.

2.5 Pulmonary function tests

Pulmonary function testing was performed by the respiratory physiology departments at the Royal Brompton and Harefield NHS Foundation Trust with the following absolute and percentage predicted variables recorded: forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), FEV_1/FVC and diffusing capacity of the lung for carbon monoxide (DL_{CO}). The Spirostick™ PC spirometry system (Love Medical Ltd, Manchester, UK), Jaeger MasterScreen™ Pulmonary Function Testing system (Carefusion Ltd., Basingstoke, UK) and HDPFT 3000 Comprehensive Pulmonary Function Laboratory (nSpire Health Ltd, Hertford, UK) equipment were used. Predicted values were derived from the equations recommended by the European Community for Coal and Steel (ECCS) / European Respiratory Society (ERS) (208).

2.6 Spirometry

Spirometry was performed by myself or physiotherapists from the PR teams using an EasyOne diagnostic spirometer (model 2001, Medixintechnik, Zurich, Switzerland) according to American Thoracic Society (ATS) /ERS guidelines (209) with the following absolute and percentage predicted variables measured: FVC, FEV_1 and FEV_1/FVC. Three manoeuvres were performed and the data from the best of three reproducible FVCs was used with predicted values derived from the equations recommended by the ECCS/ERS (208). The spirometer was calibrated daily according to the manufacturer's guidelines using the *ndd* calibration adapter and calibration syringe (ndd Medical Technologies, Massachusetts, USA).

2.7 High Resolution Computed Tomography (HRCT) of the lungs

This was performed as part of routine clinical assessment following a standardised protocol at the Royal Brompton and Harefield Hospital NHS Foundation Trust, UK or the participant's referring hospital as part of the diagnostic process recommended by the National Institute for Health and Care Excellence (NICE) (1). IPF, on HRCT scan, is characterised by a UIP pattern defined as the presence of

patchy, sub-pleural reticular opacities and honeycombing with basal predominance (210). It was visually scored by two experienced sub-specialist thoracic radiologists at the Royal Brompton and Harefield NHS Foundation Trust, UK for the extent of ILD (to the nearest 5%) as described previously (211).

Figure 2.1: An example of scoring a HRCT of the lungs image.

Reproduced with the permission of Dr Joseph Jacobs.

Abbreviation: HRCT: High Resolution Computed Tomography.

2.8 Medical Research Council (MRC) Dyspnoea scale

Respiratory disability was characterised using the Medical Research Council (MRC) Dyspnoea scale (212). This is a 5-point scale where the patient grades the level of dyspnoea when performing activities of daily living (213). The scale ranges from 1: *'not troubled by breathlessness except on strenuous exercise'*, which indicates no respiratory disability to 5: *'too breathless to leave the house, or breathless when dressing or undressing'* with levels 2 to 5 representing worsening degrees of respiratory disability with impact on functional performance (figure 2.1). A modified version of the MRC Dyspnoea scale, the modified MRC (mMRC) dyspnoea scale was developed with more simplified

statements and a similar five levels of dyspnoea with physical activities (but scored from 0 to 4) and has been used in studies investigating respiratory disability in IPF (214, 215). The mMRC Dyspnoea scale shares significant moderate to strong correlations with pulmonary function parameters, HRCT of the lung scores (total ILD and fibrosis score) and exercise performance in patients with IPF, thus providing information about disease severity (66, 216). It also provides prognostic information as it predicts survival (217, 218). As the MRC and mMRC Dyspnoea scale are not sufficiently sensitive to detect short-term changes in respiratory disability, their use is generally limited to being a discriminative or stratification tool (219).

MRC Dyspnoea scale

1. Not troubled by breathlessness except on strenuous exercise
2. Short of breath when hurrying or walking up a slight hill
3. Walks slower than contemporaries on level ground because of breathlessness, or has to stop for breath when walking at own pace
4. Stops for breath after walking about 100m or after a few minutes on level ground
5. Too breathless to leave the house, or breathless when dressing or undressing

Figure 2.2: Medical Research Council (MRC) dyspnoea scale.

Abbreviations: MRC: Medical Research Council.

2.9 Anthropometry

Height was determined to the nearest centimetre using a stadiometer (Model 225, Seca, Hamburg, Germany – studies 1, 2 and 4, ward stadiometer – studies 1 and 3) with the patient in bare feet. Weight was measured with the subject lightly dressed and in bare feet (TANITA MC780, Amsterdam,

Netherlands – studies 2 and 4, ward scales – studies 1 and 3). Body mass index (BMI) was calculated using the following formula and expressed in kg/m^2: $BMI = Weight\ (kg) \div Height^2 (m)$.

2.10 Four metre gait speed (4MGS) test

Usual gait speed was measured using the 4MGS test (220). As this was discussed in detail in Chapter 1, only the method of performing the test is described in this section. 4MGS was assessed as per the National Institute on Ageing's protocol on a flat, unobstructed four metre course delineated with tape (220) by trained research, physiotherapy and physiotherapy assistant staff who followed a standard operating procedure. The patient was positioned with their toes just touching the start line and the following standardised instructions were given: *'This is our walking course. I want you to walk to the other end of the course at your usual speed, just as if you were walking down the street to go to the shops. Walk all the way past the other end of the tape before you stop. Ready….begin'.* Timing with a stopwatch (Unisex Black Sports LCD stopwatch, Argos, UK) started when the participant lifted the heel and was stopped when the participant's first foot completely crossed the four metre line. The walk test was repeated and if the two times were within 0.2 seconds, the faster of the two times was used to calculate gait speed; otherwise another test was performed until two tests were within 0.2 seconds of each other. Patients were allowed to use their usual walking aids and ambulatory oxygen, with the cylinder carried by an assistant and these factors were kept constant for within-person measurements on repeated walk tests. To express gait speed in ms^{-1}, distance walked (i.e. four metres) was divided by time expressed in seconds: $\frac{4}{4MGS\ time\ (seconds)}$. For example, if a patient took five seconds to walk four metres, the 4MGS time would be 0.80 ms^{-1}.

2.11 Exercise Capacity

2.11.1 Six minute walk test (6MWT)

The 6MWT is a 'self-paced test of walking capacity' and is recommended by NICE for assessing exercise capacity in patients with IPF (1, 96, 221). As this test was discussed in detail in Chapter 1 only the method of performing the test is described in this section. Guidelines on how to conduct a 6MWT, published by the American Thoracic Society and a European Respiratory Society / American Thoracic Society task force, were followed for this research (96). The test was performed on a 30 metre walking course and patients were read standardised instructions before starting the test:

'*The aim of this test is to walk as far as possible for six minutes. You will walk along this hallway between the markers, as many times as you can in six minutes. I will let you know as each minute goes past, and then at six minutes I will ask you to stop where you are. Six minutes is a long time to walk, so you will be exerting yourself. You are permitted to slow down, to stop, and to rest as necessary, but please resume walking as soon as you are able. Remember that the objective is to walk AS FAR AS POSSIBLE for six minutes, but don't run or jog'* (96).

Do you have any questions'?

During the test, the participant was read the following standardised instructions at each minute informing him / her of progress: (96)

- At one minute: *'You are doing well. You have five minutes to go'*
- At two minutes: *'Keep up the good work. You have four minutes to go'*
- At three minutes: *'You are doing well. You are halfway'*
- At four minutes: *'Keep up the good work. You have only two minutes left'*
- At five minutes: *'You are doing well. You have only one minute to go'*
- At six minutes: *'Please stop where you are'*

Oxygen saturations, heart rate and level of dyspnoea using the Borg scale (222) were recorded before and after the test with recovery time to pre-test levels and limiting factor to the test (e.g. breathlessness) also noted. The oxygen saturations and heart rate were also recorded each minute during the test. If a participant stopped during the test, the number of stops and time spent resting were recorded (223). Patients were allowed to use a walking aid and/or prescribed ambulatory oxygen with the cylinder carried by an assistant. These factors were kept constant within-participant measurements on repeated walk tests (223). A practice test was performed if the participant had not recently undertaken a 6MWT, with a 30 minute interval between tests (96). The furthest distance of the two tests was recorded to account for the learning effect of the 6MWT (96).

2.11.2 Incremental shuttle walk (ISW) test

The incremental shuttle walk (ISW) test is a progressive, 'externally paced, maximal exercise test' (96, 224) that is widely used to assess exercise capacity as part of PR programmes in the UK. It was developed in patients with chronic obstructive pulmonary disease (COPD) and was shown to be reliable, valid and a significant predictor of survival and hospital readmission in this group with a MCID of 47.5 metres (225-231).

Guidelines on how to conduct the ISW, published by Singh *et al* and an ERS / American Thoracic Society task force, were followed in this thesis (96, 223). It was performed on a flat, non-slip 10 metre walking course with cones placed nine metres apart to avoid abrupt changes in direction (96, 223, 224). Standardised instructions were played to patients from a calibrated CD (Glenfield Hospital, Leicester, UK), instructing them to:

'*walk for as long as possible there and back along the 10 metre course keeping to the speed indicated by the beeps on the CD. You will hear these beeps at regular intervals. You should walk at a steady pace aiming to turn around the cone at one end of the course when you hear the first beep and at the other end when you hear the next'* (224).

The test comprises 12 levels and walking speed during the first level is set at 0.50 ms^{-1} (i.e. 20 seconds per shuttle), and increases each minute by 0.17 ms^{-1} (96, 224). On completion of each level patients were instructed to '*Increase your speed now*' (96, 224). If the patient did not walk within half a metre of a cone before the beep sounded the patient was advised '*You're not going fast enough; try to make up the speed this time*' (96, 224). The test was terminated if the patient was more than half a metre from the cone on the next shuttle when the beep sounded and the reason for termination recorded e.g. dyspnoea, leg fatigue. Oxygen saturations, heart rate and level of dyspnoea using the Borg scale (222) were recorded before and after the test with recovery time to baseline also measured. Patients were allowed to use a walking aid and or ambulatory oxygen if prescribed with the cylinder carried by an assistant; these factors were kept constant for within-participant measurements on repeated walk tests. In order to mitigate the learning effect associated with the test, two tests were performed with 30 minutes rest between tests with the furthest distance achieved used for analysis (96, 223, 224). This value provided the baseline exercise prescription for walking / treadmill training during PR using the following equation: $VO_2max = 4.19 (1.12 – 7.17) + 0.025 (0.018 - 0.031) x$ *ISW distance* (232).

2.11.2a Validity, responsiveness and MCID of the ISW in IPF

Although the ISW is one of the most widely used exercise outcome measures used in UK PR programmes, limited data exist in patients with IPF, where the 6MWT is the most established field walking test. At the start of my fellowship, only one published study, involving 10 patients, had examined the ISW in patients with IPF where the test, performed on a 10 metre course, was compared to that performed on an 'ISW programmed' treadmill (233). Consequently, as part of the data collection for this thesis, the validity, responsiveness and MCID of the ISW was determined in patients with IPF. This work was published as a research letter in Thorax and is briefly summarized in the following paragraphs which have been reproduced with permission of the BMJ Publishing Group Ltd (Appendix 1) (234).

2.11.2b Validity, responsiveness and MCID of the ISW in IPF: Methods

In two prospective observational cohort studies, patients were recruited from respiratory outpatient clinics at the Royal Brompton and Harefield NHS Foundation Trust, UK between February 2015 and July 2016. Inclusion criteria were patients diagnosed with IPF by a specialist ILD multidisciplinary team according to international guidelines (7), ability to provide informed consent and referred for outpatient PR as part of clinical care. Exclusion criteria were significant co-morbidities that would limit exercise capacity or make it unsafe. The studies were approved by the London Riverside Research Ethics Committee (14/LO/2247, 15/LO/0015) and all patients provided informed consent.

In cohort 1, spirometry, BMI, MRC (235), ISW (96), and 6MWT (96) were measured in 50 outpatients with IPF. In cohort 2, the ISW (96) and Chronic Respiratory Questionnaire (CRQ) (236) were assessed before and after an eight-week PR programme as described in section 2.15 of this chapter. At the post-PR assessment, prior to the measurement of the other outcome measures, patients also completed a five-point Global Rating of Change Questionnaire (GRCQ) comprising the question: 'How do you feel overall after pulmonary rehabilitation?' Responses were rated on a five-point Likert scale, ranging from '1: much better' to '5: much worse'. The study schemas are shown in Appendix 3.

Pearson's correlation coefficient was used to evaluate the relationship between the ISW and 6MWT and simple linear regression to predict 6MWT from ISW data. Outcomes and effect size following PR were compared using the paired t-test and Cohen's d respectively. The change in ISW according to GRCQ responses were evaluated using the one-way ANOVA test. Distribution-based estimates of the MCID used 0.5*standard deviation (SD), and standard error of measurement (SEM) using the formula $SEM = SD\ x\ \sqrt{1 - (test - retest\ reliability)}$, assuming an intra-class correlation of 0.80 (237). For the anchor-based method, the MCID was estimated to be the mean change in ISW for those who reported feeling '2: a little better' on the GRCQ (195).

2.11.2c Validity, responsiveness and MCID of the ISW in IPF: Results – Validation of the ISW

For this study, 64 patients were invited to participate: 11 declined, three did not meet the inclusion criteria and 50 enrolled. The baseline characteristics of this cohort are shown in table 2.2. There was a strong correlation between the ISW and 6MWT (r =0.81, p <0.0001) (figure 2.3). The formula to predict 6MWT using ISW data was: mean (95% confidence interval): 6MWT = 0.69 (0.54 to 0.84) * ISW + 160.30 (116.30 to 202.20) metres; r^2=0.65, p<0.0001.

Table 2.2: Baseline characteristics of patients: Validity and reliability (n=50).

Variable	**Baseline**
Gender: male (%)	72
Age (years)	75 (7)
FEV_1/FVC ratio	81.2 (6.8)
FVC (Litres)	2.2 (0.7)
FVC (% predicted)	70.0 (19.9)
MRC	3 (1)
BMI (kg/m^2)	26.9 (4.6)
LTOT (%)	8
ABOT (%)	12
ISW (metres)	264 (146)
6MWT (metres)	342 (145)

Baseline data are reported as mean (standard deviation) unless stated otherwise.

Abbreviations: Abbreviations: 6MWT: Six Minute Walk Test; ABOT: Ambulatory Oxygen Therapy; BMI: Body Mass Index; FEV_1/FVC: ratio of Forced Expiratory Volume in one second and Forced Vital Capacity; ISW: Incremental Shuttle Walk Test: LTOT: Long-Term Oxygen Therapy; MRC: Medical Research Council Dyspnoea score.

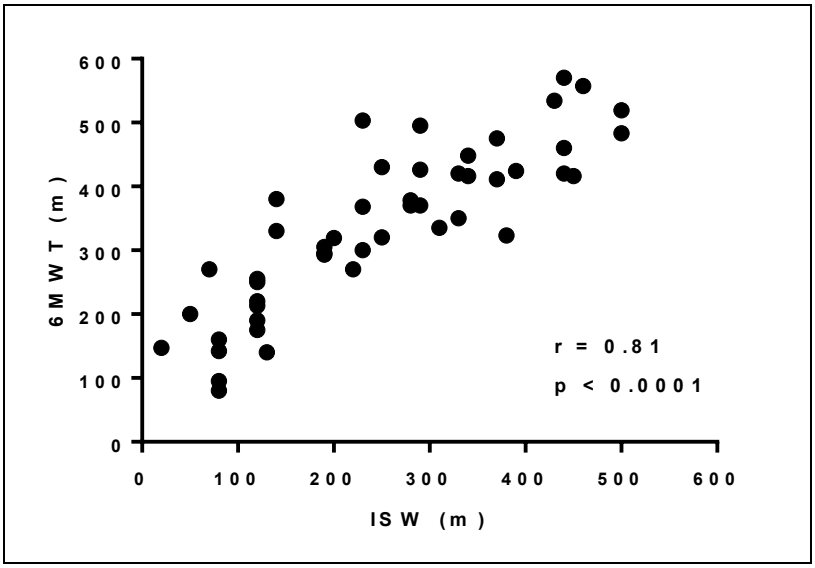

Figure 2.3: Correlation between the ISW and 6MWT.

Abbreviations: ISW: Incremental Shuttle Walk Test; 6MWT: Six Minute Walk Test.

2.11.2d Validity, responsiveness and MCID of the ISW in IPF: Results – Responsiveness of the ISW and estimation of the MCID

In this cohort, 82 patients were invited: five declined, two did not meet the inclusion criteria, and 77 were enrolled. Seventy two patients (93.5%) completed PR. The baseline characteristics and response to PR are in table 2.3. The effect sizes for the ISW, CRQ-dyspnoea and CRQ-total were 0.29, 0.68 and 0.49 respectively.

Table 2.3: Baseline characteristics of patients: Responsiveness (n=72).

Variable	Baseline	Change with PR	p-value
Gender: male (%)	69	NA	NA
Age (years)	74 (7)	NA	NA
FEV_1/FVC ratio	0.78 (0.09)	0 (-0.01 to 0.01)	0.67
FVC (Litres)	2.3 (0.7)	-0.02 (-0.08 to 0.03)	0.44
FVC (% predicted)	76.7 (19.8)	0.0 (-1.8 to 1.8)	0.78
MRC	3 (1)	-0.5 (-0.8 to -0.3)	<0.001
BMI (kg/m^2)	27.9 (4.9)	0.0 (-0.3 to 0.2)	0.21
LTOT (%)	8	NA	NA
ABOT (%)	15	NA	NA
ISW (metres)	285 (175)	54 (38 to 70)	<0.001
CRQ – Dyspnoea	16.7 (15.8)	4.2 (2.7 to 5.7)	<0.001
CRQ – Fatigue	15.4 (5.5)	2.0 (1.0 to 3.0)	<0.001
CRQ – Emotion	33.7 (9.1)	1.8 (0.4 to 3.3)	<0.001
CRQ – Mastery	19.9 (5.3)	1.9 (1.0 to 2.7)	<0.001
CRQ – Total score	85.7 (22.4)	9.9 (6.1 to 13.6)	<0.001

Baseline data are reported as mean (standard deviation) unless stated otherwise.

Abbreviations: ABOT: Ambulatory Oxygen Therapy; BMI: Body Mass Index; CRQ: Chronic Respiratory Questionnaire; FEV_1/FVC: ratio of Forced Expiratory Volume in one second and Forced Vital Capacity; ISW: Incremental Shuttle Walk Test; LTOT: Long-Term Oxygen Therapy; MRC: Medical Research Council Dyspnoea score.

For distribution-based methods, the ISW MCID estimate was 35 metres using 0.5*SD, and 31 metres using SEM. The distribution of response to the GRCQ was 1: 'much better' in 46%, 2: 'a little better'

in 42%, 3: 'the same' in 9%, 4: 'a little worse' in 3% and 5: 'much worse' in 0%. Due to the small number of patients, responses 3-5 were combined. The mean (95% CI) changes in ISW for responses 1, 2 and 3-5 were 69 (47 to 92) metres; 46 (18 to 74) metres and 14 (-34 to 61) metres respectively (p=0.03) (figure 2.4).

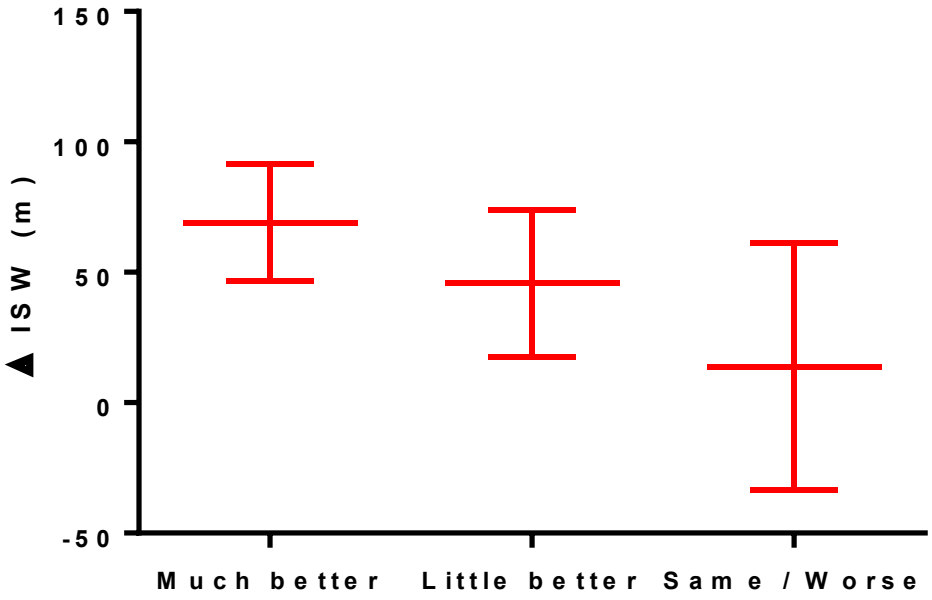

Figure 2.4: Mean (95% confidence interval) change in the ISW following PR according to the Global Rating of Change Questionnaire.

Abbreviations: ISW: Incremental Shuttle Walk Test; PR: Pulmonary Rehabilitation.

2.11.2e Validity, responsiveness and MCID of the ISW in IPF: Discussion and conclusion

This study is the first to assess the validity, responsiveness to PR and provide estimates of the MCID of the ISW in IPF-specific cohorts. This research was undertaken in respiratory outpatient clinics and a PR unit that adheres to UK and international PR guidelines, suggesting the results would be generalisable, but future studies are necessary to corroborate the findings. The strong correlation between the ISW and 6MWT provides evidence for concurrent validity of the ISW in IPF, and supports previous data demonstrating significant correlation between ISW and distance walked on a

treadmill in patients with IPF (233). The anchor-based estimate of the MCID of the ISW in IPF also corroborates the previously reported anchor-based estimate of the MCID in COPD (231).

The 6MWT was not used as an anchor in the responsiveness study because the participating PR programmes only used the ISW, although, for future studies a comparison between both tests following PR would be informative. However, the use of the GRCQ follows an established anchor for determining the MCID, in line with the method used by Singh *et al* to determine the MCID of the ISW in COPD (231). There were also few patients reporting deterioration with PR, hence the data findings support the MCID for improvement, and not deterioration. Although there is no gold standard technique or consensus on method of determining the MCID (195), this study used both distribution- and anchor-based methods to provide a range of MCID estimates. The anchor-based approach is favoured as it may capture the patient experience better than statistically derived, distribution-based estimates. Reassuringly the anchor-based estimate of the MCID for the ISW (46 metres) was very similar to the MCID observed in COPD (47.5 metres) (231). In summary, the ISW is valid and responsive to PR in patients with IPF with MCID estimates from 31 to 46 metres.

2.12 Muscle Strength

2.12.1 Assessment of quadriceps maximum voluntary contraction with strain gauge chair

Isometric maximum voluntary contraction of the quadriceps muscle (QMVC) of the dominant leg was assessed using a specially designed chair which was calibrated daily. This technique is commonly used to quantify muscle strength in chronic respiratory disease (238, 239) including ILD (fibrotic interstitial pneumonia (240)). The device comprised a mounted strain gauge and signal conditioning amplifier (Department of Clinical Engineering, Royal Brompton & Harefield NHS Foundation Trust, London, UK) using a technique described by Edwards *et al* (241). Patients were positioned in the chair with hips and knees flexed to of 90°. A non-extensible strap was placed around the hips to minimise pelvic movement. Another non-extensible strap was secured around the ankle, proximal to the malleoli, to ensure the knee remained flexed at 90° during testing. This strap was connected to a

strain gauge (Strainstall, Isle of Wight, UK: range 0 – 150kg) mounted on a horizontal cross bar, at the back of the chair, which was adjusted so that the ankle strap was parallel to the femur at the level of the ankle (figure 2.5).

During testing, patients were instructed to avoid using other muscle groups that may increase contraction force (for example back arching, lifting buttocks off the chair), and asked to cross the upper limbs on the chest. The test involved the patient pushing the lower limb against the ankle strap and holding the position for three to four seconds. The test protocol was as follows: a warm-up consisting of four contractions at approximately 50% effort and four at approximately 75% effort, followed by six contractions at maximal effort with a 20 second interval between contractions to allow time for recovery. Strong verbal encouragement was provided by the assessor to obtain a maximal effort.

During each manoeuvre, as the patient exerted strain on the ankle strap, force was exerted on the load cell of the strain gauge, with the voltage produced passing through a custom-made amplifier (Department of Clinical Engineering, Royal Brompton and Harefield NHS Foundation Trust, UK) and digitised through a PowerLab 16/30 recording unit (ADInstruments, Oxford, UK). The signals were recorded and analysed on a HP Compaq 6005 computer (Hewlett Packard, Bracknell, UK) running LabChart 7.3.7 software (ADInstruments, Oxford, UK) sampling at 10 kHz. The highest value of at least three reproducible efforts (i.e. within 10% of each other) that could be sustained over one second was recorded in kilogrammes.

Figure 2.5: Assessment of QMVC using the specially designed chair.

Abbreviation: QMVC: Quadriceps Maximum Voluntary Contraction.

2.12.2 Assessment of handgrip strength

Handgrip strength was determined using a JAMAR® Hydraulic Hand Dynamometer (Lafayette, Indiana, USA) using a reliable and valid technique (242-244). The device was calibrated annually by the manufacturer. Evaluation of handgrip strength with a hand held dynamometer has been used in a number of studies investigating muscle strength in ILD including IPF (245, 246).

Measurements of the dominant hand were made with the patient seated in a straight-backed chair with the feet flat on the floor. The shoulder was positioned in neutral with the elbow flexed at 90° and with the forearm in a neutral, unsupported position (figure 2.6). The appropriate grip length was chosen to accommodate the size of the participant's hand. The participant was asked to squeeze the device as hard as possible in one movement for three to four seconds with strong verbal encouragement provided. A minimum of three attempts were made until the difference in recorded grip strength was within 10%. Twenty seconds between attempts was allowed to facilitate recovery.

The average force of the three highest and most reproducible efforts was calculated and recorded in kilograms. This was then converted to % predicted of normal based on age, gender, height and handedness as described by Spruit *et al* (247).

Figure 2.6: Handgrip strength assessment using the JAMAR® Hydraulic Hand Dynamometer.

2.13 Health status

A copy of each questionnaire is shown in Appendix 4.

2.13.1 King's Brief Interstitial Lung Disease Questionnaire (KBILD)

The KBILD questionnaire is a self-administered, ILD-specific measure of health status developed in response to a paucity of instruments pertinent to patients with ILD (111). It has been shown to be valid (moderate relationship with FVC % predicted and physical summary of the Short Form 36, strong relationship with SGRQ (111, 112)), reproducible (112) and responsive to PR (113, 114) and longitudinal change (116) in patients with ILD, including those with IPF .

It is a 15-item questionnaire comprising three domains: psychological (seven items), breathlessness and activities (four items), chest symptoms (three items) and a total score (15 items),and takes five to seven minutes to complete (111). Scores for each domain and the total score range from 0: 'worst health status' to 100: 'best health status' (111). The KBILD can be scored using a Rasch analysis or impact factor scoring system which both yield similar results (112); the latter method was used in this research. Using the Rasch analysis method, the MCID estimate for the total score is five point increase in response to longitudinal change (116), however, the MCID of the questionnaire using the impact factor scoring system has not been reported. Similarly, the using the impact factor scoring system, the MCID estimate of the total score is four points in response to PR (114).

2.13.2 Chronic Respiratory Disease Questionnaire (CRQ)

The CRQ interviewer-administered (CRQ-IA) was developed for use in clinical trials to measure changes in health status in those with chronic airflow limitation (248). The self-administered version of this questionnaire CRQ-SA, with an individualised dyspnoea domain, has been shown to be valid (249) and responsive to change following PR (249, 250), and longitudinal change (250) in patients with ILD and IPF. This version of the questionnaire was used in this research and takes five to 10 minutes to complete (236).

The CRQ-SA comprises four domains, dyspnoea, fatigue, emotion and mastery, and an overall total score (236). For the dyspnoea domain, patients recorded the five most important activities that made them short of breath over the previous two weeks and rated the level of dyspnoea experienced when performing each activity on a seven-point Likert scale, ranging from 1: '*extremely short of breath*' to 7: '*not at all short of breath*' *(236)*. During subsequent assessments, patients evaluated the same five activities chosen during the first assessment. The remaining domains are

evaluated with items on the questionnaire: fatigue (four items); emotion (seven items); and mastery (four domains), also using a similar seven-point Likert scale for each item (236).

The total score of the CRQ-SA ranges from 7 to 140 with higher figures associated with better health status. Each domain is also scored separately and illustrates changes in individual components of health status (domain score range: dyspnoea: 5 to 35; fatigue: 4 to 28; emotion: 7 to 49; mastery: 4 to 28). The MCID, which has only been evaluated in COPD, has been estimated at a *mean* 0.5 point change per item (251) which translates to an increase of 2.5 points for the dyspnoea domain score; 2.0 points for fatigue; 3.5 points for emotion; 2.0 points for mastery and 10.0 points for the total score.

2.14 Pulmonary Rehabilitation (PR)

PR was the intervention delivered to assess the responsiveness of the 4MGS test. It comprised an eight week outpatient exercise and multidisciplinary education programme, organised and delivered according to the British Thoracic Society Quality Standards for Pulmonary Rehabilitation (252). Each week involved two supervised sessions of exercise and education (one hour each), and at least one additional home-based unsupervised exercise session.

Experienced respiratory physiotherapists supervised the exercise sessions which involved progressive, individually tailored aerobic and resistance training. Initial walking speed on the treadmill was prescribed at 60 to 80% of predicted peak oxygen consumption based on the ISW performance (253) with the aim of patients exercising for 15 minutes continuously at Borg Dyspnoea Scale level 3 to 4 (moderate to somewhat severe breathlessness). This exercise was progressed by increasing walking speed and the treadmill incline with the aim of exercising at a Borg Dyspnoea Scale level of 3 to 4. Initial endurance cycling was set at a workload to achieve level 3 to 4 on the

Borg Dyspnoea Scale with the aim of patients completing 15 minutes of continuous training. It was progressed by increasing the resistance and revolutions per minute.

Lower limb resistance training was based on the American College of Sport's Medicine resistance training guidelines (254, 255) with an initial prescription of two sets of eight seated leg press and knee extension repetitions based on 60 to 70% of a one-repetition maximum. This exercise was progressed by increasing the number of sets and repetitions to a maximum of 4 sets of 12 repetitions as well as increasing the resistance. Other lower limb exercises included sit-to-stand, knee extension, hip flexion and hip abduction exercises with appropriate free weights and ankle weights. Upper limb resistance training comprised biceps curls, shoulder press and upright row with free weights. The initial prescription for these upper and lower limb resistance exercises was one set of 15 repetitions which was progressed to two sets of 20 repetitions with heavier weights. Patients received an individualised, written home exercise programme during PR and an individualised structured, written plan for on-going exercise maintenance on completion of PR.

A multidisciplinary team, including physiotherapists, psychologists, dieticians, nurses, doctors, occupational therapists, dieticians, social workers, speech and language therapists and expert patients, delivered the education sessions. The aim was to develop patients' understanding and holistic management of their disease and topics included physical activity and exercise, medication use, diet, smoking cessation, coping strategies, as well as managing infections through early recognition, rescue medication and appropriate general practice/hospital presentation. Patients received a booklet of the topics covered in these sessions.

2.15 Composite scores of mortality in IPF

2.15.1 The Composite Physiologic Index (CPI)

Data from pulmonary function testing were used to calculate the Composite Physiologic Index (CPI), a measure of disease severity which indicates the extent of fibrosis whilst accounting for the presence of emphysema on a high resolution computed tomography (HRCT) thorax scan, using the following equation: $CPI = 91 - (0.65\ x\ DLCO\%) - (0.53\ x\ FVC\%) + (0.34\ x\ FEV1\%)$ (82). Lower CPI values indicate less severe disease and higher values; more severe disease (82). It has been shown to predict mortality more accurately than FVC and DL_{CO} in patients with biopsy proven UIP (82). In contrast, in a service audit of 167 patients with IPF, CPI was predictive of disease progression and performed better than the GAP staging system but not as well as DL_{CO} and long-term oxygen initiation (69). An increase in five points in CPI from baseline to 12 months predicts mortality and is considered a clinically meaningful change (84).

2.15.2 The Gender, Age and lung Physiology (GAP) index

This index is a multi-dimensional staging tool that can predict mortality in patients with IPF (85). It is calculated based on a simple scoring system of four variables: gender, age, FVC % predicted and DL_{CO} % predicted and scores range from zero to eight (85). The total score is used to classify patients into one of three stages: stage I: zero to three points; stage II: four to five points and stage III: six to eight points. One, two and three year mortality can be predicted from each stage (85). The scoring system for the index and staging system and the predicted mortality according to the staging system is shown in figure 2.7 (85).

	Predictor	Points
G	Gender	
	Female	0
	Male	1
A	Age, y	
	≤60	0
	61–65	1
	>65	2
P	Physiology	
	FVC, *% predicted*	
	>75	0
	50–75	1
	<50	2
	DLCO, *% predicted*	
	>55	0
	36–55	1
	≤35	2
	Cannot perform	3
	Total Possible Points	8

Stage	I	II	III
Points	0–3	4–5	6–8
Mortality			
1-y	5.6	16.2	39.2
2-y	10.9	29.9	62.1
3-y	16.3	42.1	76.8

Figure 2.7: The GAP index and staging system (85).

Printed with permission from the Annals of Internal Medicine (Appendix 1).

Abbreviations: DL_{CO}: Diffusing Capacity of the Lung for Carbon Monoxide; FVC: Forced Vital Capacity; GAP index: Gender, Age and lung Physiology index.

2.16 Mortality and non-elective hospital admission

Survival status and date of death, where applicable, were retrieved from patient hospital records via the 'Spine', a national database maintained by the NHS Care Records Service. The date and number of non-elective hospital episodes and were ascertained from hospital and general practice records.

Chapter 3 : The reliability and validity of the four metre gait speed and the phenotypic characteristics of the slow gait speed phenotype in idiopathic pulmonary fibrosis

This chapter was published in Respirology on 14th November 2017 (256). Permissions to use published materials in this thesis are shown in Appendix 1.

3.1 Aims

The aims of this study were: 1) to determine the inter-observer and test-retest reliability of the 4MGS test in IPF patients; 2) to assess the concurrent validity of the 4MGS test in IPF patients; and 3) to describe and compare the phenotypic characteristics of IPF patients according to the slow gait speed phenotype and 6MWT prognostic cut-point.

3.2 Hypothesis

- The intra-class correlation coefficient (ICC) of 4MGS inter-observer and test-retest reliability is >0.6
- 4MGS shares a moderate correlation (r>0.4) with validated outcome measures of exercise capacity, dyspnoea and health status in IPF.
- IPF patients with a slow 4MGS have worse exercise capacity, dyspnoea and health status in comparison to those with preserved 4MGS.

3.3 Methods

3.3.1 Study participants

All participants were prospectively recruited from outpatient respiratory, pulmonary rehabilitation and ambulatory oxygen assessment clinics at the Royal Brompton and Harefield NHS Foundation Trust, UK between January 2015 and December 2015. The inclusion criteria were patients diagnosed with IPF by a specialist ILD multidisciplinary team according to international guidelines (7), able to walk five metres and provide informed consent, whereas those with co-morbidities that would limit walking ability or make exercise unsafe (e.g. unstable ischemic heart disease) were excluded. All participants provided informed written consent and the studies were approved by the London-Riverside Research Ethics Committee (14/LO/2248, 15/LO/0015) and registered on clinicaltrials.gov (NCT02445157, NCT02436278).

3.3.2 Inter-observer and test-retest reliability

Participants for this study were recruited from outpatient respiratory and pulmonary rehabilitation (PR) clinics at Harefield Hospital. For inter-observer reliability two assessors measured 4MGS on the same occasion; one assessor also assessed pulmonary function (208), Composite Physiologic Index (CPI) (82), Gender, Age and lung Physiology (GAP) index (85), anthropometry, Medical Research Council Dyspnoea scale (MRC) (66) and co-morbidities using the age-adjusted Charlson co-morbidity index (257) (figure 3.1). Seven days later, the same assessor measured 4MGS of the same participant for the evaluation of test-retest reliability (figure 3.2). The procedure for assessing these outcome measures is described in Chapter 2 but a brief description of the measurement of gait speed is provided here. 4MGS was measured on a flat, four metre course with a standing start with the participant instructed to walk at his/her usual speed (189). Two tests were performed with minimal

rest and the faster of the two, measured by stopwatch, was used to calculate gait speed. Patients walked using their usual walking aid or ambulatory oxygen, if prescribed.

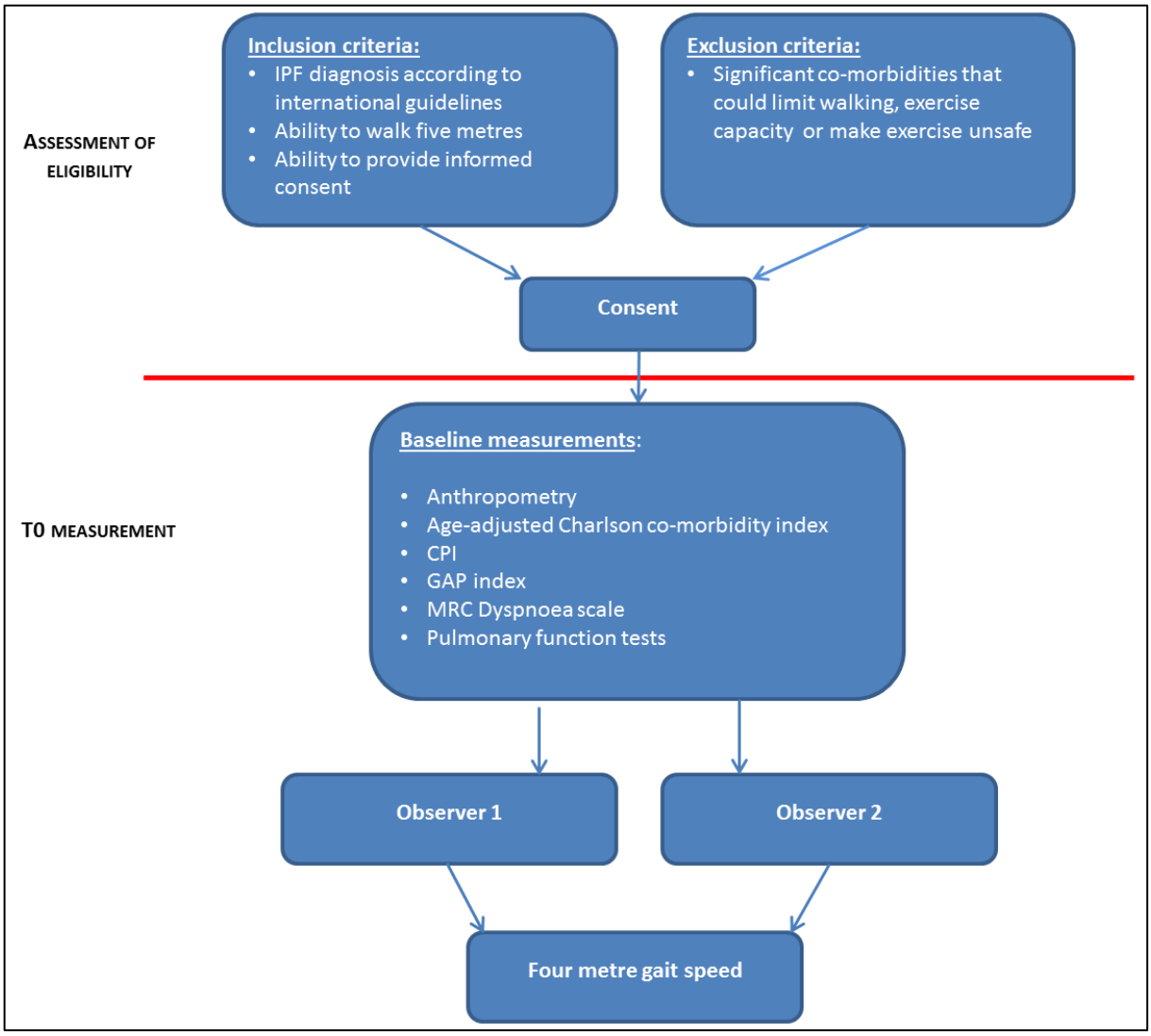

Figure 3.1: Inter-observer reliability study schema.

Abbreviation: CPI: Composite Physiologic Index; IPF: Idiopathic Pulmonary Fibrosis; GAP: Gender, Age and lung Physiology index; MRC: Medical Research Council Dyspnoea scale.

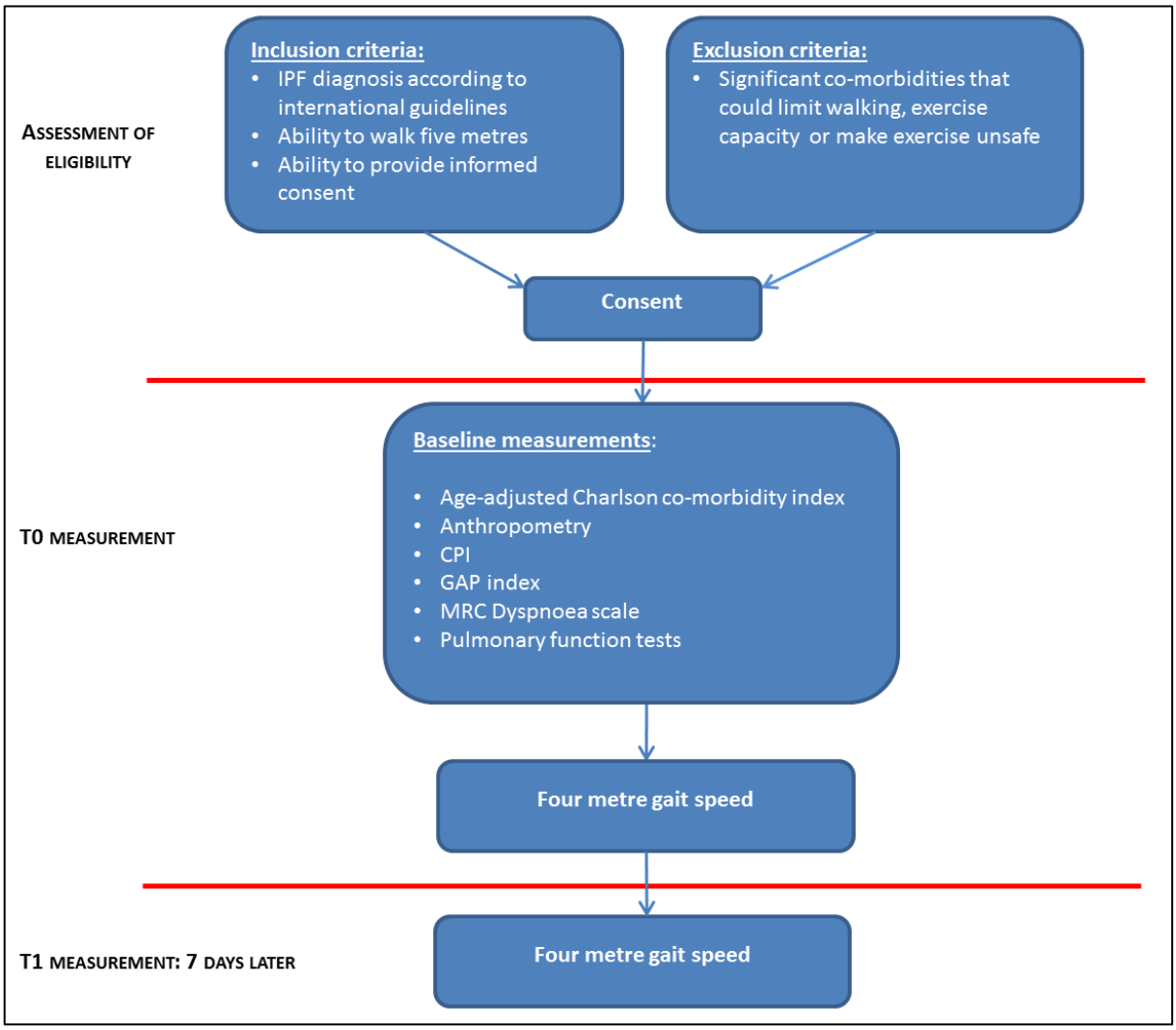

Figure 3.2: Test-retest reliability study schema.

Abbreviation: CPI: Composite Physiologic Index; IPF: Idiopathic Pulmonary Fibrosis; GAP: Gender, Age and lung Physiology index; MRC: Medical Research Council Dyspnoea scale.

3.3.3 Concurrent validity

The concurrent validity of 4MGS was assessed using a prospective study using two independent cohorts. The first cohort was recruited from a specialist ILD clinic at the Royal Brompton Hospital, UK. The outcome measures evaluated in this study are described in Chapter 2 and included anthropometric measurements, 4MGS, pulmonary function tests (208), CPI (82), GAP index (85), high resolution computed tomography (HRCT) scan of the chest (211), 6MWT (88, 96), King's Brief Interstitial Lung Disease questionnaire (KBILD) (111) and the MRC Dyspnoea scale (212, 213) (figure

3.3). Co-morbidities were quantified using the age-adjusted Charlson co-morbidity index (257). An independent second validation cohort was recruited from an ambulatory oxygen assessment clinic at Harefield Hospital; patients completed the 4MGS test, anthropometric measurements; spirometry (208), 6MWT (88, 96) MRC Dyspnoea scale (66), and age-adjusted Charlson co-morbidity index (257)(figure 3.4).

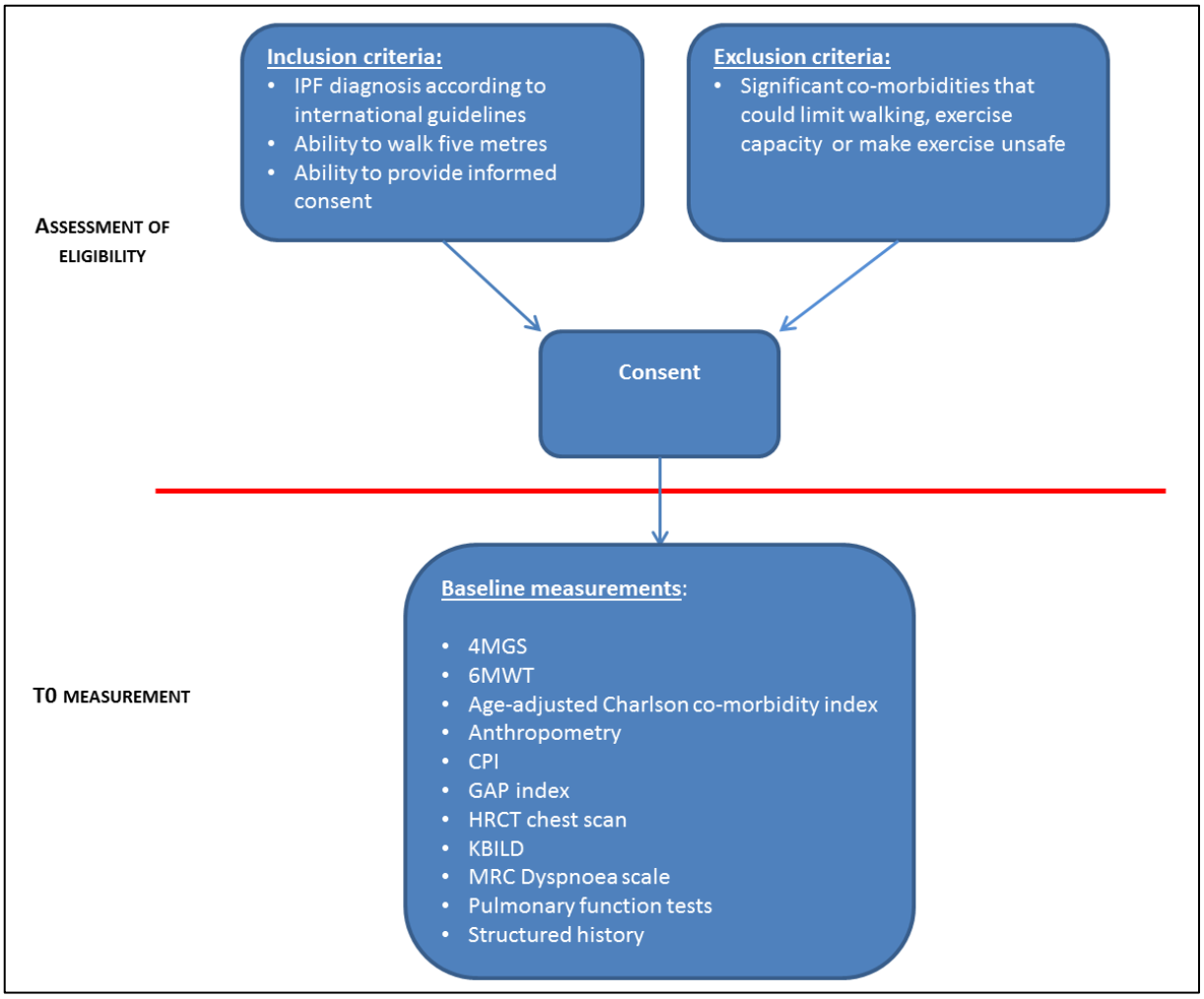

Figure 3.3: Concurrent validity study schema – first validation cohort.

Abbreviations: 4MGS: Four metre gait speed; 6MWT: Six minute walk test; CPI: Composite Physiologic Index; GAP: Gender, Age and lung Physiology index; HRCT: High resolution computed tomography; IPF: Idiopathic pulmonary fibrosis; KBILD: King's Brief Interstitial Lung Disease questionnaire; MRC: Medical Council Dyspnoea scale.

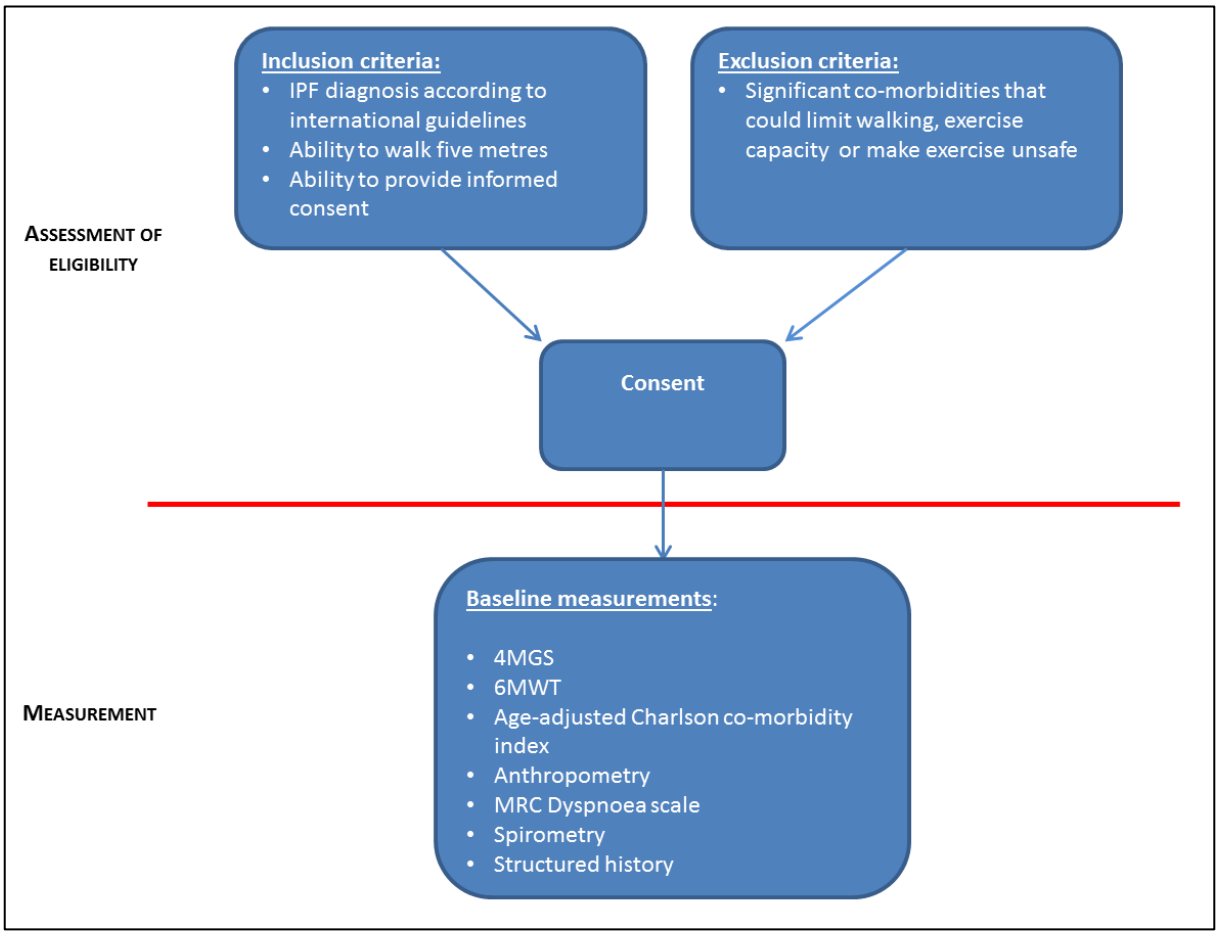

Figure 3.4: Concurrent validity study schema – second validation cohort.

Abbreviations: 4MGS: Four Metre Gait Speed; 6MWT: Six Minute Walk Test; IPF: Idiopathic Pulmonary Fibrosis; MRC: Medical Council Dyspnoea scale.

3.3.4 Stratification according to slow and preserved gait speed phenotypes

Patients in the first validation study were stratified according to the slow gait speed phenotype recommended by expert consensus groups (slow gait speed: <0.80 ms^{-1}; preserved gait speed: ≥0.80 ms^{-1}) (143, 144), and the 6MWT prognostic cut-point (6MWT <250 and ≥250 metres (94)). The between-group differences in phenotypic characteristics were calculated.

3.3.5 Statistical analysis

For the reliability analysis, assuming a 5% significance level and 80% power with two observations, a minimum of 39 patients would be required to show an intra-class correlation coefficient (ICC) >0.6 when the true coefficient is 0.8 (258). For the validation studies, to demonstrate a moderate strength correlation (r>0.4) between 4MGS and 6MWT against the null hypothesis (r=0) with 90% power at a p-value threshold of 0.05 would require a minimum of 62 patients.

Single measure ICCs of consistency and random effect were calculated with 95% confidence intervals (95% CI) to examine inter-observer and test-retest reliability. Measurement variability was determined by calculating the standard error of measurement (SEM) and percentages of SEM (SEM %). Bland–Altman plots were plotted to demonstrate the 95% limits of agreement. Pearson's correlation coefficient (Spearman's rank for non-parametric data) was used to quantify the correlation between 4MGS and other measures, as well as between 6MWT and other measures. Multivariable regression was used to investigate determinants of 4MGS. 6MWT, MRC, GAP index, FVC % predicted, body mass index, age-adjusted Charlson Co-morbidity Index and KBILD total score were considered as independent variables. Age, gender, forced vital capacity (FVC) % predicted and diffusing capacity of the lung for carbon monoxide (DL_{CO}) % predicted were not considered as they are components of the GAP index. After checking for co-linearity between independent variables (r<0.5), a stepwise approach was used to retain or remove them from the model; entry criterion p<0.05, removal criterion p≥0.10 (259). Between-group differences were assessed using unpaired t-tests (Mann Whitney U test for nonparametric data). Data analyses were performed using GraphPad Prism 6 and 7 (GraphPad Software, La Jolla, USA) and SPSS versions 22 and 24 (IBM, New York, USA). Statistical significance was considered at p<0.05.

3.4 Results

3.4.1 Inter-observer and test-retest reliability

Sixty patients were approached to participate in the study: 13 declined and one did not meet the inclusion criteria (unable to walk five metres). The baseline characteristics of the recruited 46 patients are shown in table 3.1.

Table 3.1: Baseline characteristics of the participants in the inter-observer and test-retest reliability studies (n=46).

Variable	**Baseline**
Gender: male (%)	72
Age (years)	75 (7.6)
MRC	3 (1)
BMI (kg/m^2)	27.1 (5.8)
FEV_1/FVC ratio	80.0 (7.4)
FVC (litres)	2.3 (0.7)
FVC (% predicted)	71.9 (20.8)
DL_{CO} (% predicted)	47.4 (21.3)
CPI	49.1 (18.6)
GAP index	4 (1)
GAP Stage 1 (%)	19
GAP Stage 2 (%)	67
GAP Stage 3 (%)	14
Age-adjusted Charlson Co-morbidity Index	3 (0, 4)
LTOT (%)	15
ABOT (%)	30
Walking aid (%)	7
Pirfenidone (%)	26
Nintedanib (%)	0
4MGS (ms^{-1})	0.94 (0.25)

Data reported as mean (standard deviation) unless otherwise stated.

Abbreviations: 4MGS: Four Metre Gait Speed; ABOT: Ambulatory Oxygen Therapy; BMI: Body Mass Index; CPI: Composite Physiologic Index; DL_{CO}: Diffusing Capacity of the Lung for Carbon Monoxide; FEV_1/FVC: ratio of Forced Expiratory Volume in one second and Forced Vital Capacity; FVC: Forced Vital Capacity; GAP: Gender, Age and lung Physiology index; LTOT: Long Term Oxygen Therapy; MRC: Medical Research Council Dyspnoea score.

4MGS showed high inter-observer and test-retest reliability with ICC (95% confidence interval (CI)) values of 0.996 (0.992 to 0.998) (table 3.2) and 0.983 (0.970 to 0.991) (table 3.3) respectively. The mean difference between test occasions and observers was 0.001ms^{-1} and 0.01ms^{-1} respectively with no significant change in gait speed between the two occasions (p=0.85) or between observer values (p=0.42). Measurement variability was low with SEM and SEM% values of 0.002 and 0.16% for inter-observer and 0.0002 and 0.65% for test-retest reliability respectively. Similarly, narrow limits of agreement between observers (0.05 ms^{-1} to -0.04 ms^{-1}) and occasions (0.09 ms^{-1} to -0.09 ms^{-1}) were demonstrated in the Bland Altman plots (figure 3.5). However, there appeared to be a trend of decreased accuracy in patients who walked more quickly, particularly in the inter-observer group.

Table 3.2: Summary of inter-observer reliability data for 4MGS (n=46)

Variable	**Observer 1 (mean (SD))**	**Observer 2 (mean (SD))**	**ICC (95% CI)**	**SEM (ms^{-1})**	**SEM (%)**
4MGS (ms^{-1})	0.94 (0.25)	0.93 (0.26)	0.996 (0.992 to 0.998)	0.002	0.16

Abbreviations: 4MGS: Four metre gait speed; ICC: Intra-class correlation coefficient; CI: Confidence interval; SD: Standard deviation; SEM: Standard error of measurement.

Table 3.3: Summary of test-retest reliability data for 4MGS (n=46).

Variable	**Observer 1 (mean (SD))**	**Observer 2 (mean (SD))**	**ICC (95% CI)**	**SEM (ms^{-1})**	**SEM (%)**
4MGS (ms^{-1})	0.93 (0.25)	0.93 (0.25)	0.983 (0.970 to 0.991)	0.0002	0.65

Abbreviations: 4MGS: Four metre gait speed; ICC: Intra-class correlation coefficient; CI: Confidence interval; SD: Standard deviation; SEM: Standard error of measurement.

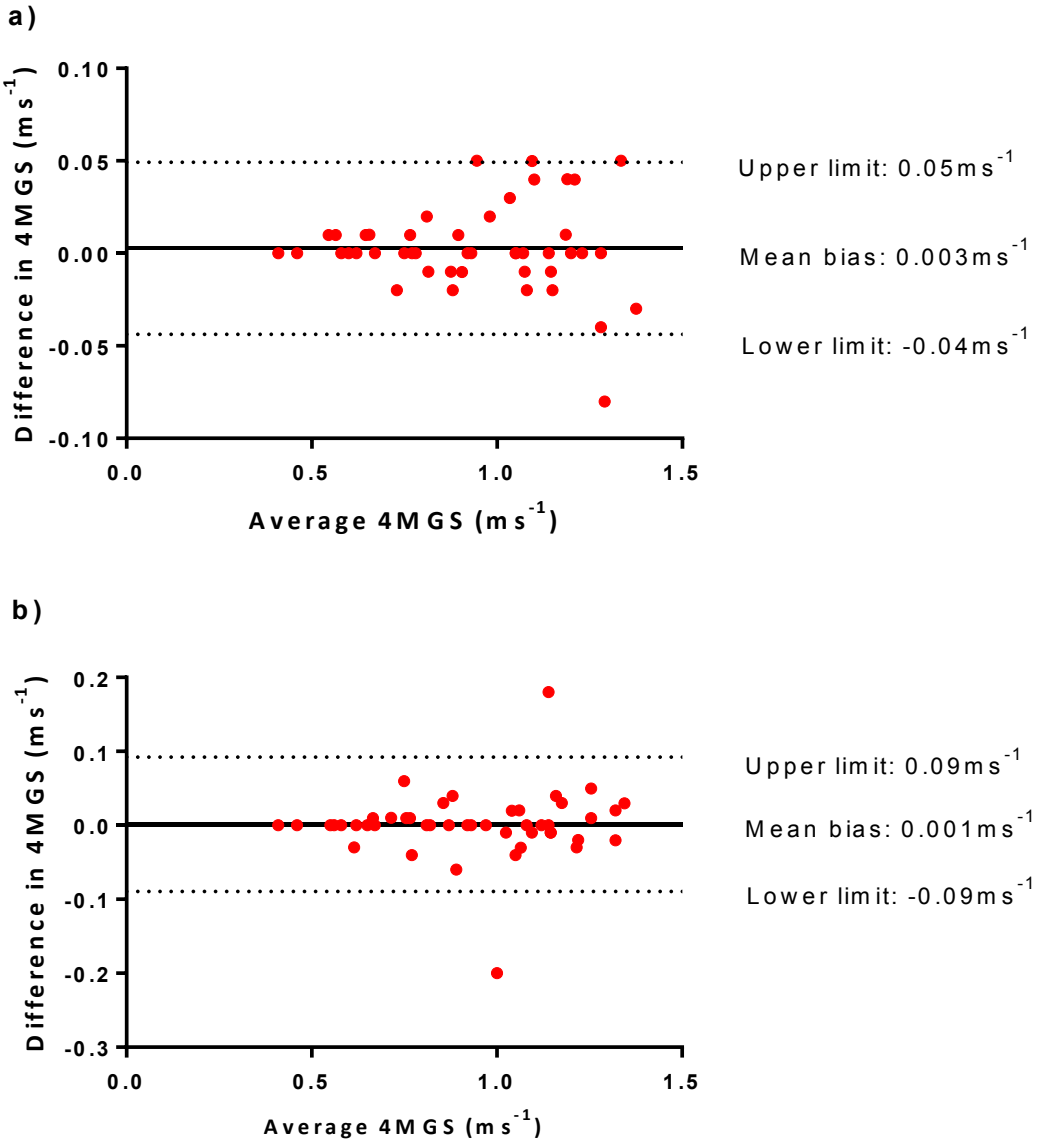

Figure 3.5: Bland-Altman plots for a) inter-observer and b) test-retest reliability.

Abbreviation: 4MGS: Four Metre Gait Speed.

3.4.2 Concurrent validity

For the first validation cohort, 87 patients were approached: 17 declined to participate and five did not meet the inclusion criteria (n=2: unstable cardiac condition; n=2: walking limited by lower limb pain; n=1: unable to walk five metres). The baseline characteristics of the 65 recruited patients and

the relationship between 4MGS and other outcome measures are reported in table 3.4. Seven patients used a walking aid whilst seven other patients were prescribed ambulatory oxygen.

4MGS shared a strong correlation with 6MWT ($r=0.76$, $p<0.0001$), a moderately strong relationship with health status (KBILD total score: $r=0.44$, $p=0.0003$), and negative correlations with MRC ($r=-0.56$, $p<0.0001$) and GAP index ($r=-0.41$; $p=0.002$) (table 3.4 and figure 3.6). No significant relationships were seen between 4MGS and HRCT extent of disease, nor with pulmonary function parameters such as FVC % predicted or DL_{CO} % predicted (table 3.4). Similarly, no significant correlations were observed between the 6MWT and FVC or HRCT extent of disease (table 3.5).

Table 3.4: Baseline characteristics and relationship (r-value) between 4MGS and other outcome measures in the first validation cohort (n=65).

Variable	**Baseline**	**r-value (95% CI)**	**p-value**
Gender: male (%)	89	-	-
Age (years)	72 (7)	-0.35 (-0.54 to -0.11)	0.005
MRC	3 (1)	-0.56 (-0.71 to -0.36)	<0.001
BMI (kg/m^2)	27.3 (4.4)	-0.01 (-0.26 to 0.23)	0.91
FEV_1/FVC ratio	81.2 (6.8)	0.12 (-0.13 to 0.35)	0.35
FVC (litres)	2.6 (0.7)	0.14 (-0.10 to 0.37)	0.25
FVC (% predicted)	73.2 (16.5)	0.15 (-0.10 to 0.38)	0.24
DL_{CO} (% predicted)	43.8 (14.3)	0.13 (-0.14 to 0.38)	0.35
CPI	49.7 (10.8)	-0.13 (-0.38 to 0.14)	0.35
GAP index	4 (1)	-0.41 (-0.61 to -0.16)	0.002
GAP Stage 1 (%)	22	-	-
GAP Stage 2 (%)	67	-	-
GAP Stage 3 (%)	11	-	-
Age-adjusted Charlson Co-morbidity Index	0 (0, 5)	-0.13 (-0.37 to 0.13)	0.31
LTOT (%)	3	-	-
ABOT (%)	11	-	-
Walking aid (%)	11	-	-
Pirfenidone (%)	5	-	-
Nintedanib (%)	2	-	-
4MGS (ms^{-1})	0.89 (0.25)	-	-
6MWT (metres)	355 (132)	0.76 (0.63 to 0.85)	<0.001
KBILD – Psychological	60.4 (22.1)	0.34 (0.11 to 0.54)	0.006
KBILD – Breathlessness and activities	40.9 (19.2)	0.45 (0.23 to 0.62)	<0.001
KBILD – Chest symptoms	66.7 (24.0)	0.42 (0.19 to 0.60)	<0.001
KBILD – Total	56.7 (13.8)	0.44 (0.22 to 0.62)	<0.001
Total lung ILD extent on HRCT (%)	33.6 (13.6)	-0.05 (-0.30 to 0.21)	0.71

Baseline data are reported as mean (standard deviation) unless stated otherwise.

Abbreviations: 4MGS: Four Metre Gait Speed; 6MWT: Six Minute Walk Test; ABOT: Ambulatory Oxygen Therapy; BMI: Body Mass Index; CPI: Composite Physiologic Index; CI: Confidence Interval; DL_{CO}: Diffusing Capacity of the Lung for Carbon Monoxide; FEV_1/FVC: ratio of Forced Expiratory Volume in one second and Forced Vital Capacity; FVC: Forced Vital Capacity; GAP: Gender, Age and lung Physiology index; HRCT: High Resolution Computed Tomography; ILD: Interstitial Lung Disease: KBILD: King's Brief Interstitial Lung Disease questionnaire; LTOT: Long-Term Oxygen Therapy; MRC: Medical Research Council Dyspnoea score.

Table 3.5: Baseline and relationship (r-value) between 6MWT and other outcome measures in the first validation cohort (n=65).

Variable	**Baseline**	**r-value (95% CI)**	**p-value**
FVC (litres)	2.6 (0.7)	0.16 (-0.09 to 0.39)	0.20
FVC (% predicted)	73.2 (16.5)	0.23 (-0.02 to 0.45)	0.07
Total lung ILD extent on HRCT (%)	33.6 (13.6)	0.16 (-0.13 to 0.42)	0.30

Baseline data are reported as mean (standard deviation).

Abbreviations: 6MWT: Six Minute Walk Test; FVC: Forced Vital Capacity; High Resolution Computed Tomography.

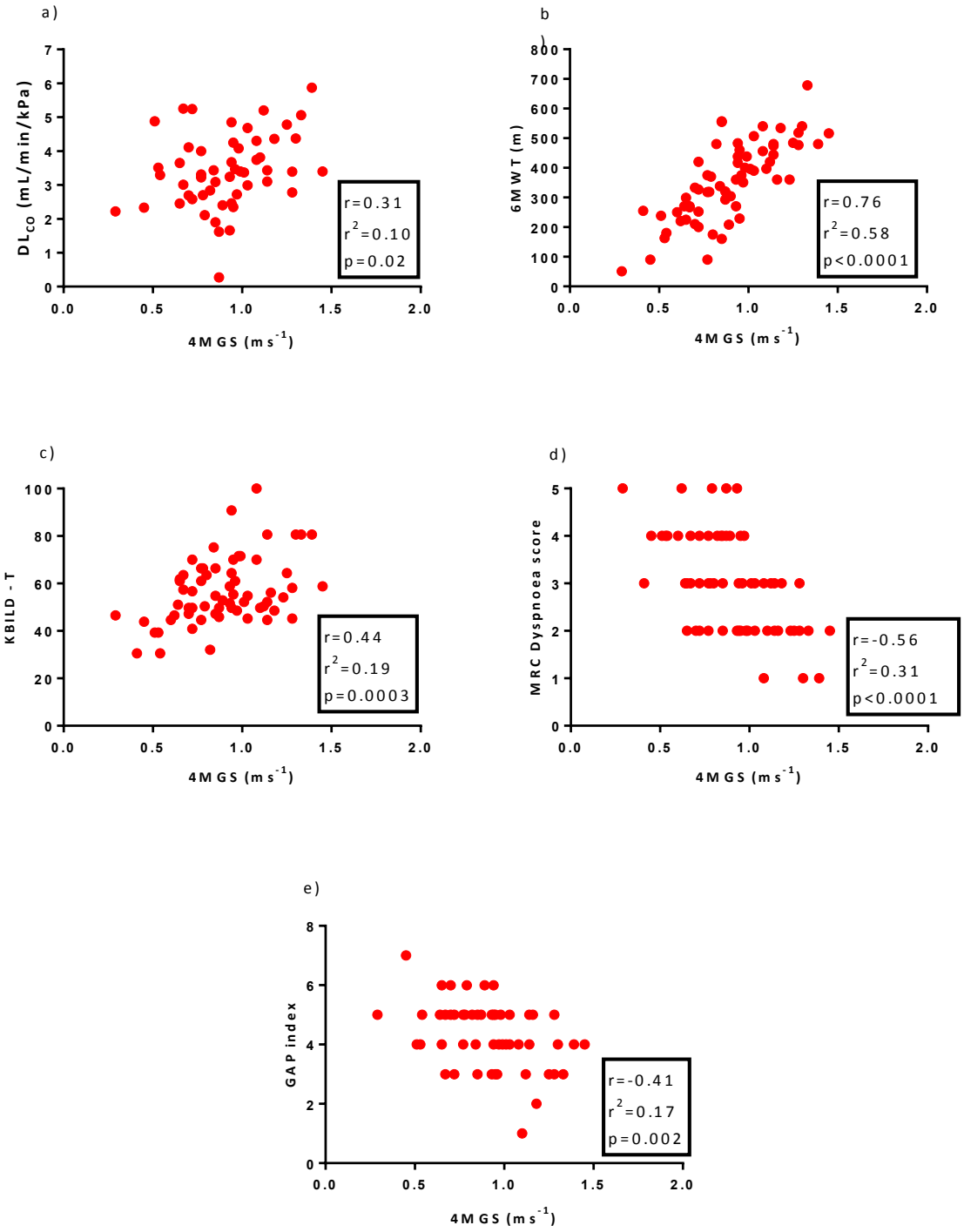

Figure 3.6: The relationship between 4MGS and a) DL_{CO}; b) 6MWT; c) KBILD total score; d) MRC Dyspnoea score and e) GAP index in the first validation cohort.

Abbreviations: 4MGS: Four Metre Gait Speed; 6MWT: Six Minute Walk Test; DL_{CO}*: Diffusing Capacity of the Lung for Carbon Monoxide; GAP: Gender, Age and lung Physiology index; KBILD-T: King's Brief Interstitial Lung Disease questionnaire–total score; MRC: Medical Research Council Dyspnoea score.*

The baseline characteristics of the second validation cohort (n=62) undergoing ambulatory oxygen assessment are in table 3.6. Similar to the first validation cohort, 4MGS correlated strongly with 6MWT (r=0.85, p<0.0001) and negatively with MRC (r=-0.59, p=0.0002) (table 3.6, figure 3.7). There were no significant relationships with any spirometry parameters (table 3.6).

Table 3.6: Baseline characteristics and relationship (r-value) between 4MGS and other outcome measures of the second validation cohort (n=62).

Variable	**Baseline**	**r-value (95% CI)**	**p-value**
Gender: male (%)	74	-	-
Age (years)	74 (8)	-1.0 (-0.34 to 0.15)	0.44
MRC	3 (1)	-0.59 (-0.77 to -0.33)	<0.001
BMI (kg/m^2)	27.0 (5.0)	0.20 (-0.07 to 0.44)	0.14
FEV_1/FVC ratio	0.83 (0.07)	0.06 (-0.21 to 0.33)	0.67
FVC (litres)	2.2 (0.7)	0.13 (-0.05 to 0.31)	0.20
FVC (% predicted)	69 (22)	0.25 (-0.02 to 0.48)	0.07
Age-adjusted Charlson Co-morbidity Index	0 (0, 4)	0.03 (-0.23 to 0.28)	0.84
LTOT (%)	16	-	-
ABOT (%)	29	-	-
Walking aid (%)	3	-	-
Pirfenidone (%)	8	-	-
Nintedanib (%)	2	-	-
4MGS (ms^{-1})	0.87 (0.25)	-	-
6MWT (metres)	229 (103)	0.85 (0.76 to 0.91)	<0.001

Baseline data are reported as mean (standard deviation) unless stated otherwise.

Abbreviations: 4MGS: Four Metre Gait Speed; 6MWT: Six Minute Walk Test; ABOT: Ambulatory Oxygen Therapy; BMI: Body Mass Index; CI: Confidence Interval; FEV_1/FVC: ratio of Forced Expiratory Volume in one second and Forced Vital Capacity; FVC: Forced Vital Capacity; LTOT: Long-Term Oxygen Therapy; MRC: Medical Research Council Dyspnoea score.

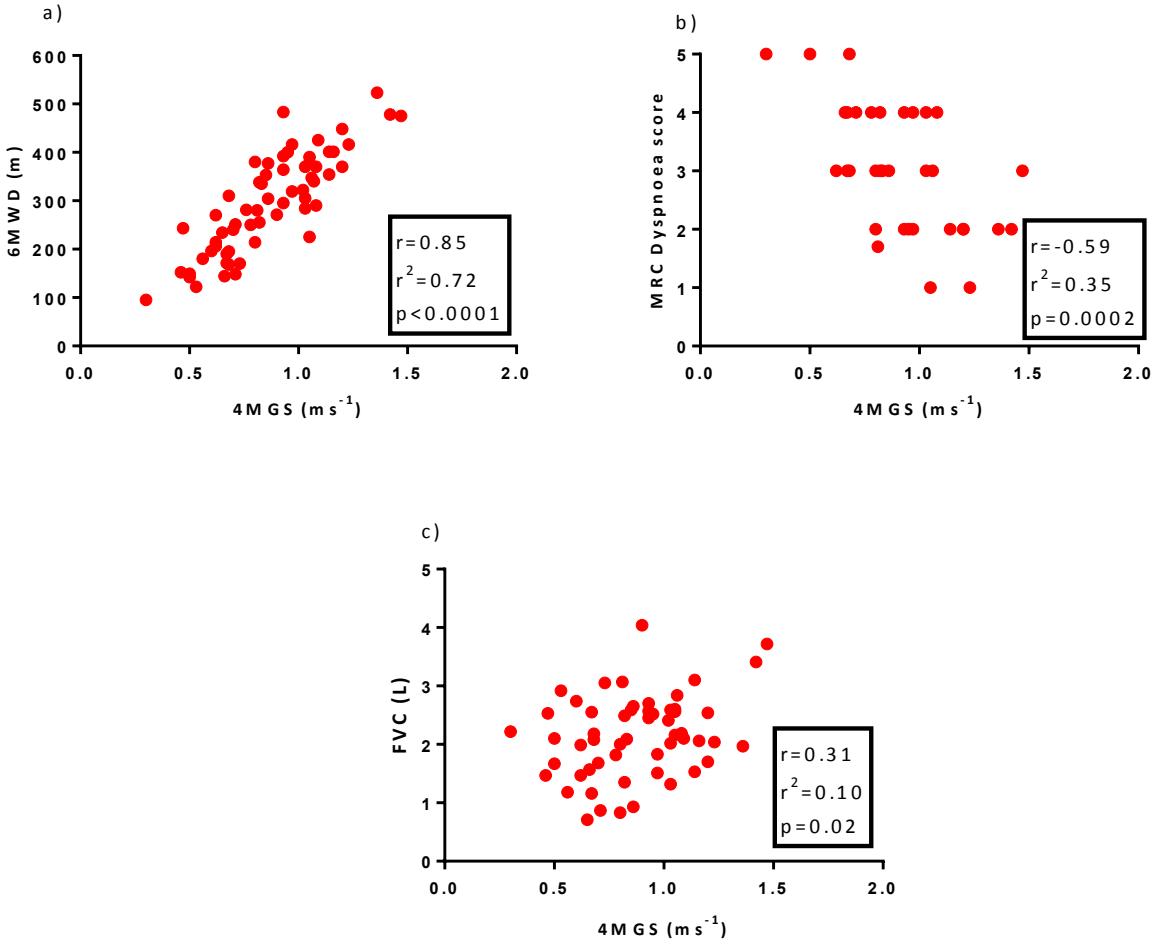

Figure 3.7: The relationship between 4MGS and a) 6MWT and b) MRC in the second validation cohort.

Abbreviations: 4MGS: Four Metre Gait Speed; 6MWT: Six Minute Walk Test; MRC: Medical Research Council Dyspnoea score; FVC: Forced Vital Capacity.

Using a stepwise multivariable linear regression model to describe 4MGS, 6MWT alone explained 57% of the variance in 4MGS (table 3.7, model 1). However the addition of GAP index explained 67% of the variance in 4MGS (table 3.7, model 3). The equation to predict 4MGS was:

Mean (95% CI) 4MGS = 0.001 (0.001 to 0.002) * 6MWT -0.040 (-0.078 to -0.002) * GAP index + 0.586 (0.356 to 0.817) ms^{-1}, r^2=0.67, p<0.0001.

Table 3.7: Multivariable linear regression models to predict 4MGS (n=65).

Model	**Covariate**	**β coefficient (95% CI)**	**p-value**	**Model r^2 (adjusted r^2)**
I	6MWT	0.001 (0.001 to 0.002)	<0.0001	0.58 (0.57)
II	6MWT	0.001 (0.001 to 0.002)	<0.0001	0.59 (0.58)
	MRC	-0.038 (-0.088 to 0.011)	0.13	
III	6MWT	0.001 (0.001 to 0.002)	<0.0001	0.67 (0.66)
	GAP index	-0.040 (-0.078 to -0.002)	0.04	

Abbreviations: 6MWT: 6 Minute Walk Test; CI: Confidence Interval; GAP: Gender, Age and lung Physiology index; MRC: Medical Research Council Dyspnoea score.

3.4.3 Stratification according to slow and preserved gait speed phenotypes

In the first validation cohort, 24 (37%) patients had a 'slow' 4MGS and 41 (63%) had a 'preserved' 4MGS. Those with slow 4MGS were older, but there were no differences in gender distribution, pulmonary function parameters, radiological quantification of ILD or use of oxygen therapy or anti-fibrotic medication. However large deficits in exercise capacity, respiratory disability, health status and multi-dimensional prognostic index were observed in the slow 4MGS group (table 3.8 and figure 3.8). In contrast, when stratified according to the 6MWT prognostic cut-point, significant between-group differences were only observed in MRC, 4MGS as well as use of a walking aid and long-term

oxygen therapy (table 3.8). Although, there was no significant between group difference in radiological quantification of ILD, the 6MWT prognostic cut-point appeared to be better able to detect differences in this measure than the 4MGS phenotype. Despite both the 4MGS and 6MWT phenotypes detecting significant differences in respiratory disability and walking aid use, the 6MWT had lower p-values which may suggest it is the superior measure. However, it is important to note that the 6MWT <250m group had only 14 patients in it, which invalidates the t-test used to detect beween group differences. This study should be repeated with a larger sample size to clarify the results presented in this thesis.

Table 3.8: Phenotypic characteristics and between-group differences according to 4MGS and 6MWT prognostic cut-points (n=65).

Variable	**Slow gait speed <0.80 ms^{-1} (n=24)**	**Preserved gait speed ≥0.80 ms^{-1} (n=41)**	**Mean between-group difference (95% CI)**	**p-value**	**6MWT <250m (n=14)**	**6MWT ≥250m (n=51)**	**Mean between-group difference (95% CI)**	**p-value**
Gender: male (%)	24 (100)	34 (83)	10 (-17)	0.03	13 (93)	45 (88)	32 (-5)	0.62
Age (years)	75 (7)	71 (7)	-4 (-8 to -1)	0.02	74 (8)	72 (7)	-2 (-7 to 2)	0.33
MRC	3.4 (1.0)	2.7 (1.0)	-0.7 (-0.2 to -0.1)	0.01	4 (1)	3 (1)	-1.1 (-1.7 to -0.5)	<0.001
BMI (kg/m^2)	27.2 (4.0)	27.3 (4.7)	0.1 (-2.2 to 2.4)	0.91	28.8 (5.5)	26.8 (4.0)	-2.0 (-4.6 to 0.6)	0.13
FEV_1/FVC ratio	80.4 (8.2)	81.7 (6.0)	1.3 (-2.2 to 4.8)	0.46	80.9 (9.4)	81.5 (6.0)	1.5 (-2.6 to 5.7)	0.46
FVC (litres)	2.6 (0.7)	2.6 (0.6)	0.01 (-0.33 to 0.35)	0.95	2.5 (0.7)	2.6 (0.6)	0.1 (-0.3 to)	0.75
FVC (% predicted)	69.0 (14.9)	75.6 (17.0)	6.6 (-1.9 to 15.1)	0.12	69.7 (15.3)	74.3 (16.7)	4.6 (-5.3 to 14.5)	0.36
DL_{CO} (% predicted)	44.2 (16.7)	42.5 (14.3)	-1.7 (10.4 to 6.9)	0.69	44.3 (19.8)	43.7 (12.5)	-0.6 (-10.1 to 8.8)	0.89
CPI	50.4 (12.9)	49.3 (9.6)	-1.1 (-7.3 to 5.1)	0.73	49.6 (14.4)	49.7 (9.7)	0.1 (-7.0 to 7.2)	0.98
GAP index	5 (1)	4 (1)	-0.8 (-1.4 to -0.2)	0.01	5 (1)	4 (1)	-0.4 (-1.2 to 0.3)	0.24
Age-adjusted Charlson Co-morbidity Index	0 (0, 5)	2 (0, 5)	2 (0, 2)	0.98	2 (0, 5)	0 (0, 4)	-1.5 (-2.0, 2.5)	0.71
4MGS (ms^{-1})	0.64 (0.13)	1.04 (0.17)	0.40 (0.32 to 0.48)	<0.001	0.66 (0.19)	0.96 (0.23)	0.30 (0.26 to 0.43)	<0.001

LTOT (%)	8	0	-8	0.06	14	0	-14	<0.01
ABOT (%)	13	10	-3	0.73	21	8	-13	0.15
Walking aid (%)	21	5	-16	0.045	29	6	19	0.02
Pirfenidone (%)	8	2	-6	0.27	7	4	-3	0.61
Nintedanib (%)	0	2	2	0.44	0	2	2	0.60
6MWT (metres)	250 (92)	416 (112)	167 (133 to 220)	<0.001	174 (59)	404 (99)	230 (175 to 285)	<0.001
KBILD - Psychological	52.7 (16.0)	65.0 (23.9)	12.3 (1.2 to 23.3)	0.03	52.1 (16.8)	62.7 (22.9)	10.5 (-2.6 to 23.7)	0.12
KBILD – Breathlessness and activities	32.1 (16.0)	46.2 (19.2)	14.1 (4.8 to 23.5)	0.004	32.9 (15.3)	43.2 (1.7)	10.3 (-1.1 to 21.7)	0.08
KBILD – Chest symptoms	56.7 (23.2)	72.8 (22.7)	16.1 (4.3 to 27.9)	0.01	65.5 (26.6)	67.0 (23.5)	1.5 (-13.1 to 16.1)	0.84
KBILD - Total	50.8 (11.1)	60.2 (14.2)	9.4 (2.6 to 16.2)	0.007	50.9 (11.4)	58.3 (14.1)	7.3 (-0.9 to 15.6)	0.08
Total lung ILD extent on HRCT (%)	33.2 (15.4)	33.9 (12.9)	0.7 (-6.9 to 8.2)	0.86	38.9 (13.8)	32.5 (13.5)	-6.4 (-15.4 to 2.6)	0.16

Data are reported as mean (standard deviation) unless stated otherwise.

Abbreviations: 4MGS: Four Metre Gait Speed; 6MWT: Six Minute Walk Test; ABOT: Ambulatory Oxygen Therapy; BMI: Body Mass Index; CPI: Composite Physiologic Index; CI: Confidence Interval; DL_{CO}: Diffusing Capacity of the Lung for Carbon Monoxide; FEV_1/FVC: ratio of Forced Expiratory Volume in 1 second and Forced Vital Capacity; FVC: Forced Vital Capacity; GAP: Gender, Age and lung Physiology index; HRCT: High resolution computed tomography; ILD: Interstitial Lung Disease; KBILD: King's Brief Interstitial Lung Disease questionnaire; LTOT: Long-Term Oxygen Therapy; MRC: Medical Research Council Dyspnoea score.

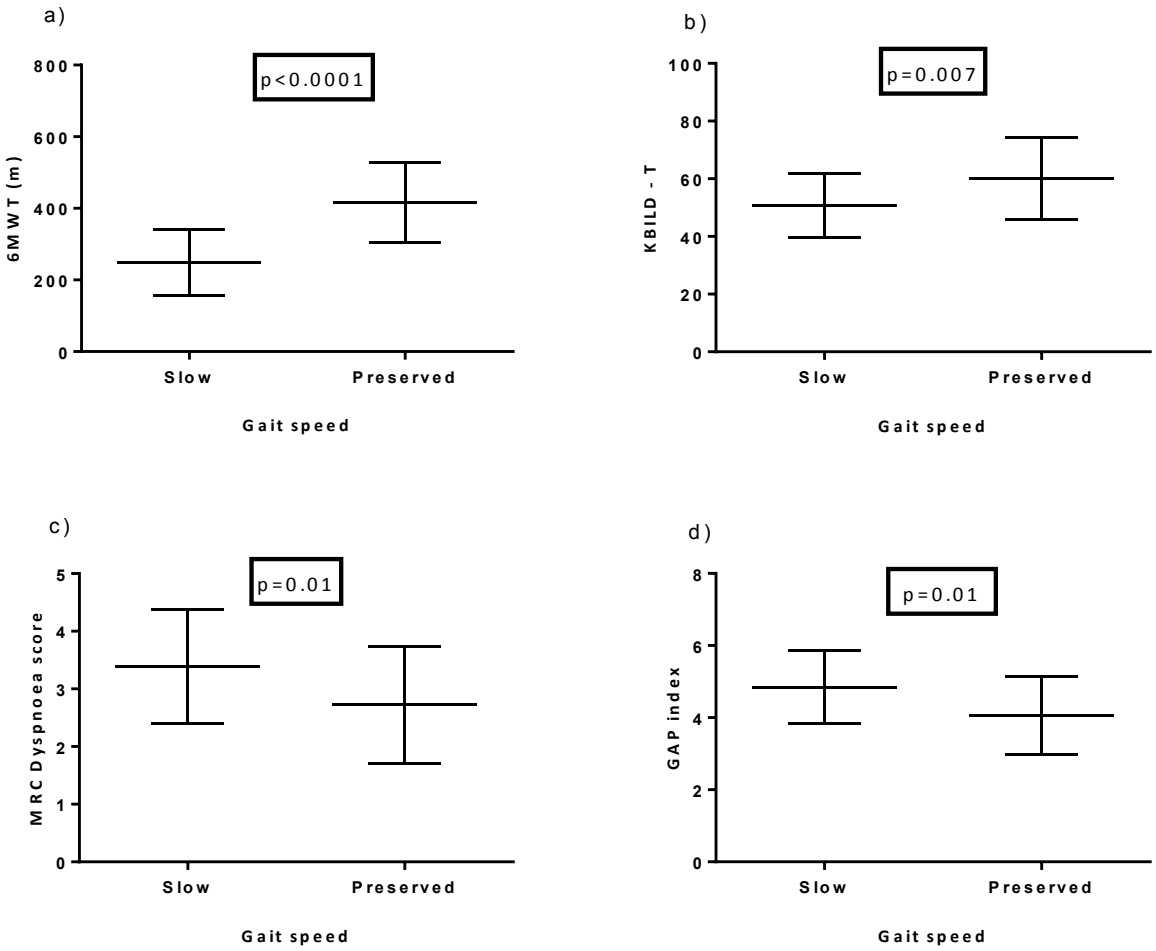

Figure 3.8: Slow and preserved gait speed in first validation cohort a) 6MWT; b) KBILD T; c) MRC Dyspnoea score; d) GAP index.

Abbreviations: 6MWT: Six Minute Walk Test; GAP: Gender, Age and lung Physiology index; KBILD-T: King's Brief Interstitial Lung Disease questionnaire – Total score; MRC: Medical Research Council Dyspnoea score.

3.5 Discussion

This study determined the reliability and validity of 4MGS in an IPF-specific population. The findings demonstrated high inter-observer and test-retest reliability and, in two independent cohorts, 4MGS correlated strongly with the 6MWT and moderately with measures of dyspnoea, health status and a multi-dimension prognostic index. When used to stratify patients according to the slow gait speed phenotype, 4MGS could identify differences in phenotypic characteristics such as exercise capacity,

health status, dyspnea, prognosis index and use of a walking aid despite similar pulmonary function and radiological parameters. In contrast, only differences in dyspnoea, gait speed were observed when patients were stratified according to the 6MWT prognostic cut-point. Accordingly, it is proposed that 4MGS provides similar, perhaps supplementary, information to the 6MWT and has potential as a simple tool in the assessment and stratification of patients with IPF.

Critique of method

Usual gait speed was measured in this study. As discussed in section 1.4.5 of the first chapter, although maximal walking speed has been assessed in some studies (139, 152), much of the data on the prognostic function of gait speed involve usual gait speed, and there is no evidence to indicate that maximal gait speed is more reliable than usual gait speed (152, 260). Additionally, four metres is an appropriate distance to measure gait speed as it is sufficiently short to enable measurement in most clinical settings and households (200, 206) but long enough to ensure measurement accuracy (139, 206). Some authors have commented that the use of a walking aid could contribute to within-sample variability. However, neither Weiss *et al* nor Kon *et al* showed evidence of poor consistency or increased measurement bias of gait speed in a large observational study of 201 women and 80 COPD patients respectively who used walking aids (189, 261).

Comparison to previous studies

Inter-observer and test-retest reliability

This study demonstrated that 4MGS is reliable in IPF with high inter-observer and test-retest reliability. Data on these psychometric properties in IPF have not been published but a number of studies in respiratory (e.g. chronic obstructive pulmonary disease (COPD) patients (189), Acute Respiratory Distress Syncrome (ARDS) survivors (190)) and non-respiratory conditions (e.g.

community-dwelling (150, 153) and frail (203) elders, stroke survivors (149, 154), people with cognitive impairments (151) and disabled women (139)) have reported that gait speed, measured over a variety of distances, is reliable. This study revealed high ICCs for both inter-observer (ICC: 0.996) and test-retest reliability (ICC: 0.983) which are similar to previously published data where ICCs ranged from 0.88 to 0.99 (table 3.9) (149-151, 189, 190) and 0.79 to 0.99 (table 3.10) (149, 151, 153-155, 189, 190, 203) for inter-observer and test-retest reliability respectively.

Measurement variability for both forms of reliability was low in this study (SEM %: <1%) and is comparable to inter-observer measurement variability reported in COPD (SEM %: 1.4%) (table 3.9) (189) as well as test-retest variability in both COPD (SEM %: 1.5%) (189) and healthy elders (SEM %: 0.8%) (table 3.10) (153). This study demonstrated lower measurement variability for test-retest reliability than the COPD and healthy elders studies despite a longer time period between testing (COPD: 24 to 48 hours (189); healthy elders: same session (153); this study: 7 days) (table 3.9). It was also lower than that reported for stoke survivors (SEM %: 5.1%) (149) despite having the same between-testing time period (7 days) (table 3.9). Differences in disease groups, operator training and/or adherence to a standardised operating procedure may explain why the results of this were towards the lower end of previously reported variability data.

It is noteworthy that although the Bland-Altman plot limits of agreement for both inter-observer and test-retest reliability were narrow in this study, there appeared to be a trend of decreased accuracy in patients who walked more quickly, particularly in the inter-observer group. Only one other study has analysed reliability data using Bland-Altman plots and the same pattern was also evident despite narrow limits of agreement (189). This trend could have arisen due to observer error (slower reaction times at fast walking speeds) or participant error (increased variation in walking speed in those who walk more quickly). Despite this, the absolute limits of agreement are small and suggest that the

4MGS test is reliable and likely to be responsive to intervention and sensitive to change over time, an essential characteristic of any useful outcome measure.

Table 3.9: Summary of comparable inter-observer reliability data for usual gait speed.

Author	**n**	**Population**	**Test distance (metres)**	**ICC**	**SEM (SEM %)**
Nevitt *et al* (150)	27	Community elders	5	0.96	-
Munoz-Mendoza *et al* (151)	21	Cognitively impaired patients	4	0.96	-
Munoz-Mendoza *et al* (151)	21	Cognitively impaired patients	6	0.88	-
Faria *et al* (149)	16	Stroke patients	10	0.96	-
Kon *et al* (189)	58	COPD patients	4	0.99	0.003 (1.4)
Chan *et al* (190)	306	ARDS survivors	4	0.97	-

Abbreviations: ARDS: Acute Respiratory Distress Syndrome; COPD: Chronic Obstructive Pulmonary Disease; ICC: Intra-class Correlation Coefficient; SEM: Standard Error of Measurement.

Table 3.10: Summary of comparable test-retest reliability data for usual gait speed.

Author	n	Population	Test distance (metres)	Duration between tests	ICC	SEM (SEM %)
Guralnik *et al* (155)	102	Women with mild to severe disability	4	Every week for 4 weeks	0.88	-
Jette *et al* (203)	105	Frail older people	2.4	2 weeks	0.79	-
Flansbjer *et al* (154)	50	Six to 46 months post-stroke	10	1 week	0.94	-
Munoz-Mendoza *et al* (151)	21	Patients with cognitive impairment	4	1 week	0.91	-
Faria *et al* (149)	16	Stroke survivors	10	1 week	0.94	0.06 (5.1)
Peters *et al* (153)	43	Healthy older people	4	Same session	0.96	0.008 (0.8)
Kon *et al* (189)	80	COPD	4	24 – 48 hours	0.97	0.012 (1.5)
Chan *et al* (190)	360	ARDS survivors	4	Same day	0.88 to 0.99	-

Abbreviations: ICC: Intra-class Correlation Coefficient; SEM: Standard Error of Measurement; COPD: Chronic Obstructive Pulmonary Disease; ARDS: Acute Respiratory Distress Syndrome.

Concurrent validity

This study demonstrates the concurrent validity of 4MGS in two independent IPF-specific cohorts with moderate to strong correlations with exercise capacity, dyspnoea, health status and a multi-dimension prognostic index. Neither 4MGS nor 6MWT demonstrated significant relationships with either pulmonary function or radiological parameters. This lack of association with disease-specific measures may be seen as an advantage as it suggests that 4MGS may reflect the non-pulmonary manifestations of IPF not captured by disease-specific measures. Conversely, it could also be a disadvangage as 4MGS may not detect changes in disease state e.g. worsening disease severity,

impact of interventions targeting lung function. Furthermore, 4MGS was not simply a reflection of co-morbidity burden as there was no relationship between 4MGS and the age-adjusted Charlson co-morbidity index.

These results are corroborated by existing data on gait speed in chronic respiratory disease (187, 189, 190, 193) and ILD (86, 194, 197). Similar to this study, Kon *et al* reported strong correlations between 4MGS and exercise capacity (incremental shuttle walk test: r=0.78:), moderate correlations with dyspnoea (MRC: r=-0.55) and health status (St. George's Respiratory Questionnaire (SGRQ): r=-0.44:) and no relationship with forced expiratory volume in one second (FEV_1) % predicted in 586 stable COPD patients (189). Karpman *et al* also reported similar results: usual and maximal speed 4MGS correlated with exercise capacity (6MWT: r=0.77 to 0.80) in 130 COPD patients (193). In contrast, in another study involving 511 COPD patients, significant relationships between gait speed and pulmonary function parameters (FEV_1 (L): r=0.31 to 0.45) and health status (SGRQ: r=-0.42 to -0.56) were observed (187). However, gait speed was calculated from 6MWT rather than measured using a specific gait speed test which may have affected the accuracy of the results (187). In a secondary analysis of two studies involving ARDS survivors (n=122, n=184), 4MGS shared weak to moderate strength correlations with exercise capacity (6MWT: r=0.37 and 0.62) and moderate correlations with health status (Short-Form 36: r=0.57 and 0.58; Euro-Quol-5 Dimensions-3 Level mobility domain: r=0.42 and -0.44) (190). This was the only study to demonstrate just a weak relationship between 4MGS and exercise capacity; the reasons for this are unclear, although it may be explained by a younger sample (mean (SD) age 46.0 (12.9) years) (190).

No study has formally investigated the validity of 4MGS in IPF but data are available on patients living with ILD (86, 194). DePew *et al* studied 70 patients with chronic lung disease (n=55 ILD – IPF data not reported) and demonstrated, like our study, a strong correlation between 4MGS and 6MWT (r=0.70) and a significant negative correlation with MRC (r=-0.44) in the whole group (194). Mendes *et al*

measured the short physical performance battery (SPPB) (a component of which is usual gait speed measured over 2.4 metres) in 26 advanced ILD patients (n=23 IPF) listed for lung transplantation, and demonstrated lower SPPB scores compared with 12 age-matched controls (197). Absolute gait speed values were not reported and the relationship between gait speed and measures of functional status were not presented. Furthermore, 2.4 metres may not be sufficiently long to ensure measurement accuracy (206) and has worse test-retest reliability compared to using four metres (203). In a study involving 52 ILD patients (n=20 IPF), Ryerson *et al* reported a weak but significant relationship between gait speed and measures of dyspnoea (Baseline Dyspnoea Index: r=-0.36; University of California San Diego Shortness of Breath Questionnaire: r=0.37) (86). To my knowledge, this study is the first to report the reliability of 4MGS, provide evidence to support its validity as a measure of functional status and stratification tool in adequately powered IPF-specific cohorts.

Stratification according to slow and preserved gait speed phenotypes

This study demonstrated that IPF patients could be stratified according to the slow gait speed phenotype cut-off recommended by expert consensus groups (143, 144). There were differences between those with slow and preserved 4MGS in exercise capacity, health status, dyspnoea and prognosis index despite similar pulmonary function and radiological parameters. Although there are no data on the slow gait speed phenotype in IPF, our results are corroborated by data observed in COPD patients (189). Similar to this study, in COPD patients (n=586) stratified according to 4MGS, those with the slow gait speed phenotype had significantly worse exercise capacity, dyspnoea and health status in comparison to those with preserved gait speed, despite no significant difference in FEV_1 % predicted between the groups (189).

The slow gait speed phenotype cut-off was originally identified in geriatric populations and has mostly been used for the prediction of adverse health outcomes such as functional decline,

institutionalization, onset of disability and mortality (139, 143, 144, 262, 263). The predictive ability of 4MGS in IPF will be discussed in Chapters 5 and 6.

Limitations

There are some limitations to 4MGS and this study. First, there is a recognised 'ceiling effect' associated with 4MGS (264), and therefore it may have more value as an assessment or stratification tool in patients with more advanced IPF or limited functional capacity than in those with well-preserved functional status. Second, 4MGS is not a measure of peak exercise capacity (142), but an indicator of functional impairment, particularly in frail older adults, and has been previously used as a functional outcome measure in interventional pharmacological trials (148) as well as a surrogate marker of sarcopenia and frailty (146). Third, as the study participants were primarily outpatients attending specialist ILD clinics at tertiary centres, these data need to be corroborated in other IPF populations and settings. Fourth, it was not possible to comment on the longitudinal validity of 4MGS in IPF, particularly with regards to prognostic value.

4MGS has several attractive properties. It is cheap and quick to perform, and requires little physical space. As walking is familiar to the vast majority of adults, the test is easy to understand and has been shown to be reliable even in people with cognitive dysfunction (151). These properties mean that 4MGS could be adopted in almost any environment including the home (206) or hospital bedside (196). It is postulated that 4MGS may play a particular role in measuring functional performance in advanced IPF when field walking tests, such as the 6MWT, become less acceptable to or impossible for patients with severe ventilatory limitation or dyspnoea (46). Furthermore, the 6MWT, which requires a 30 metre course (96), is not feasible in some healthcare settings, such as the home, nursing home, hospice, acute care or many clinic settings, and the need to repeat the test due to its learning effect makes it more time-consuming than simpler functional performance tests such as the 4MGS test.

This study also suggest that the 4MGS test is not just a shorter, simpler, less time-consuming 6MWT; although the two measures correlated strongly, 6MWT only explained 57% of the variance in the 4MGS test. Although, the addition of the GAP index explained 66% of the variance in 4MGS, a question remains about other potential contributors. These could include co-morbidities such as pulmonary hypertension, extent of fibrosis on HRCT scan, muscle strength, dynamic balance, frailty and use of oxygen therapy (note that MRC score, health-related quality of life, Charlson Co-morbidity index had been considered in the model). Despite the simplicity of the 4MGS test, this study showed that stratifying according to 'slow gait speed' identified patients with significantly reduced exercise capacity, increased dyspnoea and poor health status in comparison to those with preserved gait speed. However, there were no significant differences in pulmonary function or HRCT results between slow and preserved gait speed groups, suggesting that extra-pulmonary factors such as ageing, skeletal muscle dysfunction, and frailty (265, 266) contribute significantly to walking speed. The incorporation of 4MGS into the routine assessment of patients with IPF would be feasible to implement in many healthcare settings, and would supplement information provided by traditional pulmonary function tests and thoracic imaging.

3.6 Conclusion

The findings from this study suggest that the 4MGS test, a simple functional performance measure used in gerontology, is reliable and valid in patients with IPF. Compared to those with preserved gait speed, the slow gait speed phenotype is characterised by significantly reduced exercise capacity, increased dyspnoea and impaired health status despite comparable pulmonary function and HRCT abnormalities.

In the next chapter, I examine whether 4MGS is responsive to intervention and estimate the minimum clinically important difference.

Chapter 4 : The responsiveness of four metre gait speed in patients with idiopathic pulmonary fibrosis and estimation of the minimum clinically important difference

Sections of this chapter was published in Respirology on 14th November 2017 (256). Permissions to use them in this thesis are shown in Appendix 1.

4.1 Introduction

In Chapter 3, the four metre gait speed (4MGS) was shown to have high inter-observer and test-retest reliability in patients with idiopathic pulmonary fibrosis (IPF) and to correlate with the most commonly used field-walking test in this population, the six minute walk test. I concluded that 4MGS may have a role as a simple functional assessment tool in IPF. However, the utility of 4MGS as an outcome measure is partly dependent on its ability to detect change. Usual gait speed has been used as a measure of functional performance in older people (143, 152, 267) as well as patients living with chronic obstructive pulmonary disease (COPD) (142) and neurological conditions (200). Several observational and experimental studies have demonstrated that usual gait speed can increase following intervention. Examples include response in gait speed to rehabilitation following a stroke (181), hip fracture (186, 268) and an acute hospital admission (183). In COPD, gait speed has been shown to increase after pulmonary rehabilitation (PR) (264, 269). Furthermore, 4MGS has been used as a functional outcome measure in interventional pharmacological trials, for example in patients with multiple sclerosis (148). 4MGS is recognised by international expert working groups, including representatives from the United States Food and Drug Agency, as the functional test closest to being ready for pharmacological trials in older adults with frailty or sarcopenia (146, 270).

The ability of an outcome measure to detect change is an important aspect of concurrent validity (271) and is necessary for data interpretation both in clinical and research settings (272). This is facilitated by the minimum clinically important difference (MCID) of the outcome measure: *'the smallest change that is important to patients'* (273). The MCID enables the assessor to understand the clinical significance of change data and forms an important part of the evidence required by regulatory agencies for approval for use in clinical trials (274). There is no clear consensus on the methods used to estimate an MCID, but a combination of anchor- and distribution-based approaches with triangulation of methods is recommended (272). Anchor-based approaches use a clinical or patient-based external indicator to allocate participants into specific groups e.g. no change, small improvements, small disimprovements, large improvements, large disimprovements in the outcome of interest (272). Examples of anchor-based techniques include a global rate of change questionnaire (GRCQ) scored on a Likert scale (272), linear regression using the established MCID of the external anchor (195) and Receiver Operating Characteristic (ROC) curves to discriminate between participants who achieve and don't achieve the established MCID of the external anchor (272). The advantages of using an anchor-based approach is that it accounts for the clinical significance of the intervention and is considered clinically robust and meaningful (275, 276). Conversely, a limitation of the GRCQ method is that it may be subject to recall bias if the question relates to a past experience as well as reporting bias (272). Simiarly, the linear regression and ROC methods require a correlation coefficient of >0.3 between the variable of interest and the external anchor (266).

Distribution-based methods estimate an MCID based on the distribution of observed scores in a sample (272). This method uses various equations involving measures of statistical variability to express the observed change in a standardized metric (272). Methods include half the standard deviation, the minimal detectable change at 95% confidence and standard error of measurement (264, 272). Distribution-based methods are an indirect way of estimating the MCID that do not consider participants' experiences (272). Additionally, the change in the outcome of interest is based

on statistical variability which may vary depending on patient ability or baseline measurements (273). Estimates of the MCID of usual gait speed tests following rehabilitation for acute stroke, hip fracture, acute hospital admission and COPD range from 0.08 ms^{-1} to 0.18 ms^{-1} (181, 183, 186, 264, 268).

To date, only one study has published on the responsiveness of gait speed to PR in patients with interstitial lung disease (ILD) (n=54, of which IPF n=22) (86). The authors showed graphically that 4MGS improved following PR, but absolute data were not reported rendering interpretation difficult (86). Furthermore estimates of the MCID were not provided. Responsiveness of 4MGS has not previously been explored in an IPF-specific population, and the MCID of the 4MGS test in IPF is not known.

4.2 Aims

The aims of this study were to determine: 1) the responsiveness of 4MGS to PR and 2) the MCID of 4MGS in patients with IPF.

4.3 Hypothesis

- The 4MGS test is responsive to PR in patients with IPF.

4.4 Methods

4.4.1 Study participants

Participants were prospectively recruited from the PR units at the Royal Brompton and Harefield Hospital NHS Foundation Trust and St. Thomas' Hospital Pulmonary Rehabilitation Unit at Guy's and St. Thomas' NHS Foundation Trust, UK between February 2015 and July 2016. The inclusion criteria

were: 1) IPF diagnosis by a specialist ILD multidisciplinary team according to international guidelines; 2) ability to walk five metres; 3) ability to provide informed consent; 4) providing consent to participate in a supervised outpatient PR programme. Exclusion criteria were significant co-morbidities that would limit walking ability or exercise capacity (e.g. lower limb amputation) or make exercise unsafe (e.g. unstable ischaemic heart disease). All participants provided informed written consent. The study was approved by the London-Riverside Research Ethics Committee (14/LO/2247) and registered on clinicaltrials.gov (NCT02530736).

4.4.2 Responsiveness of 4MGS to pulmonary rehabilitation

The Food and Drug Association stipulates that outcome measures seeking regulatory approval should demonstrate the capacity to detect clinical benefit (75). Accordingly, PR was chosen as the intervention to determine if 4MGS could detect a change in walking speed in patients with IPF as it is known to improve exercise capacity measured using field walking tests (24). Pharmacological therapies for IPF (pirfenidone or nintedanib) were not considered suitable interventions as although they have been shown to reduce the rate of decline in forced vital capacity (FVC) (33, 34, 36, 37), they have not been shown to improve functional outcome or health related quality of life (37).

The PR programmes at the Royal Brompton and Harefield Hospitals and St. Thomas' Hospital are multi-disciplinary outpatient services that patients attend twice a week for an eight week period, as described in Chapter 2. The following outcome measures, described in Chapter 2, were assessed before and after PR: 4MGS (220); anthropometry; spirometry (208, 209); Medical Research Council (MRC) Dyspnoea score (212); the incremental shuttle walk test (ISW) (224); quadriceps maximum voluntary contraction (QMVC) (238, 239); handgrip strength (243, 244, 277); the King's Brief Interstitial Lung Disease (KBILD) questionnaire (111) and the Chronic Respiratory Questionnaire (CRQ) (236). Co-morbidities were evaluated using the age-adjusted Charlson co-morbidity Index

(257). Following PR, to evaluate self-reported response to the intervention, patients rated their response to the following question *'How do you feel your overall condition has changed after rehabilitation?'* on a five point Global Rating of Change Questionnaire (GRCQ). The scale ranged from '*1: I feel much better'* to *'5: I feel much worse'*. The schema for this study is presented in figure 4.1.

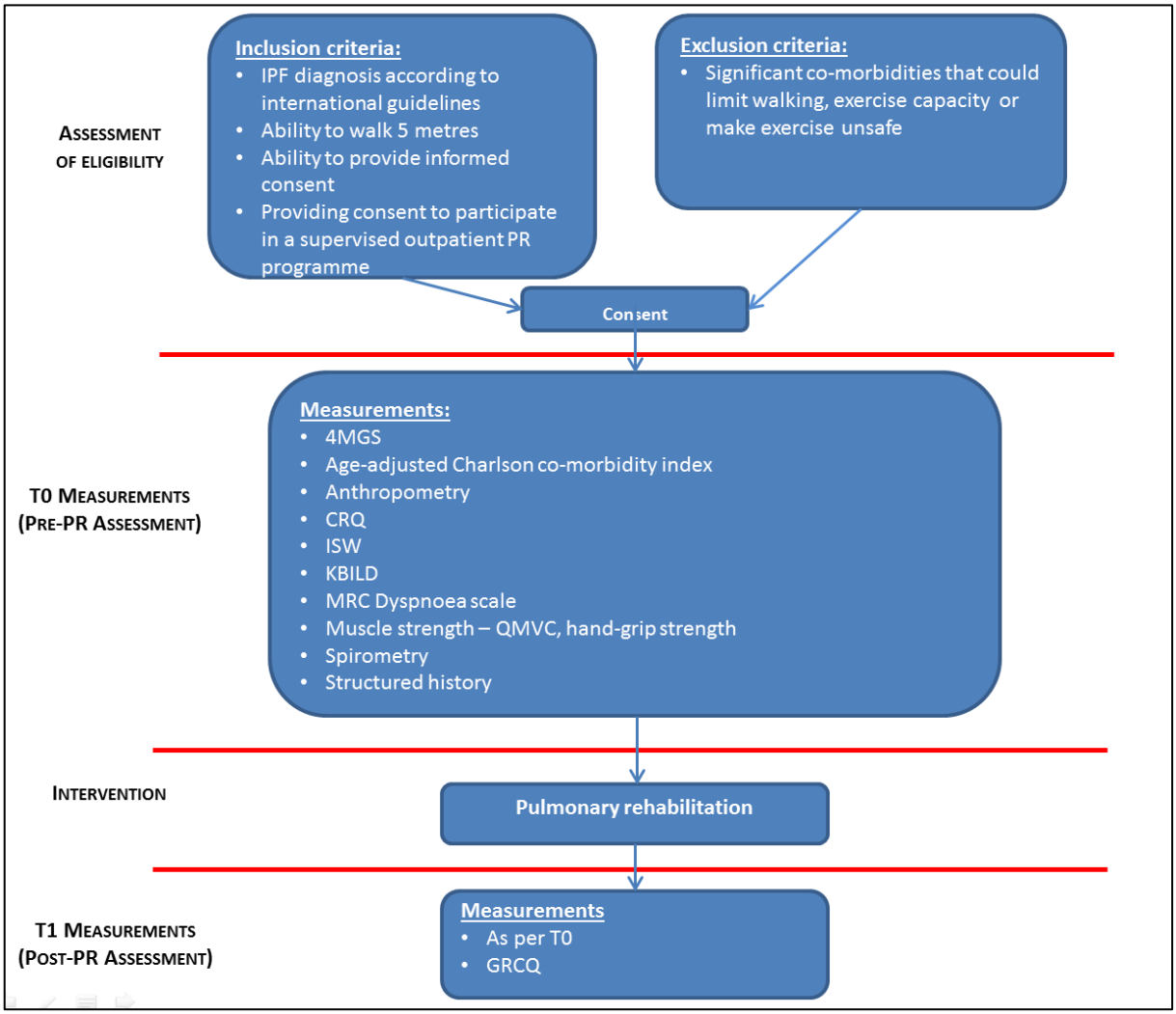

Figure 4.1: Responsiveness of 4MGS to PR study schema.

Abbreviation: 4MGS: Four Metre Gait Speed; CRQ: Chronic Respiratory Questionnaire; IPF: Idiopathic Pulmonary Fibrosis; GRCQ: Global Rating of Change Questionnaire; ISW: Incremental Shuttle Walk Test; KBILD: King's Brief Interstitial Lung Disease questionnaire; MRC: Medical Research Council Dyspnoea scale; PR: Pulmonary Rehabilitation; QMVC: Quadriceps Maximum Voluntary Contraction.

4.4.3 Statistical analysis

For anchor-based approaches of determining the MCID, a minimum correlation of r>0.3 between the outcome of interest and external anchor is required (272). To show a correlation of r>0.3 between change in 4MGS and change in either ISW, KBILD or CRQ with 80% power at the 0.05 significance level would require a minimum of 84 patients.

Baseline characteristics of patients who completed and did not complete PR were compared with independent t-tests (Mann-Whitney U test for non-parametric data) for continuous data and chi-square test for categorical data. PR completion was defined as attending at least 50% of the sessions and the post-PR assessment. Paired t-tests were used to compare outcomes before and after PR (Wilcoxon signed-rank test for nonparametric data) and effect sizes was calculated using Cohen's d. Effect sizes of change in gait speed according to FVC severity (mild to moderate (FVC ≥50% predicted) and severe (FVC<50% predicted) disease) were calculated. The relationship of baseline 4MGS with change in 4MGS and change in ISW were compared using Pearson's rank correlation and constructed scatterplots of these variables stratified according to baseline 4MGS quartiles. One-way analysis of variance was used to evaluate between quartile differences.

Both distribution- and anchor-based approaches were used to estimate the MCID. The distribution-based calculations used were half the standard deviation (0.5 * SD) and the minimal detectable change at 95% confidence (MDC_{95} = standard error of measurement * 1.96 * √2). The standard error of measurement was calculated as follows: SEM= SD of baseline 4MGS * √1- test-retest reliability of 4MGS. Based on data from Chapter 2, the test-retest value of 4MGS was 0.99. For the anchor–based methods, *a priori* criteria for establishing the validity of external anchors were: a statistically significant correlation between change in 4MGS and change in anchor, e.g. ISW, KBILD (domains and total score), CRQ (domains and total score), and a correlation coefficient >0.3 (calculated using Pearson's correlation coefficient) (272). For external anchors fulfilling these criteria, linear regression was used to estimate change in 4MGS corresponding to the established MCID for the anchors (195).

Receiver Operating Characteristic (ROC) curves were also used to determine the change in 4MGS cut-off with equal sensitivity and specificity to discriminate between those who improved their external anchor by the established MCID and those who did not (195, 278). The MCID was also estimated using the mean change in 4MGS in patients who reported '2: *I feel a little better*' on the GRCQ following PR (195). Data analyses were performed using GraphPad Prism 7 (GraphPad Software, USA) and SPSS version 24 (IBM, USA). Statistical significance was considered to be $p<0.05$.

4.5 Results

4.5.1 Baseline characteristics

One-hundred and nine patients referred to the Royal Brompton and Harefield Hospital PR programmes were invited to participate in the study: 10 declined, five did not meet the inclusion criteria (n=2: chose a home exercise programme; n=1: unstable cardiac condition; n=1: foot-drop; n=1: unable to walk five metres) and 94 agreed to participate. Only one patient with IPF was referred to Guy's and St. Thomas' Pulmonary Rehabilitation Unit during the recruitment period of the study and consented to participate in the study. Of the 95 patients, five did not complete PR. The reasons for non-completion were: n=2: no reason provided; n=1: converted to a home-exercise programme; n=1: admitted to hospital; n=1: underwent cardiac investigations. The baseline characteristics of the whole cohort, PR completers and PR non-completers are in table 4.1. A test for differences in baseline characteristics between the completers and non-completers was not appropriate due to the small number of non-completers, however, descriptively non-completers were less likely to use oxygen therapy, and had a worse exercise capacity and quality of life compared to completers.

Table 4.1: Baseline characteristics of the whole cohort (n=95), PR completers (n=90) and PR non-completers (n=5).

Variable	**Whole cohort**	**PR completers**	**PR non-completers**
Gender: male (%)	70	70	60
Age (years)	74 (7)	74 (7)	74 (12)
MRC	3 (1)	3 (1)	3 (3, 4)
BMI (kg/m^2)	27.4 (4.9)	27.2 (4.8)	30.9 (22.6, 36.4)
FEV_1/FVC	0.79 (0.08)	0.79 (0.08)	0.80 (0.07)
FVC (litres)	2.2 (0.7)	2.2 (0.7)	2.2 (0.6)
FVC (% predicted)	73.0 (21.8)	72.4 (21.8)	75 (66, 105)
Age-adjusted Charlson co-morbidity Index	0 (0, 4)	0 (0, 4)	0 (0, 6)
Self-reported hospitalisations in past year	0 (0, 0)	0 (0, 0)	0 (0, 0)
Self-reported chest infections in past year	1 (0, 2)	1 (0, 2)	1 (0, 1)
Oxygen therapy			
Long-term: (%)	11	11	0
Ambulatory: (%)	16	17	0
Walking aid: (%)	2	2	0
Pirfenidone: (%)	15	16	0
Nintedanib: (%)	0	0	0
4MGS (ms^{-1})	0.92 (0.25)	0.92 (0.25)	0.96 (0.21)

ISW (m)	269 (169)	271 (172)	210 (150, 315)
Handgrip strength (kg)	26.2 (7.7)	26.2 (7.5)	26.0 (14.2, 39.6)
QMVC (kg)	28.6 (20.9, 35.2)	28.6 (21.5, 34.9)	25.4 (13.0, 38.5)
KBILD-Psychological domain	58.7 (17.0)	59.0 (16.0)	56.9 (34.6, 73.2)
KBILD-Breathlessness and activities domain	41.6 (17.0)	42.0 (17.4)	30.3 (30.3, 45.2)
KBILD-Chest and symptoms domain	66.9 (18.0)	67.1 (18.3)	63.7 (54.3, 74.5)
KBILD-Total score	56.1 (10.4)	56.4 (10.4)	52.9 (41.7, 62.1)
CRQ-Dyspnoea domain	16.4 (5.4)	16.5 (5.5)	16.0 (14.5, 17.0)
CRQ-Fatigue domain	15.1 (5.0)	15.3 (5.0)	11.0 (8.0, 15.5)
CRQ-Emotion domain	33.2 (8.2)	33.4 (8.1)	33.0 (18.0, 37.5)
CRQ-Mastery domain	19.5 (4.9)	19.6 (4.8)	15.0 (13.0, 24.0)
CRQ-Total score	84.2 (19.9)	84.8 (19.8)	76.0 (55.0, 92.0)

Data reported as mean (standard deviation) or median (25^{th}, 75^{th} centile) unless stated otherwise.

Abbreviations: 4MGS: Four Metre Gait Speed; BMI: Body Mass Index; CRQ: Chronic Respiratory Questionnaire; FEV_1: Forced Expiratory Volume in One Second; FVC: Forced Vital Capacity; ISW: Incremental Shuttle Walk Test; KBILD: King's Brief Interstitial Lung Disease questionnaire; MRC: Medical Research Council Dyspnoea score; QMVC: Quadriceps Maximum Voluntary Contraction.

4.5.2 Response to PR

The baseline characteristics and the response to PR of the 90 patients who completed the programme are shown in table 4.2. 4MGS improved significantly with PR: mean (95% confidence interval (CI)) change 0.15 (0.11 to 0.18) ms^{-1}. The effect sizes with PR for 4MGS, ISW, KBILD total score and CRQ total score were 0.55, 0.56, 0.27 and 0.56 respectively. The effect sizes with PR for 4MGS according to disease severity were 0.74 for mild to moderate disease (FVC ≥ 50% predicted

and 0.40 for severe disease (FVC <50% predicted). Baseline 4MGS correlated weakly with change in ISW (r=0.23, p=0.03) but not with change in 4MGS (r=-0.07, p=0.50).

Table 4.2: Baseline characteristics and response to PR of patients who completed PR (n=90).

Variable	**Baseline**	**Change with PR**	**p-value**
Gender: male (%)	70	NA	NA
Age (years)	74 (7)	NA	NA
MRC	3 (1)	-0.6 (-0.8 to -0.4)	<0.001
BMI (kg/m^2)	27.2 (4.8)	-0.1 (-0.2 to 0.1)	0.17
FEV_1/FVC	0.79 (0.08)	0 (-0.01 to 0.01)	0.72
FVC (L)	2.2 (0.7)	-0.02 (-0.08 to 0.03)	0.44
FVC (%)	72.4 (21.8)	0.14 (-1.8 to 2.1)	0.89
Age-adjusted Charlson co-morbidity Index	0 (0, 4)	NA	NA
Self-reported hospitalisations in past year	0 (0, 0)	NA	NA
Self-reported chest infections in past year	1 (0, 2)	NA	NA
Oxygen:			
Long-term: (%)	11	NA	NA
Ambulatory: (%)	17	NA	NA
Walking aid :(%)	2	NA	NA
Pirfenidone: (%)	16	NA	NA
4MGS (ms^{-1})	0.92 (0.25)	0.15 (0.11 to 0.18)	<0.001
ISW (m)	271 (172)	50 (36 to 54)	<0.001
Handgrip strength (kg)	26.2 (7.5)	0.5 (-0.6 to 1.6)	0.36
QMVC (kg)	28.6 (21.5, 34.9)	0.1 (-2.3, 2.5)	0.54

KBILD-Psychological domain	59.0 (16.0)	4.6 (1.6 to 7.7)	0.003
KBILD-Breathlessness and activities domain	42.0 (17.4)	5.3 (1.8 to 8.9)	0.004
KBILD-Chest and symptoms domain	67.1 (18.3)	5.7 (1.4 to 10.0)	0.01
KBILD-Total score	56.4 (10.4)	3.9 (2.0 to 5.7)	<0.001
CRQ-Dyspnoea domain	16.5 (5.5)	4.1 (2.8 to 5.4)	<0.001
CRQ-Fatigue domain	15.3 (5.0)	1.6 (0.7 to 2.4)	0.001
CRQ-Emotion domain	33.4 (8.1)	1.5 (0.2 to 2.8)	0.03
CRQ-Mastery domain	19.6 (4.8)	1.4 (0.6 to 2.2)	0.001
CRQ-Total score	84.8 (19.8)	8.5 (5.2 to 11.8)	<0.001

Baseline data reported as mean (standard deviation) or median (25^{th}, 75^{th} centile) unless stated otherwise. Change data reported as mean (lower and upper 95% confidence limit) change or median (25^{th}, 75^{th} centile) change.

Abbreviations: 4MGS: Four Metre Gait Speed; BMI: Body Mass Index; CRQ: Chronic Respiratory Questionnaire; FEV_1: Forced Expiratory Volume in One Second; FVC: Forced Vital Capacity; ISW: Incremental Shuttle Walk Test; KBILD: King's Brief Interstitial Lung Disease questionnaire; MRC: Medical Research Council Dyspnoea score; NA: Not Applicable; PR: Pulmonary Rehabilitation; QMVC: Quadriceps Maximum Voluntary Contraction.

The significant relationship betweewn change in 4MGS and ISW (r=0.23, p=0.03) with PR is represented graphically in figure 4.2. The data were also stratified according to baseline 4MGS quartiles and are shown in figure 4.3. There were no significant between-quartile differences for either change in 4MGS (p=0.92) or ISW (p=0.24). For patients in quartile 1 (baseline 4MGS <0.77 ms^{-1} – slowest gait speed), the mean (95% CI) change in 4MGS with PR was 0.13 (0.06 to 0.21) ms^{-1} and the mean (95% CI) change in ISW was 37 (11 to 62) metres. For this quartile, the effect sizes for 4MGS and ISW were 0.80 and 0.50 respectively. With PR, patients in quartile 4 (baseline 4MGS ≥1.09

ms^{-1} – fastest gait speed) improved 4MGS by (mean (95% CI) change): 0.14 (0.07 to 0.21) ms^{-1} and ISW by 70 (38 to 101) metres, corresponding to effect sizes of 1.08 and 0.45 respectively.

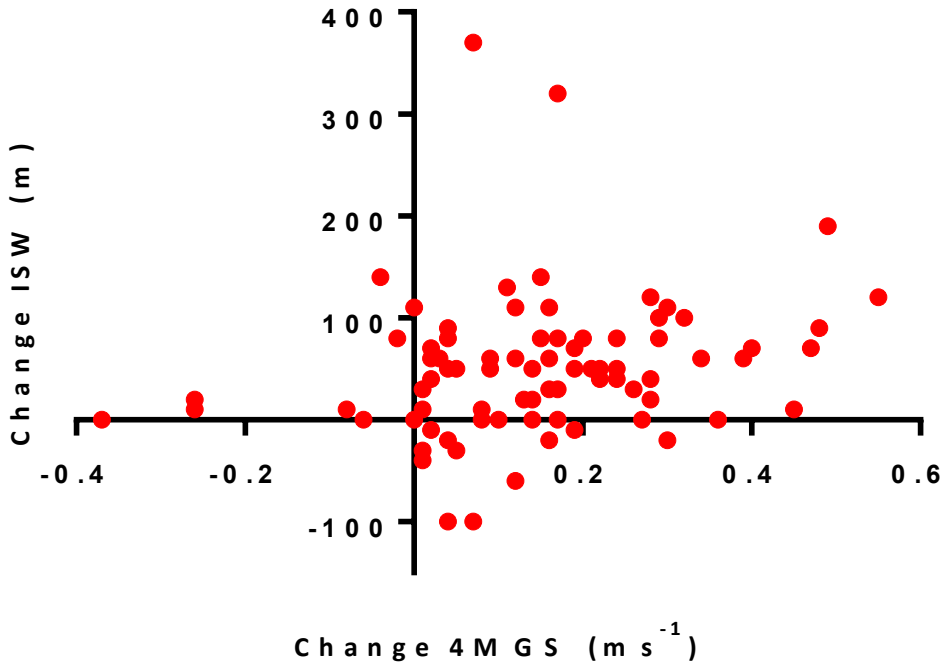

Figure 4.2: Relationship between change in 4MGS and change in ISW with PR

Abbreviations: 4MGS: Four Metre Gait Speed; ISW: Incremental Shuttle Walk test; PR: Pulmonary Rehabilitation.

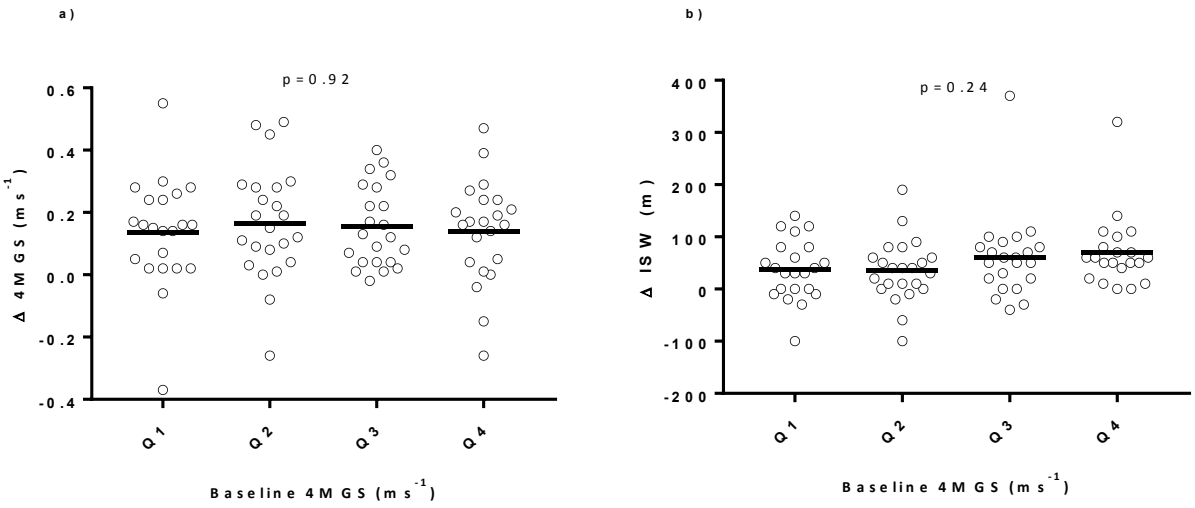

Figure 4.3: Scatterplot diagram showing individual patient values (circles) and mean change (solid line) in a) 4MGs and b) ISW following PR stratified according to baseline 4MGS quartiles: Q1: <0.77 ms^{-1}; Q2: 0.77 to 0.88 ms^{-1}; Q3: 0.89 to 1.08 ms^{-1} and Q4: ≥1.09 ms^{-1}.

Abbreviations: Δ: Change with PR; 4MGS: Four Metre Gait Speed; ISW: Incremental Shuttle Walk test; PR: Pulmonary Rehabilitation.

4.5.3 Estimation of the minimum clinically important difference

The MCID estimates using distribution methods were 0.08 ms^{-1} (MDC_{95}) and 0.13 ms^{-1} (0.5 * SD). There was no relationship between change in 4MGS and change in the CRQ emotion domain or KBILD (domains and total score) but there were significant but weak correlations with change in the ISW and CRQ dyspnea domain (table 4.3). The correlation coefficient for change in 4MGS with change in the CRQ mastery domain and total score was >0.3 (table 4.3) and they were subsequently used as anchors to estimate the MCID using linear regression and ROC plots.

Table 4.3: Relationship between change in 4MGS and change in other variables (n=90).

Variable	Slope	Y-intercept	r-value	p-value
Δ ISW	0.001	0.13	0.23	0.03
Δ KBILD-Psychological domain	0.001	0.16	0.08	0.53
Δ KBILD-Breathlessness and activities domain	0.001	0.16	0.06	0.65
Δ KBILD-Chest and symptoms domain	0.001	0.16	0.07	0.60
Δ KBILD-Total score	0.002	0.17	0.08	0.51
Δ CRQ-Dyspnoea domain	0.007	0.13	0.26	0.01
Δ CRQ-Fatigue domain	0.008	0.14	0.21	0.05
Δ CRQ-Emotion domain	0.004	0.15	0.14	0.21
Δ CRQ-Mastery domain	0.015	0.13	0.35	0.001
Δ CRQ-Total score	0.003	0.13	0.31	0.005

Abbreviations: Δ: Change between pre-and post-PR values; 4MGS: Four Metre Gait Speed; ISW: Incremental Shuttle Walk Test; CRQ: Chronic Respiratory Questionnaire; KBILD: King's Brief Interstitial Lung Disease questionnaire.

Using linear regression and the established MCID for the CRQ mastery domain (+2 points) and total score (+10 points) (251), the MCID estimate for 4MGS was 0.16 ms^{-1} for both anchors (table 4.4). Using the same anchors, ROC plots identified the same MCID estimate (0.16 ms^{-1}) with c-statistics of 0.71 (CRQ mastery domain; $p<0.001$) and 0.59 (CRQ total score; $p=0.17$) (table 4.4 and figure 4.4).

Table 4.4: MCID estimates of 4MGS using linear regression and ROC plots.

Linear regression	**MCID estimate (ms^{-1})**				
CRQ-Mastery domain	0.16				
CRQ-Total score	0.16				
ROC plots	**MCID estimate (ms^{-1})**	**C-statistic**	**p-value**	**Sensitivity (%)**	**Specificity (%)**
CRQ-Mastery domain	0.16	0.71	<0.001	68.3	63.4
CRQ-Total score	0.16	0.59	0.17	61.9	57.8

Abbreviations: 4MGS: Four Metre Gait Speed; CRQ: Chronic Respiratory Questionnaire: MCID: Minimum Clinically Important Difference; ROC: Receiver Operating Characteristic.

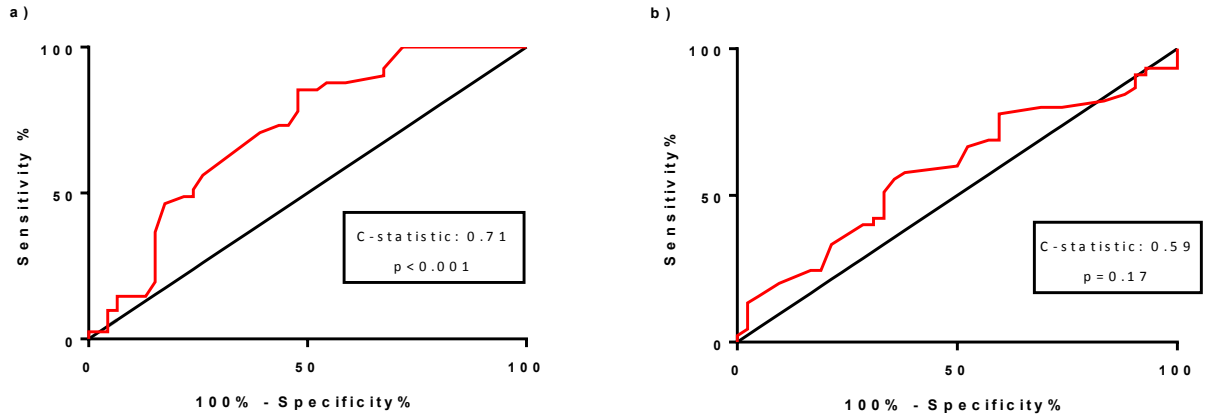

Figure 4.4: ROC plots to estimate the MCID of 4MGS using the CRQ a) mastery domain and b) total score.

Abbreviations: 4MGS: Four Metre Gait Speed; CRQ: Chronic Respiratory Questionnaire: MCID: Minimum Clinically Important Difference; ROC: Receiver Operating Characteristic.

Figure 4.5 demonstrates the mean (95% CI) changes in 4MGS according to the GRCQ responses. Forty-four percent of patients reported feeling '*1: much better*', 44% reported feeling '*2: a little better*', 9% reported feeling '*3: no different*' and 3% reported feeling '*4: a little worse*' following PR. No patient reported feeling '*5: much worse*'. Following PR the mean change in 4MGS in those reporting feeling '*2: a little better*' was 0.16 ms^{-1}.

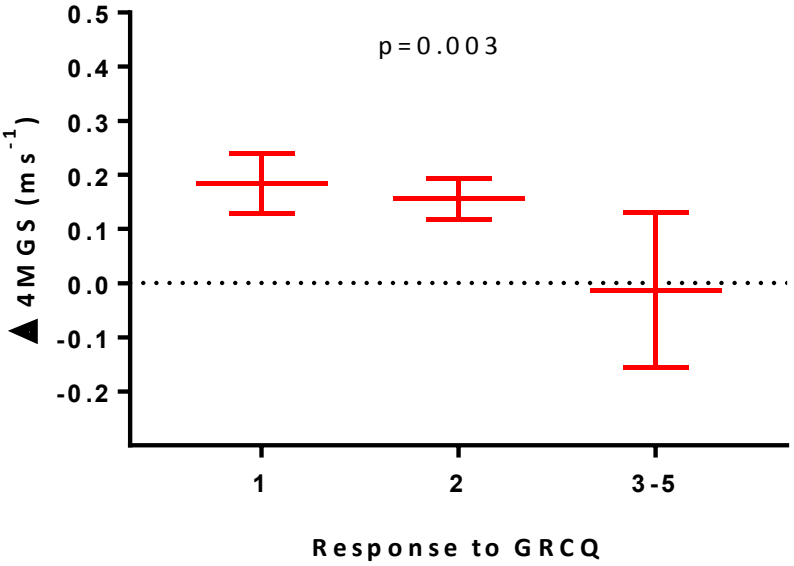

Figure 4.5: Mean (95% CI) change in 4MGS according to response the GRCQ: 1: *'I feel much better'*; 2: *'I feel a little better'*; 3: *'I feel no different'*; *4: 'I feel a little worse'* and 5: *'I feel much worse'* (responses 3–5 were combined due to small numbers in each group).

Abbreviations: Δ: Change between pre-and post-PR values; 4MGS: Four Metre Gait Speed; CI: Confidence Interval; GRCQ: Global Rate of Change Questionnaire.

All estimates of the MCID of the 4MGS test are outlined in table 4.5. Giving equal weighting to the distribution- and anchor- based methods the mean (range) MCID estimate is 0.14 (0.08 to 0.18) ms^{-1}.

In total, 56% of the whole cohort improved their gait speed by at least 0.14 ms^{-1} with 64% of both quartile 1 (slowest gait speed) and quartile 4 (fastest gait speed) achieving the MCID.

Table 4.5: Distribution- and anchor-based MCID estimates of the 4MGS test (n=90).

Distribution-based methods	**MCID estimate (ms^{-1})**				
0.5 * SD	0.13				
MDC_{95}	0.08				
Anchor-based methods					
Linear regression					
CRQ-Mastery domain	0.16				
CRQ-Total score	0.16				
ROC plots	**MCID estimate (ms^{-1})**	**C-statistic**	**p-value**	**Sensitivity (%)**	**Specificity (%)**
CRQ-Mastery domain	0.16	0.71	<0.001	68.3	63.4
CRQ-Total score	0.16	0.59	0.17	61.9	57.8
GRCQ	**MCID estimate (ms^{-1})**		**%**	**p-value**	
1: 'I feel much better'	0.18		44	0.003	
2: 'I feel a little better'	0.16		44		
3-5: 'I feel the same' / 'a little worse' / 'much worse'	-0.01		12		

Abbreviations: 4MGS: Four Metre Gait Speed; CRQ: Chronic Respiratory Questionnaire; GRCQ: Global Rate of Change Questionnaire; MCID: Minimum Clinically Important Difference; MDC_{95}: Minimal Detectable Change at 95% confidence; SD: Standard Deviation.

4.6 Discussion

This study demonstrates that 4MGS is as responsive to PR as the ISW, an established field walking test widely used by the PR community, and that changes in 4MGS correlate significantly with changes in measures of health-related quality of life. Using distribution-and anchor-based methods, the MCID estimate of 4MGS following PR was estimated to be between 0.08 ms^{-1} and 0.18 ms^{-1}. The mean

MCID estimate was 0.14 ms^{-1} with similar proportions of patients with slow (quartile 1) and fast (quartile 4) baseline 4MGS achieving this threshold.

Comparison to previous studies

There are studies of the responsiveness and MCID estimates of gait speed in chronic respiratory disease (264, 279) and gerontology populations (181, 183, 186, 268), but only limited data in IPF with no published MCID estimates. Interventions used in the evaluation of the responsiveness of gait speed tests in chronic respiratory and non-chronic respiratory disease samples have included different exercise-based rehabilitation programmes all of which aimed to improve physical and functional performance. To date, only one observational study has investigated the responsiveness of 4MGS in patients with interstitial lung disease (ILD) (86). Despite patients in this study walking at faster speeds than in the study reported in this thesis (mean (SD) 1.28 (0.43) ms^{-1} (86) versus 0.92 (0.25) ms^{-1}), the authors showed graphically that 4MGS improved with a six to nine week outpatient PR programme (p=0.01) (86). However, neither the absolute values nor effect sizes were reported leading to difficulty with data interpretation (86). Furthermore, there was no significant difference between 4MGS measured before PR and six months later (p=0.06) indicating that the effect of PR on 4MGS may be short-term in ILD patients (86). This is unsurprising as it is recognised that improvements in traditional PR outcome measures (exercise capacity, dyspnoea and health-related quality of life) return to pre-PR levels within six months of PR completion in patients with ILD (280). Accordingly, I hypothesise that the benefit of PR on 4MGS in IPF patients may not persist, but this requires confirmation.

The responsiveness of 4MGS to PR has also been investigated in COPD, the only other chronic respiratory disease that has been studied. Kon *et al* reported an improvement in 4MGS (mean (SD) 0.08 (0.13) ms^{-1}, p<0.001; effect size 0.4) following an eight week outpatient PR programme in 301 COPD patients (264). The response of 4MGS to PR in COPD patients was smaller than that observed

in the study reported in this thesis (mean (95% CI): 0.15 (0.11 to 0.18) ms^{-1}; effect size 0.8). Furthermore, the MCID estimates reported by Kon et al ranged from 0.08 ms^{-1} (anchor: GRCQ) to 0.11 ms^{-1} (MDC_{95} and the ISW MCID as an anchor) (264), lower than those observed in my study of patients with IPF. Maddocks *et al* also reported 4MGS change following PR in 816 patients with COPD, stratified according to the Fried Frailty Phenotype (279). Significant improvements in 4MGS with PR were seen with all groups (frail (mean (95% CI) change: 0.11 (0.09 to 0.14) ms^{-1}), pre-frail (0.07 (0.05 to 0.08) ms^{-1}) and not frail (0.08 (0.05 to 0.12) ms^{-1})) with the greatest relative changes in frail patients (279).

Other studies involving elderly patients have shown that various gait speed tests are responsive to exercise-based rehabilitation programmes following a short-term acute hospital admission (183), hip fracture (186, 268) and stroke (181). In 136 elderly patients admitted to an inpatient rehabilitation programme (mean duration 15 days) following an acute hospital admission, usual gait speed measured over 5.2 metres improved by mean (SD) 0.20 (0.16) ms^{-1} (183). The MCID estimates generated using distribution- (MDC_{95}) and anchor-based methods against four different comparators (subjective change in walking; change in assistive device required to walk; change in assistance required and change in speed-based classification) were comparable to the results reported in this thesis and ranged from 0.10 to 0.18 ms^{-1} (183).

Two studies involving elderly patients attending post-hip-fracture rehabilitation also demonstrated improvements in usual gait speed measured over 3.81 metres (186) and 10 metres (268). Neither authors reported the response data but documented MCID estimates of 0.08 ms^{-1} (268) and 0.08 to 0.10 ms^{-1} (186). The first report, by Palombaro *et al*, involved pooled data from three studies (n=92) and used expert opinion (five physical therapists) as well as distribution- (standard error of measurement) and anchor-based methods (anchor: Timed Up and Go test) to determine the MCID (186). The second smaller study of 16 patients attending acute rehabilitation following a unilateral

hip fracture fixation, only used a distribution-based method (MDC_{95}) to determine the MCID (268). The MCID estimates reported in these studies are at the lower end of the estimates observed in this thesis. This may be due to variations in populations, interventions or limited MCID calculation methodology. It is unlikely to have arisen from different gait speed course lengths as it is recognised that a four metre course is sufficiently long to ensure measurement accuracy (139, 206).

In 283 stroke patients with slow usual gait speed (<0.80 ms^{-1}), gait speed improved by mean (SD) 0.21 (0.17) ms^{-1} with inpatient rehabilitation when measured at 20 and 60 days post-stroke (181). Despite the slow usual gait speed, the MCID estimate calculated using an anchor-based method (ROC plot with the modified Ranking Scale as an anchor) was similar to this study: 0.16 ms^{-1} (181).

Limitations

There were some limitations to this study. First, the majority of the patients (99%) were symptomatic outpatients recruited from PR programmes at the Royal Brompton and Harefield NHS Foundation Trust a specialist, cardiorespiratory, tertiary care centre. Therefore the data need to be corroborated in other settings and other populations with IPF (for example, less or more symptomatic patients managed in primary care or the acute hospital setting respectively). Second, although 4MGS improved with PR it is not known for how long this is sustained. Third, seven MCID estimates were provided using a combination of distribution- and anchor-based methods because there is no consensus on the methodology on how to perform this type of analysis (272). Distribution-based techniques are an indirect way of estimating the MCID that do not consider patients' experiences. Instead, the change in the outcome of interest is based on a form of statistical variability e.g. standard deviation (272) which may vary depending on patient ability or baseline measurements (273). In contrast, although anchor-based approaches account for the clinical significance of the intervention and are considered more clinically robust and meaningful (275, 276),

a suitable external anchor that correlates significantly with the outcome measure of interest is required (272). There is no consensus on the necessary strength of this correlation. Revicki *et al* recommended that a correlation coefficient of >0.3 is sufficient (272) but it is thought that multiple anchors do not require this level of association (281). As gait speed is a marker of clinical well-being, it is unlikely that a single anchor would capture its multi-system properties (282), therefore the use of multiple anchors as well as several anchor- and distribution-based approaches in this study provides a degree of reassurance on its validity. Fourth, the CRQ-total score was deemed to be an acceptable external anchor (r=0.31, p=0.005), however the ROC plot provided a low c-statistic (0.59) that was not statistically significant (p=0.17). A possible explanation for this may be that the mean change in CRQ-total score with PR (8.5 points) was lower than the CRQ-total MCID (10 points) with only 48% of patients achieving the MCID. Despite this, the MCID estimate was consistent with values from other methodologies. Fifth, few patients reported that they deteriorated with PR; accordingly this data estimates the MCID for improvement only. Further studies are required to assess whether patients perceive the size of deterioration differently to the size of improvement.

Significance of findings

In Chapter 3, I described the reliability and concurrent validity of 4MGS in patients with IPF as well as the characteristics of the slow gait speed phenotype in this population. The current study provides additional information on the psychometric properties of the 4MGS test in IPF by demonstrating its responsiveness to an intervention and providing a range of MCID estimates. The capacity to detect improvement is important because outcome measures seeking regulatory approval must demonstrate this ability (75). These properties are essential traits in an outcome tool and accordingly the 4MGS test has potential as a simple assessment tool in IPF.

The effect size of change in 4MGS according to disease severity was higher in patients with mild to moderate compared to severe disease. These data support the potential for 4MGS to be used in pharmacological clinical trials in IPF, which tend to recruit patients with mild to moderate disease.

The correlation between change in 4MGS and ISW was significant but weak (r=0.23). This was similar to the strength of the relationship observed in COPD patients in the study by Kon et al (r=0.26, p<0.001) (264). The authors postulated that the reason for the weak correlation was the ceiling effect of 4MGS (264) - the difficulty in increasing walking speed in those who already walk quickly – a property also described in gerontology literature (281). However, in this study the graphical respresentation of change in 4MGS and ISW with PR did not clearly demonstrate that a ceiling effect existed in patients with IPF. However,, 4MGS was equally as responsive in the quartiles with the slowest and fastest baseline 4MGS with effect sizes of 1.0 and 0.8 respectively. This argues against a ceiling effect, and suggests that 4MGS may be a useful outcome measure in patients with IPF and reinforces its potential utility in a variety of healthcare settings. However, this analysis should be repeated with a larger sample size.

4.7 Conclusion

In conclusion, this study demonstrates that 4MGS improves with PR in patients with IPF with no evidence of a ceiling effect. The MCID estimates range from 0.08 to 0.18 ms^{-1} with a mean estimate of 0.14 ms^{-1}. The 4MGS test shows potential as a simple, practical, functional outcome measure in patients with IPF.

In the next chapter, I investigate whether 4MGS measured at the time of diagnosis of IPF can predict all-cause mortality and all-cause, non-elective hospital admission at one year.

Chapter 5 : Four metre gait speed is an independent predictor of mortality and non-elective hospital admission in patients with a new diagnosis of idiopathic pulmonary fibrosis

5.1 Introduction

In Chapters 3 and 4, I demonstrated that the four metre gait speed (4MGS) test is reliable, valid and responsive to change in patients with idiopathic pulmonary fibrosis (IPF). In large epidemiological studies of older, community-dwelling, adults usual gait speed has been shown to be a consistent predictor of all-cause mortality and hospital admission (144, 147, 152). In chronic respiratory disease, usual gait speed has also been shown to predict 90-day hospital readmission after an acute exacerbation of chronic obstructive pulmonary disease (COPD) (196) as well as future hospital admissions in patients with Acute Respiratory Distress Syndrome (ARDS) (190). To date, the prognostic validity of 4MGS in patients with IPF has not been explored. Therefore, I postulate that 4MGS may be a useful surrogate marker of all-cause, non-elective hospital admission and mortality, in patients with IPF.

5.2 Aims

The aims of this study were to determine whether baseline 4MGS at the time of diagnosis of IPF can predict: 1) all-cause mortality and 2) all-cause, non-elective hospital admission at one year.

5.3 Hypothesis

In patients with newly diagnosed IPF, those with the slow gait speed phenotype (4MGS <0.80 ms^{-1}) are at increased risk of:

- all-cause mortality at one year;
- all-cause, non-elective hospital admission at one year;

compared with those with preserved gait speed (4MGS ≥0.80 ms^{-1}).

5.4 Methods

5.4.1 Study participants

Participants were prospectively recruited to this longitudinal, cohort study from outpatient respiratory clinics at the Royal Brompton and Harefield Hospital NHS Foundation Trust, UK between March 2015 and October 2016. The inclusion criteria were: 1) new IPF diagnosis by a specialist interstitial lung disease multidisciplinary team according to international guidelines (7); 2) ability to walk five metres and 3) providing informed consent. Exclusion criteria were significant co-morbidities that would limit walking ability or exercise capacity (e.g. lower limb amputation) or make exercise unsafe (e.g. unstable ischaemic heart disease). All participants provided informed written consent; the study was approved by the London-Riverside Research Ethics Committee (15/LO/0015) and registered on clinicaltrials.gov (NCT04236278).

5.4.2 Measurements

The following outcome measures, described in Chapter 2, were assessed within two weeks of IPF diagnosis: 4MGS (220); anthropometry; pulmonary function (208, 209); Composite Physiologic Index (CPI) (82); Gender, Age and lung Physiology (GAP) index (85); Medical Research Council (MRC) Dyspnoea score (212); 6MWT (96) and King's Brief Interstitial Lung Disease (KBILD) questionnaire (111). Co-morbidities were evaluated using the age-adjusted Charlson co-morbidity Index (257). One year after the baseline assessment, data on all-cause mortality and the number of all-cause, non-elective hospital admissions in this time period were obtained from general practice and hospital records and UK National Health Service 'spine', a national database maintained by the NHS Care Records Service. The final search for these data was conducted on 27th October 2017 and the follow-up of patients who survived or had no non-elective hospital admissions in the one year period was censored at 365 days. The schema for this study is presented in figure 5.1.

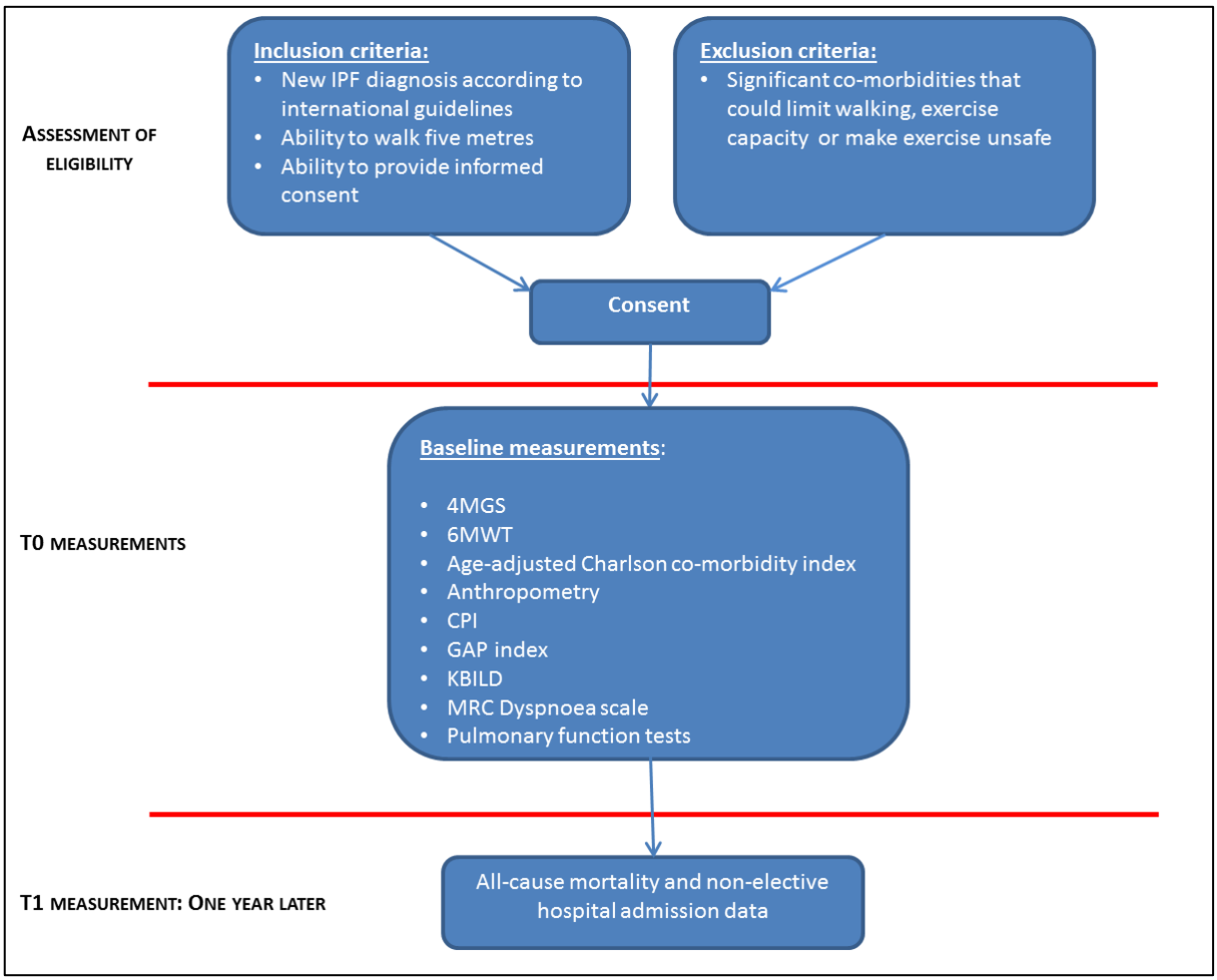

Figure 5.1: Study schema.

Abbreviations: 4MGS: Four Metre Gait Speed; 6MWT: Six Minute Walk Test; CPI: Composite Physiologic Index: GAP index: Gender, Age and lung Physiology index; IPF: Idiopathic Pulmonary Fibrosis; KBILD: King's Brief Interstitial Lung Disease questionnaire; MRC: Medical Research Council Dyspnoea score.

5.4.3 Statistical analysis

The sample size calculation was based on the area under the receiver operating characteristic (ROC) curve with one year all-cause mortality as a binary outcome predicted by a multivariable Cox proportional hazards model incorporating 4MGS. Assuming a 20% one year, all-cause mortality rate

(283), 105 patients (21 cases/events and 84 controls) would be needed to obtain a c-statistic above 0.5 where the true value is 0.7 with 80% power at the 5% significance level.

Participant characteristics were summarised using descriptive statistics. The cohort was divided according to gait speed phenotype (slow: <0.80ms^{-1} versus preserved: ≥0.80ms^{-1}) (256) and the between-group differences were analysed using the unpaired t-test (or the Mann-Whitney U test for non-parametric data) for continuous variables or the chi-square test for categorical data.

A Kaplan–Meier analysis was used to evaluate the ability of the slow gait speed phenotype to predict time to all-cause mortality and non-elective hospital admission. Significance was assessed with the log-rank test. The slow gait speed phenotype was chosen as international consensus statements and systematic reviews have suggested that a cut point of <0.80ms^{-1} is predictive of adverse health outcomes (143, 144) and its discriminative validity in IPF was demonstrated in Chapter 3 (256).

Univariable Cox proportional regression was used to assess the association between 4MGS (expressed separately as a continuous and binary variable – slow versus preserved gait speed) and all-cause mortality. Other plausible confounders were also evaluated (age; gender; smoking status; forced vital capacity (FVC) % predicted; diffusing capacity of the lung for carbon monoxide (DL_{CO}) % predicted; 6MWT; prescribed anti-fibrotic medication during the study period; number of respiratory hospital admissions in the previous year). Two models were considered in the multivariable Cox proportional regression analysis to account for 4MGS expressed separately as a continuous and binary variable. The components of the models were as follows:

- Model 1: 4MGS; age; gender; smoking status, FVC % predicted; DL_{CO} % predicted; 6MWT; prescribed anti-fibrotic medication during the study period; number of respiratory hospital admissions in the previous year.

- Model 2: Slow 4MGS; age; gender; smoking status; FVC % predicted; DL_{CO} % predicted; 6MWT; prescribed anti-fibrotic medication during the study period; number of respiratory hospital admissions in the previous year.

A backwards stepwise selection procedure was used with each variable remaining in the model if $p<0.20$ (196). Log-log plots and Schonfeld's residuals were used to test the proportional hazard assumption.

To satisfy the power calculation, Receiver Operating Characteristic (ROC) plots of models from the multivariable Cox regression analysis (including and excluding 4MGS) and baseline 4MGS were constructed and the c-statistic was used to assess discrimination (284). The ROC plots of multivariable models 1 and 2 were compared with the ROC plots of two established composite indices of mortality, the CPI and GAP index, to identify ability to determine all-cause mortality at one year. ROC plots of FVC % predicted, 4MGS and 6MWT were also constructed and the c-statistic used to assess discrimination.

The same analyses (univariable and two multivariable Cox proportional regression and ROC plot construction) were repeated for evaluating the association between 4MGS and all-cause, non-elective hospital admission at one year. The confounding variables considered in this analysis were the same as those in the mortality analysis (age; gender; smoking status; FVC % predicted; DL_{CO} % predicted; 6MWT; prescribed anti-fibrotic medication; number of respiratory hospital admissions in the previous year) and also included the number of chest infections in the previous year. The components of the two models were as follows:

- Model 1: 4MGS; age; gender; smoking status, FVC % predicted; DL_{CO} % predicted; 6MWT; prescribed anti-fibrotic medication; number of respiratory hospital admissions in the previous year; number of chest infections in the previous year.
- Model 2: Slow 4MGS; age; gender; smoking status; FVC % predicted; DL_{CO} % predicted; 6MWT; prescribed anti-fibrotic medication; number of chest infections in the previous year.

Data analyses were performed using GraphPad Prism 7 (GraphPad Software, La Jolla, USA) and SPSS version 24 (IBM, New York, USA). A p-value of <0.05 was considered statistically significant.

5.5 Results

5.5.1 Baseline characteristics

A total of 177 patients referred to respiratory outpatient services at the Royal Brompton and Harefield Hospital NHS Foundation Trust were invited to participate in the study: nine did not meet the inclusion criteria, 36 declined the study and 132 agreed to participate. Of the 132 patients, two withdrew from the study before completing the baseline assessment. The recruitment flow chart is shown in figure 5.2. The baseline characteristics of the 130 study participants are in table 5.1 and the cohort characteristics according to the slow gait speed phenotype are in table 5.2. The majority of patients were male (83%) with mean (standard deviation (SD)) or median (25^{th}, 75^{th} centile): age 72 (7) years; FVC 74.2 (18.1) % predicted; DL_{CO} 41.0 (33.8, 50.4) % predicted; MRC 3 (1) and 4MGS 0.91 (0.23) ms^{-1}. Thirty-four percent of patients had a slow gait speed and compared to those with preserved gait speed were significantly older with worse GAP index, dyspnoea, exercise capacity and health-related quality of life. They were also more likely to use a walking aid as well as long-term or ambulatory oxygen therapy.

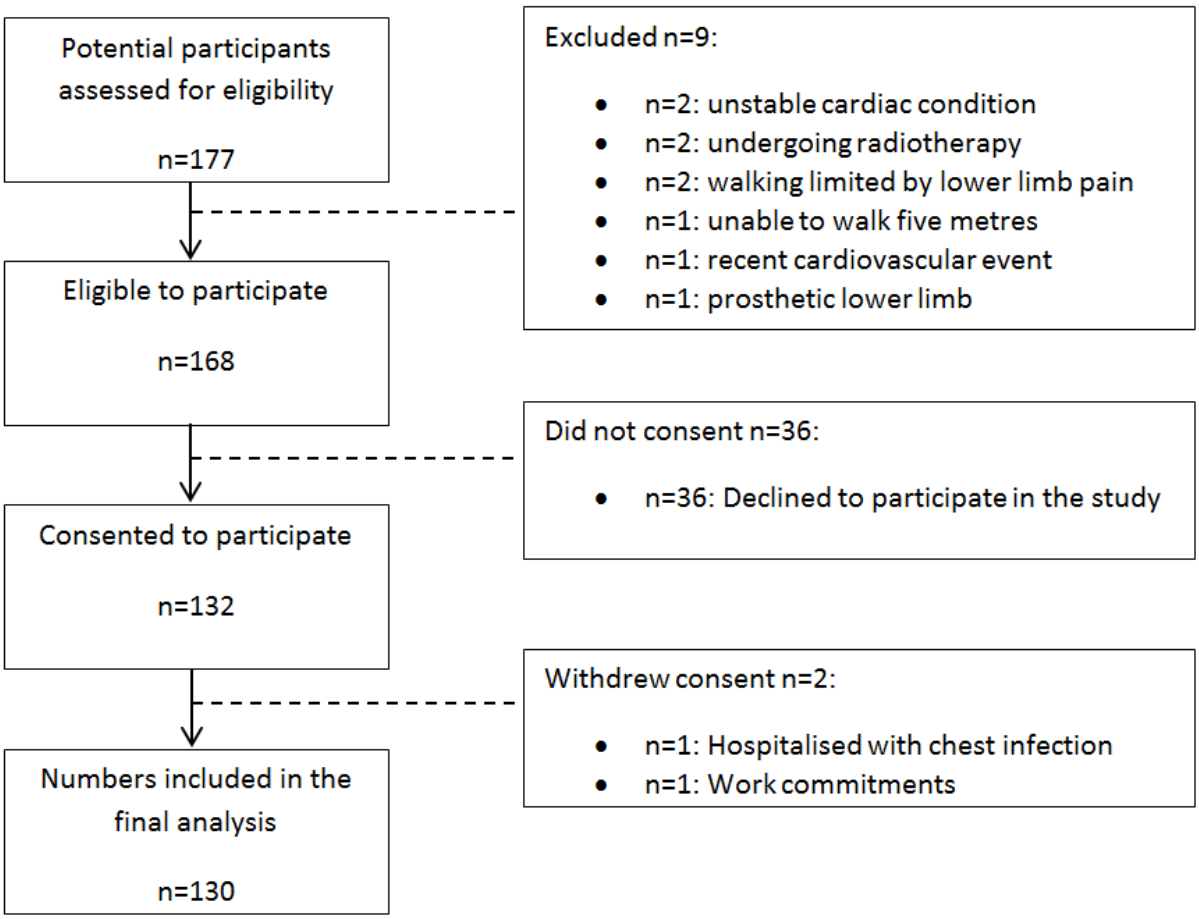

Figure 5.2: Recruitment flowchart.

Table 5.1: Baseline characteristics of the cohort (n=130).

Variable	Baseline characteristics
Gender: male (%)	83
Age (years)	72 (7)
MRC	3 (1)
BMI (kg/m^2)	27.8 (4.7)
FEV_1/FVC	0.82 (0.07)
FVC (L)	2.5 (0.7)
FVC (%)	74.2 (18.1)
DL_{CO} (mL/min/kPa)	3.3 (2.6, 4.1)
DL_{CO} (%)	41.0 (33.8, 50.4)
CPI	49.8 (12.6)
GAP index	4.4 (1.3)
Smoking status: never/former/current: (%)	29 / 68 / 3
Age-adjusted Charlson Co-morbidity Index	0 (0, 4)
COPD: (%)	9
Pulmonary hypertension: (%)	16
Ischaemic heart disease: (%)	25
Obstructive sleep apnoea: (%)	4
Self-reported hospitalisations in previous year	0 (0, 1)
Self-reported chest infections in previous year	0 (0, 1)
Self-reported completion of PR in the previous year: (%)	2

Oxygen: (%)	
Long-term	5
Ambulatory	12
Walking aid: (%)	8
Pirfenidone: (%)	5
Nintedanib: (%)	2
Prescribed anti-fibrotic medication during the study period: (%)	57
4MGS (ms^{-1})	0.91 (0.23)
6MWT (m)	365 (121)
KBILD-Psychological	60.3 (20.2)
KBILD-Breathlessness and symptoms	41.4 (20.6)
KBILD-Chest and activities	67.1 (23.4)
KBILD-Total score	56.8 (12.9)

Data reported as mean (standard deviation) or median (25^{th}, 75^{th} centile) unless stated otherwise.

Abbreviations: 4MGS: Four Metre Gait Speed; 6MWT: Six Minute Walk Test; BMI: Body Mass Index; CPI: Composite Physiologic Index; DL_{CO}: Diffusing Capacity of the Lung for Carbon Monoxide; FEV_1: Forced Expiratory Volume in One Second; FVC: Forced Vital Capacity; GAP index: Gender, Age and lung Physiology index; KBILD: King's Brief Interstitial Lung Disease questionnaire; MRC: Medical Research Council Dyspnoea score; PR: Pulmonary Rehabilitation.

Table 5.2: Baseline characteristics according to slow (<0.80ms^{-1}: n=44) and preserved (≥0.80ms^{-1}: n=86) gait speed.

Variable	**Slow**	**Preserved**	**Between-group difference**	**p-value**
Male: (%)	86	81	5	0.48
Age (years)	75 (7)	71 (6)	3 (1 to 6)	0.006
MRC	4 (1)	3 (1)	0.8 (0.5 to 1.2)	<0.001
BMI (kg/m^2)	28.1 (4.7)	27.6 (4.7)	0.5 (-1.2 to 2.2)	0.56
FEV_1/FVC	0.82 (0.08)	0.82 (0.07)	0.00 (-0.03 to 0.02)	0.72
FVC (L)	2.4 (0.8)	2.6 (0.6)	-0.2 (-0.5 to 0.1)	0.10
FVC (%)	70.0 (18.7)	76.5 (17.4)	-6.5 (-13.1 to 0.5)	0.05
DL_{CO} (mL/min/kPa)	3.2 (1.1)	3.5 (1.2)	-0.3 (-0.8 to 0.2)	0.21
DL_{CO} (%)	42.1 (15.0)	43.1 (14.6)	-1.1 (-6.8 to 4.7)	0.72
CPI	51.1 (12.7)	49.1 (12.6)	1.9 (-2.9 to 6.9)	0.42
GAP index	4.8 (1.4)	4.2 (1.2)	0.6 (0.1 to 1.1)	0.02
Age-adjusted Charlson Co-morbidity Index	0 (0, 4)	0 (0, 4)	0 (0, 0)	0.53
Self-reported hospitalisations in previous year	0 (0, 1)	0 (0, 0)	0 (0, 1)	0.25
Self-reported chest infections in previous year	1 (0, 2)	0 (0, 1)	1 (0, 1)	0.11
Oxygen: (%)				
Long-term	11	1	10	0.009

Ambulatory	18	8	10	0.09
Walking aid: (%)	18	2	16	0.001
Pirfenidone: (%)	5	6	-1	0.76
Nintedanib: (%)	0	3	-3	0.31
Prescribed anti-fibrotic medication during the study period: (%)	57	57	0	0.99
6MWT (m)	262 (88)	420 (98)	-158 (-193 to 123)	<0.001
KBILD-Psychological	55.1 (17.7)	63.0 (21.4)	-7.9 (-15.2 to -0.5)	0.04
KBILD-Breathlessness and symptoms	30.5 (17.3)	47.0 (20.0)	-16.5 (-23.5 to -9.5)	<0.001
KBILD-Chest and activities	57.9 (22.0)	71.9 (22.8)	-14.0 (-22.3 to -5.7)	0.001
KBILD-Total score	51.4 (10.8)	59.6 (13.1)	-8.2 (-12.7 to -3.7)	0.001

Data for the slow and preserved gait speed groups are reported as mean (standard deviation) or median (25^{th}, 75^{th} centile) unless stated otherwise. The between-group difference data is reported as mean (lower 95% to upper 95% confidence interval) or median (25^{th}, 75^{th} centile) unless otherwise stated.

Abbreviations: 4MGS: Four Metre Gait Speed; 6MWT: Six Minute Walk Test; BMI: Body Mass Index; CPI: Composite Physiologic Index; DL_{CO}: Diffusing Capacity of the Lung for Carbon Monoxide; FEV_1: Forced Expiratory Volume in One Second; FVC: Forced Vital Capacity; GAP index: Gender, Age and lung Physiology index; KBILD: King's Brief Interstitial Lung Disease questionnaire; MRC: Medical Research Council Dyspnoea score.

5.5.2 Prediction of all-cause mortality at one year

A total of 18% of patients (n=23) died within one year of the baseline assessment. Compared to survivors, those who died had worse FVC % predicted; GAP index; dyspnoea; exercise capacity and health-related quality of life as well as a slower gait speed (table 5.3). When patients were stratified according to the slow gait speed phenotype, there was a significantly higher mortality rate at one year amongst the patients categorised as having slow (32%) compared to preserved gait speed (11%) ($p<0.01$). The Kaplan-Meier curve demonstrated a shorter time to death in those with slow gait speed compared to preserved gait speed ($p=0.004$) (figure 5.3).

Table 5.3: Baseline characteristics of survivors (n=107) and non-survivors (n=23) at one year.

Variable	**Survivors**	**Non-survivors**	**Between-group difference**	**p-value**
Male: (%)	81	91	10	0.25
Age (years)	72 (7)	72 (7)	-0.9 (-4.0 to 2.1)	0.55
MRC	3 (1)	4 (1)	0.7 (0.3 to 1.2)	0.002
BMI (kg/m^2)	28.0 (4.4)	26.7 (5.9)	-1.4 (-3.5 to 0.8)	0.21
FEV_1/FVC	0.81 (0.07)	0.85 (0.07)	0.04 (0.01 to 0.07)	0.01
FVC (L)	2.6 (0.7)	2.2 (0.5)	-0.4 (-0.7 to -0.1)	<0.01
FVC (%)	76.9 (18.1)	62.0 (12.3)	-14.9 (-22.7 to -7.0)	<0.001
DL_{CO} (mL/min/kPa)	3.3 (2.7, 4.1)	2.6 (2.2, 3.6)	-0.7 (-0.05, 0.05)	0.05
DL_{CO} (%)	41.2 (34.9, 50.5)	36.7 (28.2, 49.0)	-4.5 (-6.7, -1.5)	0.15
CPI	48.8 (12.6)	54.6 (11.8)	5.7 (-0.4 to 11.9)	0.07
GAP index	4.3 (1.3)	5.1 (1.3)	0.8 (0.2 to 1.5)	0.01
Age-adjusted Charlson Co-morbidity Index	0 (0, 4)	2 (0, 5)	2 (0, 1)	0.46
Self-reported hospitalisations in previous year	0 (0, 0)	0 (0, 1)	0 (0, 1)	0.08
Self-reported chest infections in previous year	0 (0, 1)	0 (0, 2)	0 (0, 1)	0.34
Oxygen: (%)				

Long-term	4	9	5	0.30
Ambulatory	10	17	7	0.33
Walking aid: (%)	8	9	1	0.84
Pirfenidone: (%)	6	4	-2	0.80
Nintedanib: (%)	2	0	-2	0.51
Prescribed anti-fibrotic medication during the study period: (%)	57	57	0	0.97
4MGS (ms^{-1})	0.94 (0.22)	0.77 (0.22)	-0.17 (-0.27 to -0.07)	0.001
6MWT (m)	375 (304, 458)	290 (175, 420)	-85 (-129, -38)	<0.01
KBILD-Psychological	62.0 (20.6)	52.8 (16.7)	-9.2 (-18.3 to -0.1)	0.048
KBILD-Breathlessness and symptoms	43.3 (20.8)	32.5 (17.6)	-10.8 (-20.0 to -1.5)	0.02
KBILD-Chest and activities	67.6 (23.3)	65.2 (24.3)	-2.3 (-13.0 to 8.4)	0.67
KBILD-Total score	57.7 (13.1)	51.5 (11.0)	-6.4 (-12.2 to -0.6)	0.03

Data for the survivors and non-survivors are reported as mean (standard deviation) or median (25^{th}, 75^{th} centile) unless stated otherwise. The between-group difference data is reported as mean (lower 95% to upper 95% confidence interval) or median (25^{th}, 75^{th} centile) unless otherwise stated.

Abbreviations: 4MGS: Four Metre Gait Speed; 6MWT: Six Minute Walk Test; BMI: Body Mass Index; CPI: Composite Physiologic Index; DL_{CO}: Diffusing Capacity of the Lung for Carbon Monoxide; FEV_1: Forced Expiratory Volume in One Second; FVC: Forced Vital Capacity; KBILD: GAP index: Gender, Age and lung Physiology index; King's Brief Interstitial Lung Disease questionnaire; MRC: Medical Research Council Dyspnoea score.

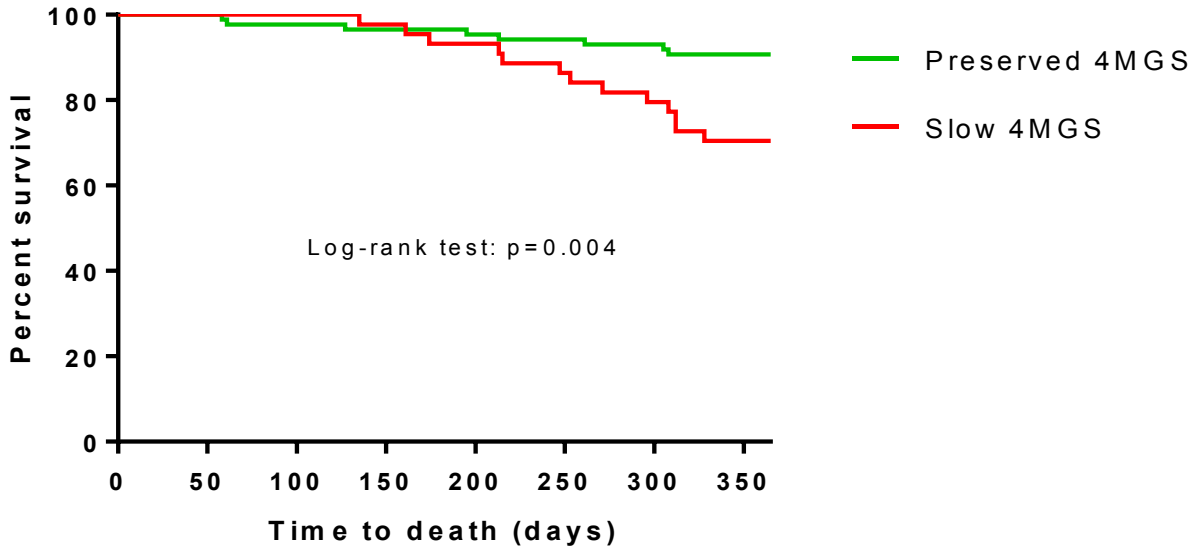

Figure 5.3: Kaplan–Meier curve demonstrating time to all-cause death within one year according to slow (4MGS <0.08 ms^{-1}) and preserved (4MGS ≥0.08 ms^{-1}) 4MGS.

Abbreviation: 4MGS: Four Metre Gait Speed.

The univariable analysis for risk of all-cause mortality is in table 5.4. When 4MGS was analysed as a continuous variable, there was a decreasing unadjusted hazard ratio (HR) for one year, all-cause mortality for each 1.00 ms^{-1} increase in gait speed (HR (95% confidence interval (CI)): 0.03 (0.01 to 0.25); p<0.01) (table 5.4). Similarly, when analysed as a binary variable, those with slow gait speed had an increased unadjusted hazard ratio (HR (95% CI): 3.71 (1.56 to 8.85), p<0.01) for all-cause mortality compared to patients with preserved gait speed (table 5.4). The results of the multivariable analysis confirmed that when 4MGS was expressed as a continuous or binary variable, it remained an independent risk factor for one year, all-cause mortality (tables 5.5 and 5.6). The ROC curve analysis showed that both multivariable model 1 and 2 demonstrated high discrimination with a c-statistic (95% CI) of 0.81 (0.72 to 0.91) and 0.79 (0.70 to 0.89) respectively; both p<0.0001. Figure 5.4a shows the ROC plot and c-statistic (95% CI) of multivariable model 1 (4MGS, age, FVC % predicted), the same multivariable model but excluding 4MGS and 4MGS alone (as a continuous variable) to predict mortality at one year; all p<0.01. The same information for multivariable models

1 and 2, CPI and GAP index (composite indices of mortality) is in figure 5.4b; all p<0.05. Figure 5.5 shows the ROC plot and c-statistic (95% CI) for FVC % predicted, 4MGS and 6MWT; all p<0.05.

Table 5.4: Univariable cox proportional regression analysis for time to all-cause death at one year.

Variables	**Univariable analysis**	
	HR (95% CI)	**p-value**
4MGS (ms^{-1})	0.03 (0.01 to 0.25)	0.001
Slow 4MGS (reference: preserved GS)	3.71 (1.56 to 8.85)	0.003
Age (years)	0.98 (0.92 to 1.04)	0.45
Gender (reference: female)	2.15 (0.50 to 9.21)	0.30
Smoking status (reference: never smokers)	2.87 (0.85 to 9.69)	0.09
FVC (% predicted)	0.96 (0.94 to 0.98)	<0.001
DL_{CO} (% predicted)	0.99 (0.95 to 1.02)	0.36
6MWT (metres)	0.99 (0.99 to 0.99)	0.001
Prescribed anti-fibrotic medication during the study period (reference: no)	0.88 (0.38 to 2.04)	0.77
Number of respiratory hospital admissions in previous year	1.25 (1.02 to 1.52)	0.03

Abbreviations: 4MGS: Four Metre Gait Speed; 6MWT: Six Minute Walk Test; CI: Confidence Interval; DL_{CO}: Diffusing Capacity of the Lung for Carbon Monoxide; FVC: Forced Vital Capacity; HR: Hazard Ratio.

Table 5.5: Univariable and multivariable cox proportional regression analysis for time to all-cause death at one year with 4MGS expressed as a continuous variable.

Covariates	**Univariable analysis**		**Multivariable analysis – Model 1***	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**
4MGS (ms^{-1})	0.03 (0.01 to 0.25)	0.001	0.03 (0.01 to 0.31)	0.004
Age (years)	0.98 (0.92 to 1.04)	0.45	0.95 (0.88 to 1.02)	0.15
Gender (reference: female)	2.15 (0.50 to 9.21)	0.30		
Smoking status (reference: never smokers)	2.87 (0.85 to 9.69)	0.09		
FVC (% predicted)	0.96 (0.94 to 0.98)	<0.001	0.95 (0.92 to 0.99)	0.005
DL_{CO} (% predicted)	0.99 (0.95 to 1.02)	0.36		
6MWT (metres)	0.99 (0.99 to 0.99)	0.001		
Prescribed anti-fibrotic medication during the study period (reference: no)	0.88 (0.38 to 2.04)	0.77		
Number of respiratory hospital admissions in previous year	1.25 (1.02 to 1.52)	0.03		

*All of the variables in the univariable analysis were included in the multivariable analysis. Final model presented.

Abbreviations: 4MGS: Four Metre Gait Speed; 6MWT: Six Minute Walk Test; CI: Confidence Interval; DL_{CO}: Diffusing Capacity of the Lung for Carbon Monoxide; FVC: Forced Vital Capacity; HR: Hazard Ratio.

Table 5.6: Univariable and multivariable cox proportional regression analysis for time to all-cause death at one year with 4MGS expressed as a binary variable.

Covariates	**Univariable analysis**		**Multivariable analysis – Model 2***	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**
Slow 4MGS (reference: preserved GS)	3.71 (1.56 to 8.85)	0.003	2.63 (1.01 to 6.87)	0.049
Age (years)	0.98 (0.92 to 1.04)	0.45		
Gender (reference: female)	2.15 (0.50 to 9.21)	0.30		
Smoking status (reference: never smokers)	2.87 (0.85 to 9.69)	0.09	2.24 (0.65 to 7.75)	0.20
FVC (% predicted)	0.96 (0.94 to 0.98)	<0.001	0.94 (0.91 to 0.97)	0.001
DL_{CO} (% predicted)	0.99 (0.95 to 1.02)	0.36		
6MWT (metres)	0.99 (0.99 to 0.99)	0.001		
Prescribed anti-fibrotic medication during the study period (reference: no)	0.88 (0.38 to 2.04)	0.77		
Number of respiratory hospital admissions in previous year	1.25 (1.02 to 1.52)	0.03		

*All of the variables in the univariable analysis were included in the multivariable analysis. Final model presented

Abbreviations: 4MGS: Four Metre Gait Speed; 6MWT: Six Minute Walk Test; CI: Confidence Interval; DL_{CO}: Diffusing Capacity of the Lung for Carbon Monoxide; FVC: Forced Vital Capacity; HR: Hazard Ratio.

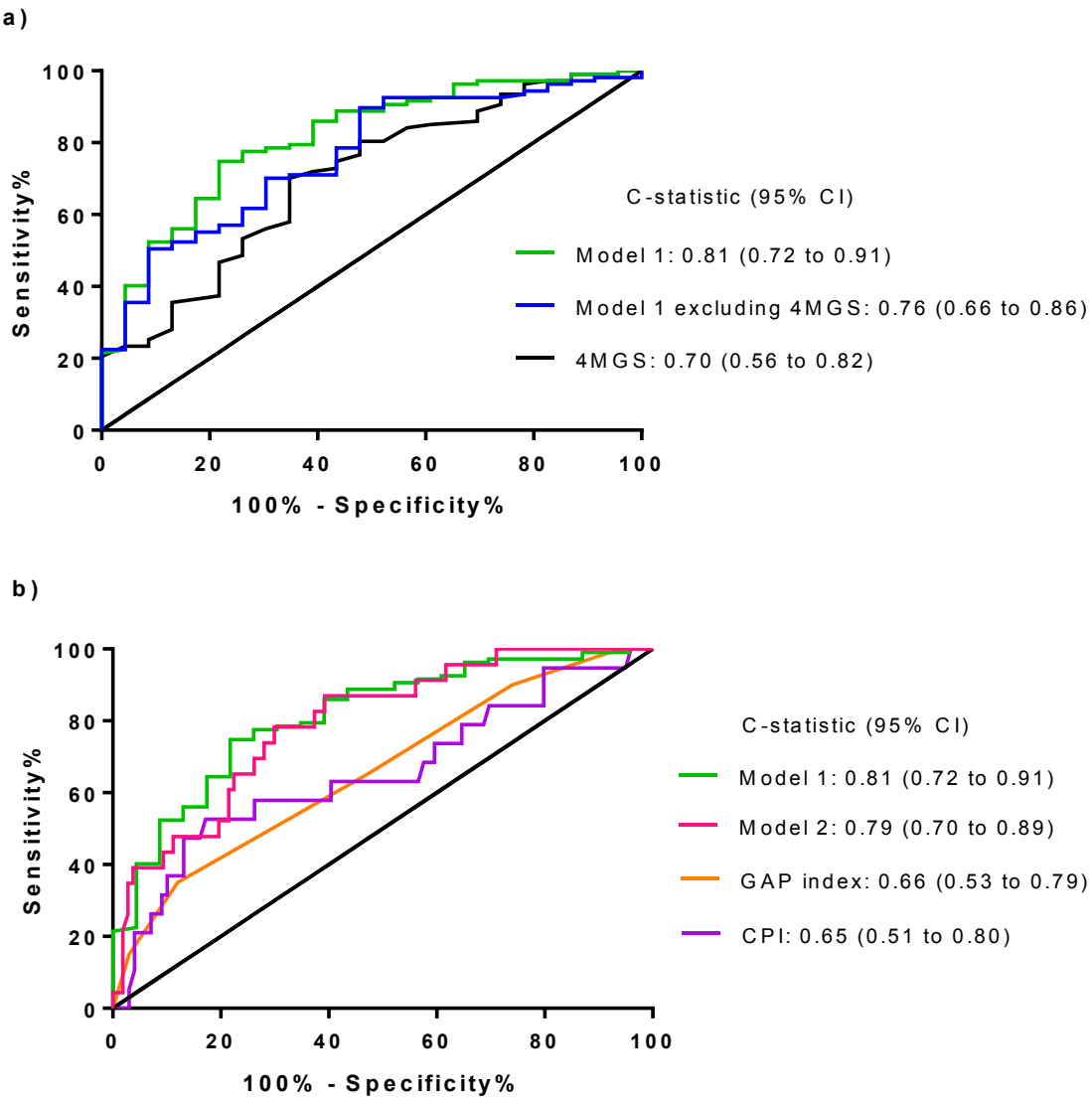

Figure 5.4: Receiver operating characteristic plots demonstrating the ability of a) multivariable model 1 (4MGS, age, FVC % predicted); model 1 excluding 4MGS (age, FVC % predicted) and 4MGS alone (continuous variable) and b) multivariable model 1 (4MG, age, FVC % predicted), multivariable model 2 (slow 4MGS, age, FVC % predicted), CPI and GAP index to predict all-cause death at one year.

Abbreviations: 4MGS: Four Metre Gait Speed; CI: Confidence Interval; CPI: Composite Physiologic Index; FVC: Forced Vital Capacity; GAP index; Gender, Age and lung Physiology index.

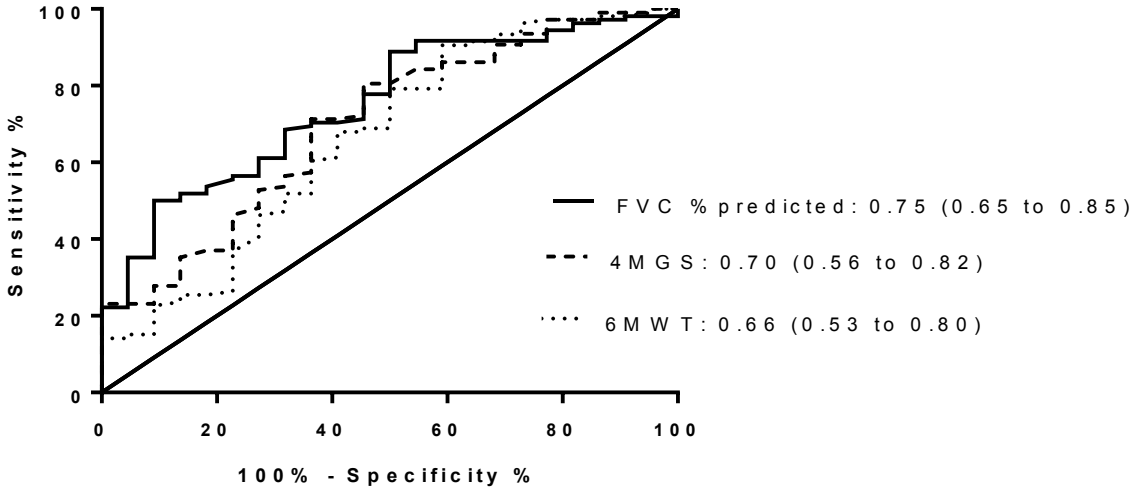

Figure 5.5: Receiver Operating Characteristic plots demonstrating the ability of FVC% predicted, 4MGS and 6MWT to predict all-cause death at one year.

Abbreviations: 4MGS: Four Metre Gait Speed; 6MWT: Six Minute Walk Test; FVC: Forced Vital Capacity.

5.5.3 Prediction of all-cause, non-elective hospital admissions at one year

Thirty-one percent of participants (n=40) had one or more non-elective hospital admissions within one year of the initial assessment. The baseline characteristics of those hospitalised and not hospitalised are in table 5.5. Patients who were hospitalised had worse FVC % predicted; DL_{CO}; CPI, GAP index; dyspnoea; exercise capacity and health-related quality of life. They were also more likely to have a slow gait speed, use a walking aid as well as long-term and ambulatory oxygen therapy. When categorized according to the slow gait speed phenotype, there were a higher number of non-elective hospital admissions amongst the patients categorised as having slow (57%) compared to preserved gait speed (19%) ($p<0.001$). Furthermore, the Kaplan-Meier curve demonstrated a shorter time to non-elective hospital admission in patients with slow versus preserved gait speed ($p<0.0001$) (figure 5.6).

Table 5.7: Baseline characteristics of hospitalised (n=40) and non-hospitalised (n=90) patients at one year.

Variable	Hospitalised	Non-hospitalised	Between-group difference	p-value
Gender: male (%)	92	79	13	0.09
Age (years)	73 (7)	72 (6)	2 (-1 to 4)	0.20
MRC score	3 (1)	3 (1)	0.8 (0.4 to 1.2)	<0.001
BMI (kg/m^2)	28.0 (5.4)	28.0 (4.3)	-0.1 (-1.9 to 1.8)	0.99
FEV_1/FVC	0.84 (0.07)	0.81 (0.08)	0.02 (-0.01 to 0.05)	0.12
FVC (L)	2.4 (0.8)	2.6 (0.7)	-0.15 (-0.42 to -0.12)	0.26
FVC (%)	68.1 (12.2)	78.4 (19.2)	-10.3 (-17.2 to -3.4)	0.004
DL_{CO} (mL/min/kPa)	2.9 (0.8)	3.6 (1.3)	-0.2 (-0.1 to -0.3)	0.003
DL_{CO} (%)	36.7 (28.4, 42.3)	43.4 (36.6, 54.2)	-6.7 (-8.2, -11.9)	0.001
CPI	56.2 (7.8)	46.6 (13.6)	9.7 (4.6 to 14.8)	<0.001
GAP index	5.0 (1.0)	4.1 (1.3)	0.9 (0.4 to 1.3)	<0.01
Age-adjusted Charlson Co-morbidity Index	0 (0, 1)	0 (0, 4)	0 (0, -4)	0.23
Self-reported hospitalisations in previous year	0 (0, 1)	0 (0, 0)	0 (0, 1)	0.09
Number of hospital admissions during the study	1 (1, 2)	0 (0, 0)	1 (1, 2)	<0.001
Self-reported chest infections in previous year	0 (0, 2)	0 (0, 1)	0 (0, 1)	0.08
Oxygen: (%)				

Long-term	14	1	13	0.004
Ambulatory	22	6	16	0.01
Walking aid: (%)	17	1	16	0.001
Pirfenidone: (%)	6	5	1	0.89
Nintedanib: (%)	3	1	2	0.55
Prescribed anti-fibrotic medication during the study period: (%)	58	57	1	0.78
4MGS (ms^{-1})	0.78 (0.20)	0.98 (0.21)	-0.20 (-0.12 to -0.04)	<0.001
6MWT (m)	294 (107)	407 (108)	-113 (-70 to -22)	<0.001
KBILD-Psychological	52.3 (17.7)	64.9 (21.0)	-12.5 (-20.5 to -4.6)	0.002
KBILD-Breathlessness and symptoms	31.3 (18.6)	46.7 (20.9)	-15.4 (-23.4 to -7.4)	<0.001
KBILD-Chest and activities	60.0 (21.2)	69.5 (24.2)	-9.4 (-18.7 to -0.1)	0.047
KBILD-Total score	51.1 (10.5)	59.8 (13.5)	-8.8 (-13.8 to -3.7)	0.001

Data for the hospitalised and non-hospitalised patients are reported as mean (standard deviation) or median (25^{th}, 75^{th} centile) unless stated otherwise. The between-group difference data is reported as mean (lower 95% to upper 95% confidence interval) or median (25^{th}, 75^{th} centile) unless otherwise stated.

Abbreviations: 4MGS: Four Metre Gait Speed; 6MWT: Six Minute Walk Test; BMI: Body Mass Index; CPI: Composite Physiologic Index; DL_{CO}: Diffusing Capacity of the Lung for Carbon Monoxide; FEV_1: Forced Expiratory Volume in One Second; FVC: Forced Vital Capacity; GAP index: Gender, Age and lung Physiology index; KBILD: King's Brief Interstitial Lung Disease questionnaire; MRC: Medical Research Council Dyspnoea score.

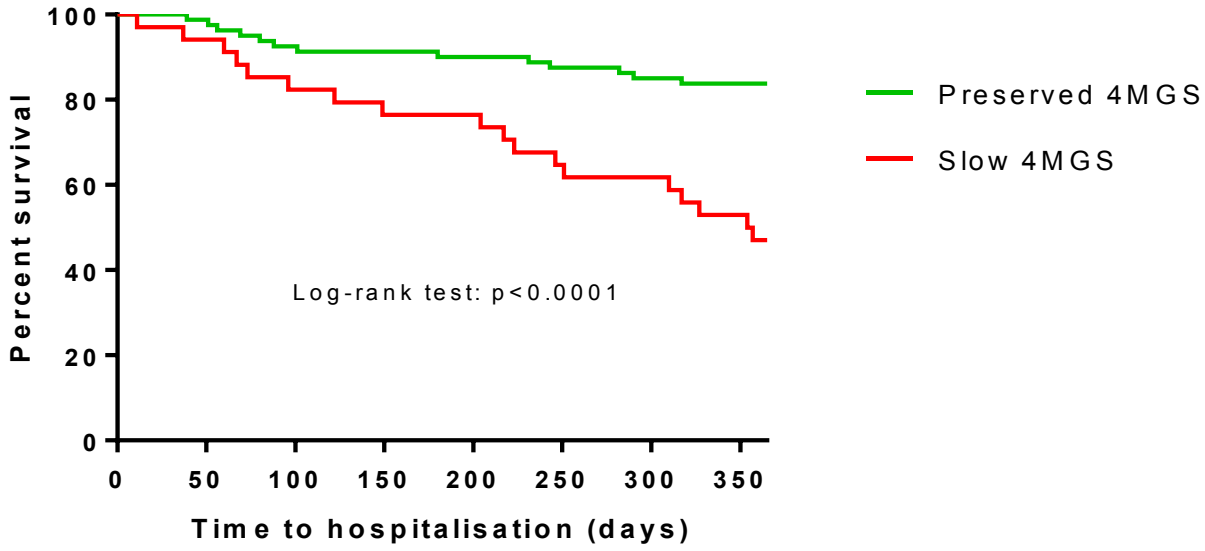

Figure 5.6: Kaplan–Meier curve demonstrating time to all-cause, non-elective hospital admission (within one year) according to slow (4MGs <0.08 ms^{-1}) and preserved (4MGS ≥0.08 ms^{-1}) 4MGS.

Abbreviation: 4MGS: Four Metre Gait Speed.

The univariable analysis for risk of all-cause hospital admission is in table 5.9. When 4MGS was analysed as a continuous variable, there was a decreasing unadjusted HR for one year, all-cause, non-elective hospital admission for each 1.00 ms^{-1} increase in gait speed (HR (95% CI): 0.03 (0.01 to 0.18)); p<0.001) (table 5.9). Similarly, when analysed as a binary variable, those with slow gait speed had an increased, unadjusted hazard ratio (95% CI) of 3.97 ((1.94 to 8.11), p<0.001) for hospital admission when compared to patients with preserved gait speed (table 5.9). The results of the multivariable analysis confirmed that when 4MGS was expressed as either a continuous or binary variable it was an independent risk factor for one year, all-cause, non-elective hospital admission (tables 5.9 and 5.10 respectively). The ROC curve analysis showed that multivariable models 1 and 2 demonstrated high discrimination with a c-statistic of 0.78 and 0.79 respectively; both p<0.0001. Figure 5.7a depicts the ROC plot and c-statistic (95% CI) of multivariable model 1 (4MGS; gender; DL_{CO} % predicted; number of chest infections in the previous year), the same multivariable model but excluding 4MGS and 4MGS alone (continuous format) to predict hospital admission at one year; all

p<0.0001. The same information for multivariable modes 1 and 2, CPI and GAP index is in figure 5.6b; all p<0.01. Figure 5.8 shows the ROC plot and c-statistic (95% CI) for 6MWT, 4MGS and FVC % predicted; all p<0.01.

Table 5.8: Univariable cox proportional regression analysis for time to all-cause, non-elective hospital admission at one year.

Variables	**Univariable analysis**	
	HR (95% CI)	**p-value**
4MGS (ms^{-1})	0.03 (0.01 to 0.18)	<0.001
Slow GS phenotype (reference: preserved GS)	3.97 (1.94 to 8.11)	<0.001
Age (years)	1.03 (0.97 to 1.09)	0.34
Gender (reference: females)	2.19 (0.67 to 7.22)	0.20
Smoking status (reference: never smokers)	2.34 (0.96 to 5.69)	0.06
FVC (% predicted)	0.98 (0.96 to 1.00)	0.02
DL_{CO} (% predicted)	0.96 (0.94 to 0.99)	0.003
6MWT (metres)	0.99 (0.99 to 0.99)	<0.001
Prescribed anti-fibrotic medication (reference: no)	0.82 (0.40 to 1.65)	0.57
Number of hospital admissions in previous year	1.19 (1.01 to 1.41)	0.04
Number of chest infections in previous year	1.10 (0.93 to 1.31)	0.26

Abbreviations: 4MGS: Four Metre Gait Speed; 6MWT: Six Minute Walk Test; CI: Confidence Interval; DL_{CO}: Diffusing Capacity of the Lung for Carbon Monoxide; FVC: Forced Vital Capacity; GS: Gait Speed; HR: Hazard Ratio.

Table 5.9: Univariable and multivariable cox proportional regression analysis for time to all-cause, non-elective hospital admission at one year with 4MGS expressed in continuous format.

Covariates	**Univariable analysis**		**Multivariable analysis – Model 1***	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**
4MGS (ms^{-1})	0.03 (0.01 to 0.18)	<0.001	0.02 (0.01 to 0.14)	<0.001
Age (years)	1.03 (0.97 to 1.09)	0.34		
Gender (reference: females)	2.19 (0.67 to 7.22)	0.20	4.33 (1.10 to 17.09)	0.04
Smoking status (reference: never smokers)	2.34 (0.96 to 5.69)	0.06		
FVC (% predicted)	0.98 (0.96 to 1.00)	0.02		
DL_{CO} (% predicted)	0.96 (0.94 to 0.99)	0.003	0.96 (0.93 to 0.99)	0.005
6MWT (metres)	0.99 (0.99 to 0.99)	<0.001		
Prescribed anti-fibrotic medication (reference: no)	0.82 (0.40 to 1.65)	0.57		
Number of respiratory hospital admissions in previous year	1.19 (1.01 to 1.41)	0.04		
Number of chest infections in previous year	1.10 (0.93 to 1.31)	0.26	0.02 (0.01 to 0.14)	0.15

*All of the variables in the univariable analysis were included in the multivariable analysis. Final model presented.

Abbreviations: 4MGS: Four Metre Gait Speed; 6MWT: Six Minute Walk Test; CI: Confidence Interval; DL_{CO}: Diffusing Capacity of the Lung for Carbon Monoxide; FVC: Forced Vital Capacity; HR: Hazard Ratio.

Table 5.10: Univariable and multivariable cox proportional regression analysis for time to all-cause, non-elective hospital admission at one year with 4MGS expressed in binary format.

Covariates	**Univariable analysis**		**Multivariable analysis – Model 2***	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**
Slow GS phenotype (reference: preserved GS)	3.97 (1.94 to 8.11)	<0.001	2.76 (1.16 to 6.58)	0.02
Age (years)	1.03 (0.97 to 1.09)	0.34		
Gender (reference: females)	2.19 (0.67 to 7.22)	0.20	3.76 (1.03 to 13.70)	0.045
Smoking status (reference: never smokers)	2.34 (0.96 to 5.69)	0.06		
FVC (% predicted)	0.98 (0.96 to 1.00)	0.02		
DL_{CO} (% predicted)	0.96 (0.94 to 0.99)	0.003	0.96 (0.94 to 0.99)	0.01
6MWT (metres)	0.99 (0.99 to 0.99)	<0.001	0.99 (0.99 to 1.00)	0.09
Prescribed anti-fibrotic medication (reference: no)	0.82 (0.40 to 1.65)	0.57		
Number of respiratory hospital admissions in previous year	1.19 (1.01 to 1.41)	0.04		
Number of chest infections in previous year	1.10 (0.93 to 1.31)	0.26		

*All of the variables in the univariable analysis were included in the multivariable analysis. Final model presented.

Abbreviations: 4MGS: Four Metre Gait Speed; 6MWT: Six Minute Walk Test; CI: Confidence Interval; DL_{CO}: Diffusing Capacity of the Lung for Carbon Monoxide; FVC: Forced Vital Capacity; Gait Speed: Gait Speed; HR: Hazard Ratio.

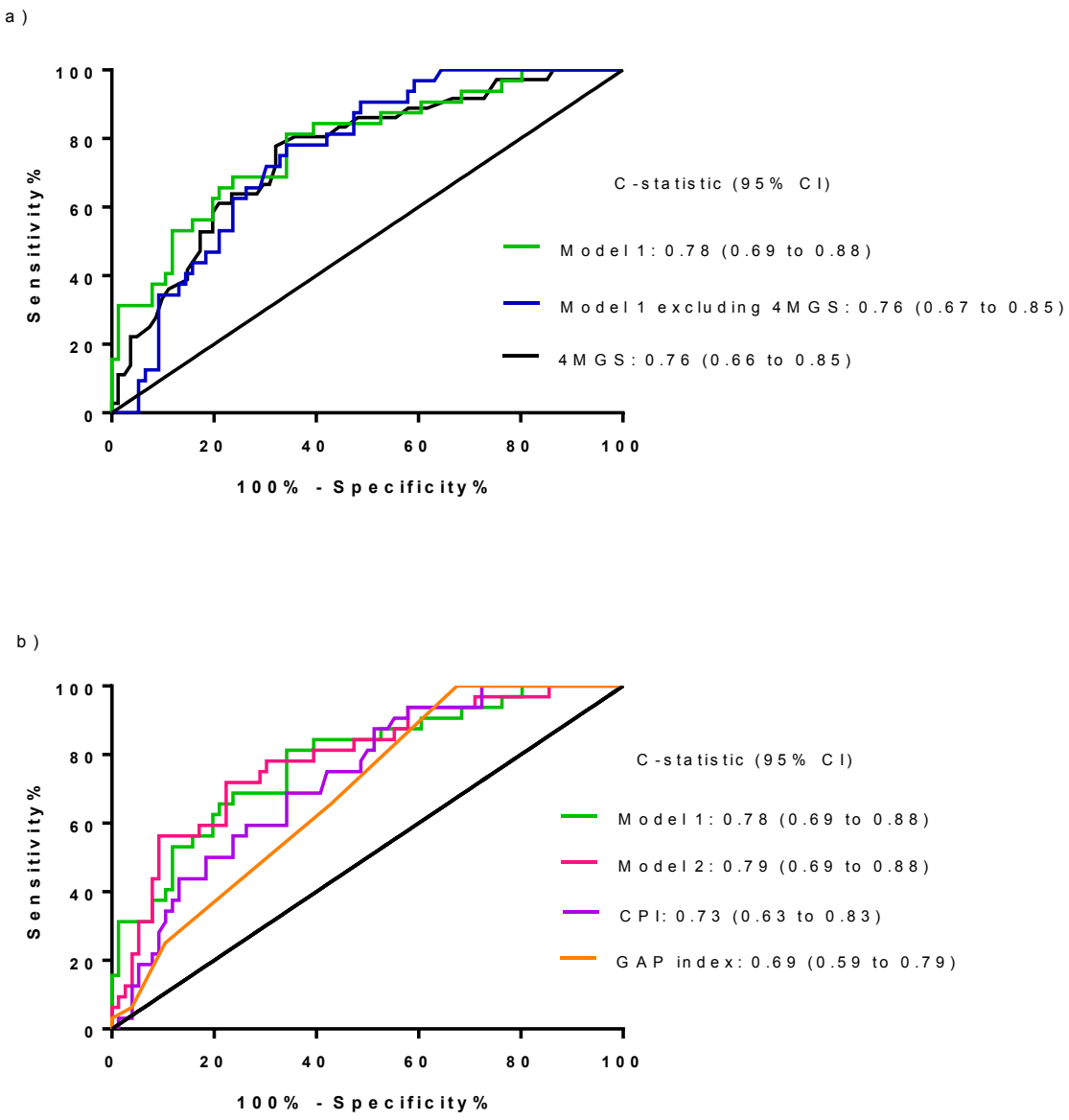

Figure 5.7: Receiver Operating Characteristic plots demonstrating the ability of a) multivariable model 1 (4MGS; gender; DLCO % predicted: number of chest infections in the previous year), model 1 excluding 4MGS (gender, DLCO % predicted, number of chest infections in the previous year) and 4MGS alone to predict all-cause, non-elective hospital admission at one year, and b) multivariable model 1 (4MGS; gender; DLCO % predicted; number of chest infections in the previous year), multivariable model 2 (slow 4MGS; gender; DLCO % predicted; number of chest infections in the previous year), CPI, GAP index to predict all-cause, non-elective hospital admission at one year.

Abbreviations: 4MGS: Four Metre Gait Speed; CI: Confidence Interval; CPI: Composite Physiologic Index; DL_{CO}: Diffusing Capacity of the Lung for Carbon Monoxide; GAP index: Gender, Age and lung Physiology index.

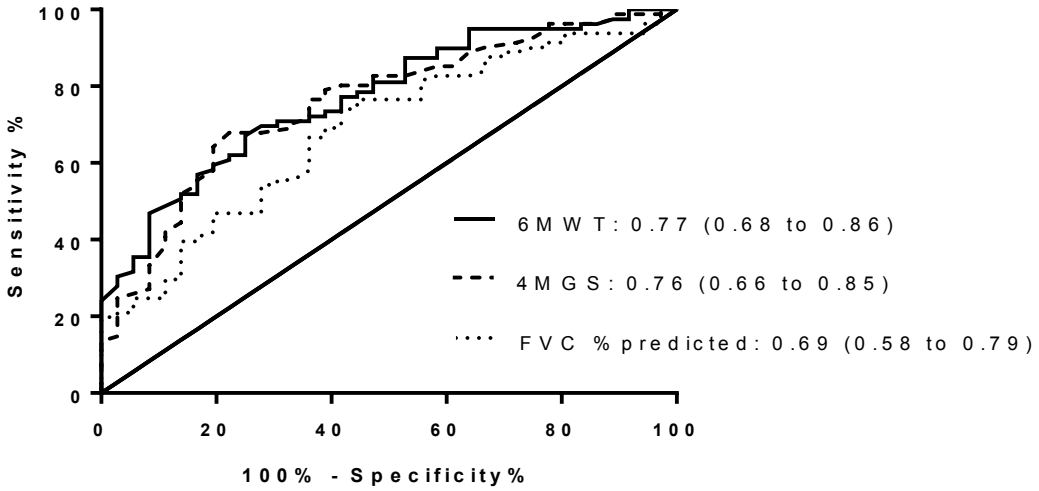

Figure 5.8: Receiver Operating Characteristic plots demonstrating the ability of FVC% predicted, 4MGS and 6MWT to predict all-cause hospital admission at one year.

Abbreviations: 4MGS: Four Metre Gait Speed; 6MWT: Six Minute Walk Test; FVC: Forced Vital Capacity.

5.6 Discussion

This is the first study to determine the prognostic ability of 4MGS to predict all-cause mortality and all-cause, non-elective hospital admissions at one year in patients newly diagnosed with IPF. The results demonstrate that patients with slow gait speed (4MGS <0.80 ms^{-1}) at diagnosis have a shorter time to all-cause death and all-cause, non-elective hospital admission at one year, compared to those with preserved gait speed (4MGS ≥0.80 ms^{-1}). When expressed as a continuous or binary variable, 4MGS is an independent predictor of mortality and hospital admissions after adjusting for potential confounding variables. The model that best predicted all-cause mortality comprised 4MGS, age and FVC % predicted and the model for non-elective hospital admission comprised slow 4MGS, gender, CPI and number of chest infections in the previous year. Both of these models demonstrate greater discrimination for predicting all-cause mortality and non-elective hospital admission respectively than the established composite prognostic indices: CPI and GAP index, but require external

validation. ROC plots demonstrated that FVC % predicted and 6MWT were respectively the best predictors of all-cause mortality and hospital admission at one year. However, this method is not a statistically sound way of identifying variables with the best predictive ability as they do not adjust for confounding variables (Cox proportional regression models, as described above, are the recommend method). Given the simplicity of the test, I propose that the 4MGS test may be useful in stratifying patients with IPF at increased risk of poor prognosis (specifically mortality and all-cause, non-elective hospital admission).

Previous research

In a meta-analysis analysis of nine cohort studies incorporating 34,485 community-dwelling older adults followed for up to 21 years, Studenski and colleagues demonstrated that gait speed was consistently and significantly associated with mortality (HR (95%CI): 0.88 (0.87 to 0.90) per 0.10 ms^{-1} increase in gait speed) (144). Gait speed has also been shown to be a predictor of hospital admission in community-dwelling older adults. In the Health Aging and Body Composition study comprising over 3,000 community-dwelling older adults, slow gait speed (defined as <1.0 ms^{-1} over six metres) was associated with increased risk of hospital admission (rate ratio (95% CI): 1.48 (1.02 to 2.13)) (169). Similarly, in a cohort of 487 older adults recruited from the primary care programs of a Medicare health maintenance organization and Veterans Affairs system, slow gait speed (defined as <0.6 ms^{-1}) independently predicted hospital admission at 12 months (267). The relationship between slow gait speed and adverse outcomes has also been demonstrated in chronic conditions such as heart failure (285) and renal failure (286).

Studies evaluating the prognostic ability of gait speed in cohorts of patients with chronic respiratory disease are limited in number. Kon *et al* measured 4MGS on the day of hospital discharge in 213 patients with a severe acute exacerbation of COPD, and identified increasing risk of hospital

readmission at 90 days with slower 4MGS (196). Those in the slowest quartile for 4MGS had an increased unadjusted odds ratio for 90 day hospital readmission (odds ratio (OR) (95%CI): 7.12 (2.61 to 19.44)) compared to the fastest quartile (196). In a study of patients with acute respiratory distress syndrome, Chan *et al* followed up two cohorts (190). In the first cohort, with every 0.11 ms^{-1} increase in gait speed, decreased unadjusted odds ratios were observed for future hospital admissions (OR (95%CI): 0.78 (0.65 to 0.92)) and mortality (OR (95%CI): 0.44 (0.26 to 0.75)) (190). In the second cohort (which included a longer follow-up period), increased gait speed was associated with reduced hospital admission (OR (95% CI): 0.77 (0.65 to 0.90)) but not mortality (OR (95%CI): 0.93 (0.70 to 1.24) per 0.11 ms^{-1} increase in gait speed) (190).

Significance of findings

In Chapters 3 and 4, I demonstrated that 4MGS has excellent inter-observer and test–retest reliability, and shows moderate-to-strong correlations with exercise capacity, health-related quality of life, and respiratory disability (256). Other studies investigating gait speed in IPF have been limited to cross-sectional psychometric studies (86, 194, 197) or assessing response to exercise-based rehabilitation (86). The current study is the first to assess the prognostic validity of 4MGS, and the first to demonstrate that 4MGS is an independent predictor of all-cause mortality and all-cause, non-elective hospital admission in IPF. I propose that 4MGS has potential as a surrogate endpoint, and merits further investigation.

Currently there are conflicting opinions about the use of surrogate end-points for clinical trials in IPF. Some have argued that 'harder' endpoints such as death or non-elective hospital admission are more meaningful to patients (39), and that existing surrogate markers have limitations or lack validity. Others advocate the use of surrogate markers in order to make clinical trials more pragmatic and affordable (40), particularly as IPF is a rare condition compared with airways disease such as COPD or

asthma. For example, it is estimated that a phase III study powered to detect a 25% decrease in mortality would require 2,600 patients with IPF, five years of follow-up and a cost in excess of US$250 million (42). I propose that 4MGS may have potential as a stratification measure identifying those at highest risk for hospital admission or mortality.

Existing surrogate endpoints in IPF include lung function measures and the 6MWT. As the most commonly recorded lung function measure in IPF, FVC has many advantages. It is valid, responsive and the physiological measure that best correlates with worsening fibrosis. Change in FVC has been associated with mortality (70, 72), and the regulatory approval of pirfenidone and nintedanib was based on demonstration of their effects on FVC change. However, there are potential limitations associated with the use of FVC as a surrogate endpoint. Missing values occur because a proportion of patients are unable to perform serial measurements due to cough, dyspnea or infection (32). A proportion of patients dying in trials as a consequence of their IPF appear to have stable FVC prior to death (32). There is also a degree of measurement variation such that FVC can vary by 5 to 9% between readings (74). Furthermore, IPF is a disease of older adults where non-pulmonary manifestations may influence mortality or hospital admission – these manifestations are not captured by FVC. Of note, although FVC was shown to be an independent predictor of mortality in this study, the inclusion of 4MGS in the multivariable model improved predictive ability. Moreover, in contrast to 4MGS, FVC was not an independent predictor of hospital admission.

Established composite prognostic indices, derived from lung function, such as the CPI and GAP index, predict mortality in patients with IPF (82, 85). However, although the GAP index accounts for missing DL_{CO} values if a patient is unable to perform the manoeuvre, both the CPI and GAP index may be limited as surrogate markers of mortality due to missing pulmonary function data. These prognostic indices were also originally derived from analyses of retrospective datasets (82, 85) in contrast to this prospective study where multivariable models incorporating 4MGS demonstrated greater predictive

capacity for all-cause mortality and all-cause, non-elective hospital admission than either CPI or GAP index.

The 6WMT is the most commonly used measure of physical performance in patients with IPF (91) and there is evidence of an association with mortality in selected patients with IPF (FVC >55% predicted) (94, 99). However, the test requires resources, including an unobstructed, straight, 30 metre course and sufficient time to perform a practice test with adequate rest between tests (96). This may limit feasibility of the 6MWT in some settings, such as in the home or primary care, and in some patients who are highly symptomatic. The prognostic validity of the 6MWT has not been demonstrated in patients with more severe disease (91, 94), partly because missing values have been observed in clinical trials due to the inability or reluctance of patients to perform sequential tests because of disease progression or symptom burden. In comparison to the 6MWT, the 4MGS test is quicker to perform, requires less space, and as a measure of usual walking speed, may be more acceptable to patients with high symptom burden.

Critique of methodology and limitations

In this study, slow 4MGS was defined as 4MGS <0.8 ms^{-1} as this cut-off has been shown to correspond to a reduction in median life expectancy in older adults (144). Additionally, the results of Chapter 3 demonstrated that stratification of IPF patients according to 4MGS <0.8 ms^{-1} identified significant impairment in measures of exercise capacity, health status, dyspnea and GAP index despite similar lung function and radiological parameters in those with slow compared to preserved gait speed (256).

There were some limitations to this study. First, the participants in this study were patients with a new diagnosis of IPF, recruited from the Royal Brompton and Harefield NHS Foundation Trust, a specialist, cardiorespiratory centre. Therefore the findings need to be corroborated in other settings and other IPF populations, particularly in those with more established or severe disease. Second, patients unable to walk five metres were excluded from the study, which may have influenced results. However, only one person was excluded for this reason, and it is most likely that inclusion would have improved rather than reduced the predictive capacity of 4MGS (171). Third, only all-cause mortality and all-cause, non-elective hospital admissions were reported. NHS spine and primary care records did not allow the cause of death to be ascertained accurately, corroborating previous data suggesting it is difficult to reliably discern if a death is IPF- or non-IPF related (75). Nonetheless, distinguishing between IPF and non-IPF related deaths and hospital admissions may have ascertained whether 4MGS is simply a clinical indicator of multi-system well-being or provides some surrogate measure of IPF severity. Fourth, it was not possible to compare the predictive ability of the most commonly used surrogate endpoint, change in FVC (over six months), to change in 4MGS as this was not measured as part of this study. This should be addressed in future research. Fifth, owing to the small number of deaths in the cohort, it was not possible to adjust for all confounding variables such as high resolution computed tomograph fibrosis score, pulmonary hypertension, extent of exercise-induced oxygen desaturation and use of long-term oxygen therapy. Future studies, with larger cohorts should include these confounding variables.

5.7 Conclusion

In summary, in patients with a new diagnosis of IPF, 4MGS - a simple measure of walking speed - can independently predict all-cause mortality and all-cause, non-elective hospital admission at one year. I propose the 4MGS test has potential as a surrogate endpoint or stratification measure in IPF.

In the next chapter, I investigate whether an improvement in 4MGS with PR is a predictor of survival and reduced all-cause, non-elective hospital admission at one year.

Chapter 6 : Change in four metre gait speed with pulmonary rehabilitation and survival in idiopathic pulmonary fibrosis

6.1 Introduction

In community-dwelling older adults, change in gait speed has been shown to be a predictor of adverse outcomes such as mortality (165, 172-175). In the preceding chapter, four metre gait speed (4MGS) was shown to be an independent predictor of all-cause mortality and all-cause, non-elective hospital admissions in patients with a new diagnosis of idiopathic pulmonary fibrosis (IPF). Further evidence to support the prognostic utility of 4MGS would include demonstrating that a change in 4MGS can influence survival and hospital admission. In Chapter 4, I showed that pulmonary rehabilitation (PR) can significantly increase 4MGS in patients with IPF. In this chapter, I will therefore test the hypothesis that increasing 4MGS with PR is associated with improved survival and reduced non-elective hospital admission at one year in patients with IPF.

6.2 Aims

The aims of this study were to:

- determine whether an improvement in 4MGS with PR is a predictor of survival at one year.
- determine a 4MGS change cut-point above which is associated with improved survival at one year.
- determine whether an improvement in 4MGS with PR is a predictor of reduced all-cause, non-elective hospital admission at one year.
- determine a 4MGS change cut-point above which is associated with longer time to first all-cause, non-elective hospital admission at one year.

6.3 Hypothesis

An increase in 4MGS with PR is associated with improved survival and increased time to all-cause, non-elective hospital admission at one year following PR in patients with IPF.

6.4 Methods

6.4.1 Study participants

The participants in this study were the same cohort that enrolled in the study discussed in Chapter 4: 'The responsiveness of four metre gait speed in patients with idiopathic pulmonary fibrosis and estimation of the minimum clinically important difference'. To recap, participants were prospectively recruited from the PR units at the Royal Brompton and Harefield Hospital NHS Foundation Trust, UK and St. Thomas' Hospital at Guy's and St. Thomas' NHS Foundation Trust, UK between February 2015 and July 2016. The inclusion criteria were: 1) IPF diagnosis by a specialist interstitial lung disease multidisciplinary team according to international guidelines; 2) an ability to walk five metres unaided; 3) ability to provide informed consent; 4) consented to participate in a supervised outpatient PR programme. Exclusion criteria were significant co-morbidities that would limit walking ability or exercise capacity (e.g. lower limb amputation) or make exercise unsafe (e.g. unstable ischaemic heart disease). All participants provided informed written consent and the study was approved by the London-Riverside Research Ethics Committee (14/LO/2247) and registered on clinicaltrials.gov (NCT02530736).

6.4.2 Measurements

The following outcome measures, described in Chapter 2, were assessed before and after PR: 4MGS (220); anthropometry; spirometry (208, 209); Medical Research Council (MRC) Dyspnoea scale (212); the incremental shuttle walk test (ISW) (224); quadriceps maximum voluntary contraction (QMVC)

(238, 239); handgrip strength (243, 244, 277); the King's Brief Interstitial Lung Disease (KBILD) questionnaire (111) and the Chronic Respiratory Questionnaire (CRQ) (236). Co-morbidities were evaluated using the age-adjusted Charlson Co-morbidity Index (257). As previously stated, the PR programmes were multi-disciplinary, outpatient services that comprised two supervised sessions per week for eight weeks. Completion of PR was defined as attending 50% of the sessions and an end of course assessment. One year after the end of course assessment, survival status and where applicable date of death and first non-elective hospital admission were obtained from general practice records and NHS Spine, a national database. The final search for these data was conducted on 29th September 2017 and patients who survived or had no hospital admissions in the one year follow-up period were censored at 365 days. The schema for this study is presented in figure 6.1.

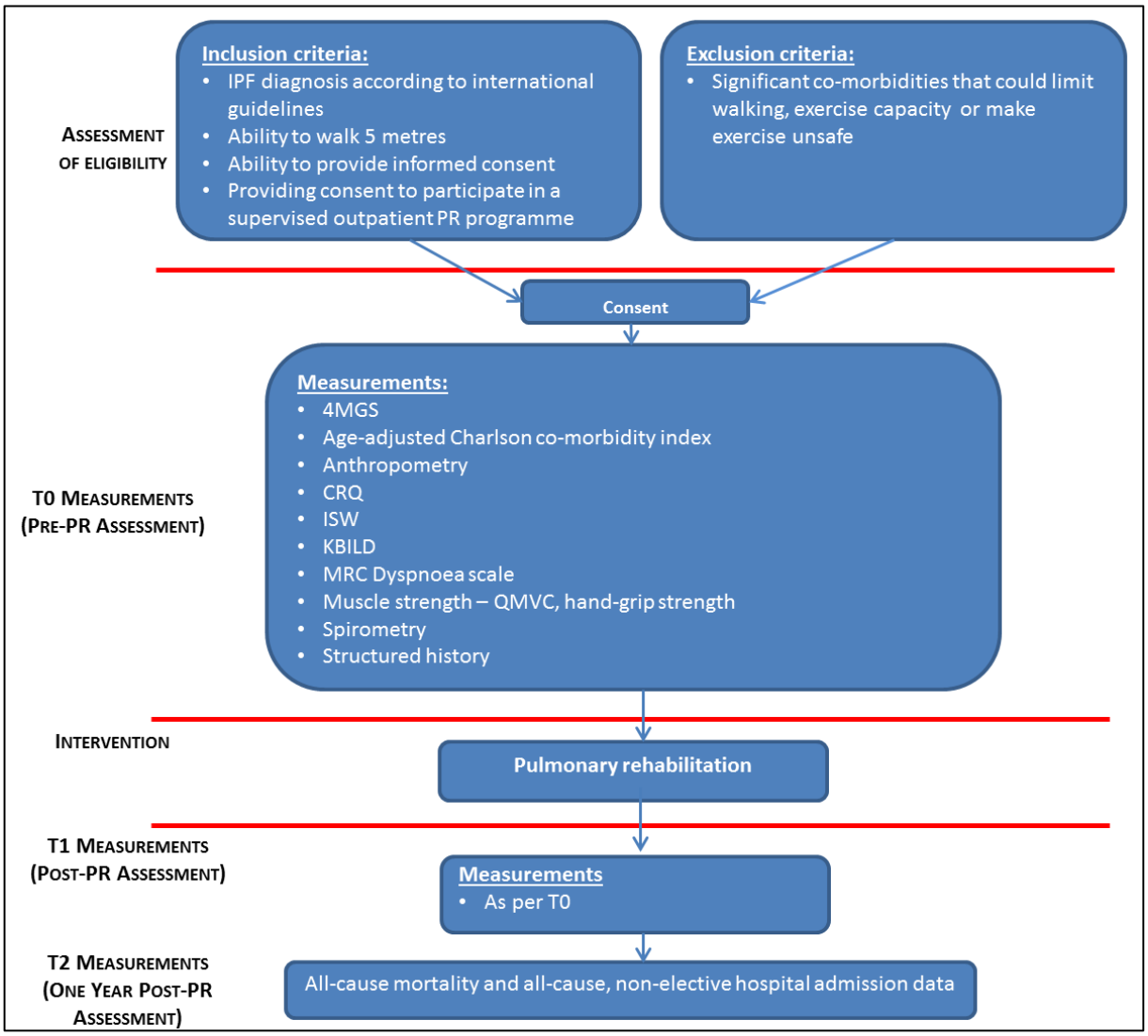

Figure 6.1: Study schema.

Abbreviations: 4MGS: Four Metre Gait Speed; CRQ: Chronic Respiratory Questionnaire; IPF: Idiopathic Pulmonary Fibrosis; ISW: Incremental Shuttle Walk Test; KBILD: King's Brief Interstitial Lung Disease questionnaire; MRC: Medical Research Council Dyspnoea scale; PR: Pulmonary Rehabilitation QMVC: Quadriceps Maximum Voluntary Contraction.

6.4.3 Statistical analysis

There was no *a priori* sample size calculation for the research question in this study. As this research was an extension of the study described in Chapter 4, the sample size calculation was based on demonstrating change in 4MGS with PR, and not the ability of 4MGS change to predict survival or hospital admission.

The patient characteristics were summarised using descriptive statistics. For continuous data, the paired t-test was used to compare outcomes before and after PR (Wilcoxon signed-rank test for non-parametric data) and the chi-square test for categorical data.

A univariable Cox proportional regression was used to assess the association between change in 4MGS and all-cause mortality. Other plausible confounding variables were also assessed: baseline 4MGS; age; gender; smoking status; FVC % predicted; prescribed anti-fibrotic medication during the study period and the number of respiratory hospital admissions in the previous year. All of these variables were considered in the multivariable Cox proportional regression analysis where a backwards stepwise selection procedure was used with each variable remaining in the model if $p<0.20$ (196). Log-log plots and Schonfeld's residuals were used to test the proportional hazard assumption. Receiver Operating Characteristic (ROC) plots of the multivariable model including and excluding change in 4MGS were constructed and the c-statistic was used to assess discrimination.

A ROC plot of the univariable model of change in 4MGS was constructed to identify a cut-point that best discriminated between patients who died and survived at one year. The between-group differences of the baseline characteristics and response to PR of the patients who achieved and did not achieve this cut-off were compared using the unpaired t-test (or Mann-Whitney U test for non-parametric data) for continuous variables or the chi-square test for categorical data. To examine the 4MGS change cut-off, a Kaplan–Meier analysis was performed comparing survival curves for those above and below the 4MGS change cut-off, with significance assessed using the log-rank test.

To evaluate the association between change in 4MGS and all-cause, non-elective hospital admission at one year, univariable and multivariable Cox proportional regression analyses as described in

chapter 5 were repeated. The confounding variables included in this analysis were also similar (baseline 4MGS; age; gender; smoking status; FVC % predicted; smoking status; prescribed anti-fibrotic medication during the study period; the number of respiratory hospital admissions in the previous year) as well as the number of chest infections in the previous year. Data analyses were performed using GraphPad Prism 7 (GraphPad Software, La Jolla, USA) and SPSS version 24 (IBM, New York, USA). A p-value of <0.05 was considered statistically significant.

6.5 Results

6.5.1 Baseline characteristics and response to PR

This information was presented in Chapter 4. For clarity, the baseline characteristics and the response to PR of the 90 patients that completed the programme are shown in table 6.1.

Table 6.1: Baseline characteristics and response to PR (n=90).

Variable	Baseline	Change with PR	p-value
Gender: male (%)	70	NA	NA
Age (years)	74 (7)	NA	NA
MRC score	3 (1)	-0.6 (-0.8 to -0.4)	<0.01
BMI (kg/m^2)	27.2 (4.8)	-0.1 (-0.2 to 0.1)	0.17
FEV_1/FVC	0.79 (0.08)	0 (-0.01 to 0.01)	0.72
FVC (L)	2.3 (0.7)	-0.02 (-0.08 to 0.03)	0.44
FVC (%)	72.8 (22.0)	-1.3 (-4.8 to 2.1)	0.46
Smoking status: never / former / current (%)	44 / 54 / 1	NA	0
Age-adjusted Charlson Co-morbidity Index	0 (0, 4)	NA	NA
Self-reported hospitalisations in past year	0 (0, 0)	NA	NA
Self-reported chest infections in past year	1 (0, 2)	NA	NA
Oxygen: (%)			
Long-term	11	NA	NA
Ambulatory	17	NA	NA
Walking stick: (%)	2	NA	NA
Pirfenidone: (%)	16	NA	NA
Nintedanib: (%)	0	NA	NA
Prescribed anti-fibrotic medication during the study period: (%)	31	NA	NA
4MGS (ms^{-1})	0.92 (0.25)	0.15 (0.11 to 0.18)	<0.001
ISW (m)	271 (172)	50 (36 to 54)	<0.001
Handgrip strength (kg)	26.2 (7.5)	0.5 (-0.6 to 1.6)	0.36
QMVC (kg)	28.6 (21.5, 34.9)	0.1 (-2.3, 2.5)	0.54
KBILD-Psychological domain	59.0 (16.0)	4.6 (1.6 to 7.7)	0.003
KBILD-Breathlessness and activities domain	42.0 (17.4)	5.3 (1.8 to 8.9)	0.004
KBILD-Chest and symptoms domain	67.1 (18.3)	5.7 (1.4 to 10.0)	0.01
KBILD-Total score	56.4 (10.4)	3.9 (2.0 to 5.7)	<0.001
CRQ-Dyspnoea domain	16.5 (5.5)	4.1 (2.8 to 5.4)	<0.001
CRQ-Fatigue domain	15.3 (5.0)	1.6 (0.7 to 2.4)	0.001

CRQ-Emotion domain	33.4 (8.1)	1.5 (0.2 to 2.8)	0.03
CRQ-Mastery domain	19.6 (4.8)	1.4 (0.6 to 2.2)	0.001
CRQ-Total score	84.8 (19.8)	8.5 (5.2 to 11.8)	<0.001

Baseline data reported as mean (standard deviation) or median (25^{th}, 75^{th} centile) unless stated otherwise. Change data reported as mean (lower confidence limit to upper confidence limit) change or median (25^{th}, 75^{th} centile) change.

Abbreviations: 4MGS: Four Metre Gait Speed; BMI: Body Mass Index; CRQ: Chronic Respiratory Questionnaire; FEV_1: Forced Expiratory Volume in One Second; FVC: Forced Vital Capacity; ISW: Incremental Shuttle Walk Test; KBILD: King's Brief Interstitial Lung Disease questionnaire; MRC: Medical Research Council Dyspnoea score; NA: Not Applicable; PR: Pulmonary Rehabilitation; QMVC: Quadriceps Maximum Voluntary Contraction.

6.5.2 Prediction of survival at one year

Eleven percent (n=10) of the cohort died within one year of completing PR. The univariable analysis for risk of all-cause mortality at one year following PR is shown in table 6.2. Change in 4MGS had a decreasing unadjusted hazard ratio (HR) for all-cause mortality at one year; for each 1.00 ms^{-1} increase in improvement in gait speed with PR (HR (95% confidence interval (CI)): 0.01 (0.00 to 0.42); p=0.02) (table 6.2). The multivariable analysis confirmed that change in 4MGS remained an independent risk factor for one year, all-cause mortality after adjusting for potential confounding variables (table 6.2). The ROC plot analysis showed that the multivariable model demonstrated high discrimination with a c-statistic (95% CI) of 0.81 (0.67 to 0.94). Figure 6.2 depicts the ROC plot and c-statistic of the multivariable model (baseline 4MGS, change in 4MGS, gender, FVC % predicted), the same multivariable model but excluding change in 4MGS and change in 4MGS alone to predict mortality at one year (both p<0.01).

Table 6.2: Univariable and multivariable Cox proportional regression analysis for time to all-cause death at one year post-PR.

Covariates	**Univariable analysis**		**Multivariable analysis***	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**
Baseline 4MGS (ms^{-1})	0.17 (0.01 to 2.12)	0.17	0.09 (0.01 to 1.12)	0.06
Change in 4MGS (ms^{-1})	0.01 (0.00 to 0.42)	0.02	0.01 (0.00 to 0.38)	0.02
Age (years)	1.01 (0.92 to 1.11)	0.85		
Gender (reference: female)	3.59 (0.45 to 28.72)	0.23	3.96 (0.43 to 36.74)	0.19
Smoking status (reference: never smokers)	0.67 (0.18 to 2.48)	0.54		
FVC (% predicted)	0.97 (0.91 to 1.02)	0.21	0.97 (0.93 to 1.01)	0.19
Prescribed anti-fibrotic medication during the study period (reference: no)	1.58 (0.45 to 5.61)	0.49		
No. of respiratory hospital admissions in previous year	0.94 (0.72 to 1.24)	0.68		

*All of the variables in the univariable analysis were included in the multivariable analysis. Final model presented.

Abbreviations: 4MGS: Four Metre Gait Speed; CI: Confidence Interval; FVC: Forced Vital Capacity; HR: Hazard Ratio.

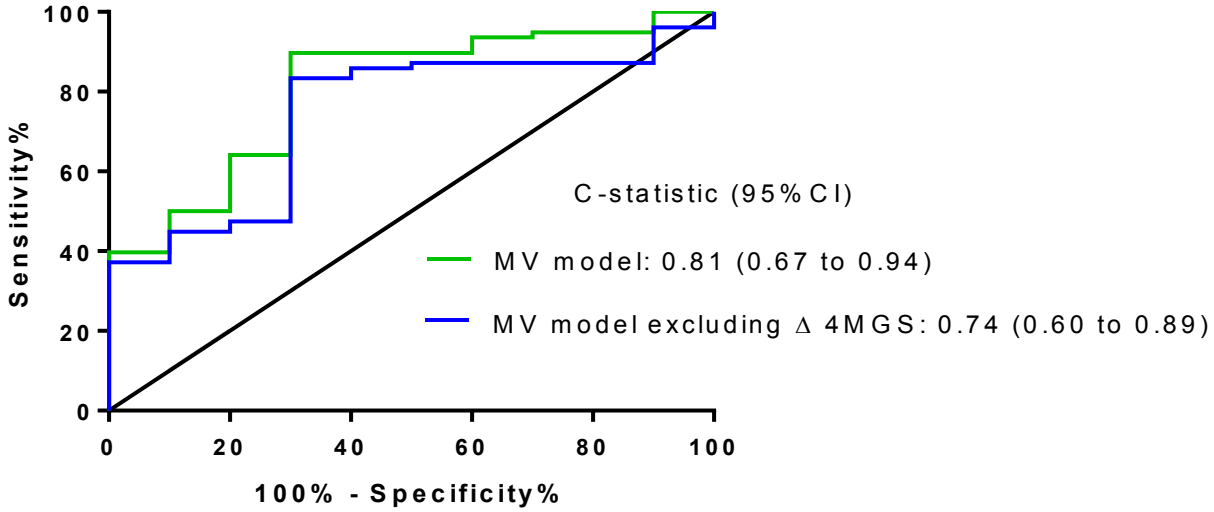

Figure 6.2: Receiver operating characteristic plot demonstrating the ability of the multivariable model (baseline 4MGS, change in 4MGS, gender, FVC % predicted); the same model excluding change in 4MGS (baseline 4MGS, gender, FVC % predicted) to predict all-cause death at one year.

Abbreviations: 4MGS: Four Metre Gait Speed; CI: Confidence Interval; FVC: Forced Vital Capacity; MV: Multivariable.

The ROC plot constructed to identify a cut-off for change in 4MGS with PR that best discriminated between patients who died and survived at one year is shown in figure 6.3. A 4MGS change with PR of ≥0.09 ms^{-1} had a c-statistic (95% CI) of 0.76 (0.62 to 0.89) (sensitivity 70%, specificity 70%; p<0.01) in identifying patients alive at one year (figure 6.3). The between-group differences of the baseline characteristics of those who achieved and did not achieve this cut-off are shown in table 6.3. The baseline characteristics of the two groups were similar but patients in the 4MGS change <0.09 ms^{-1} group were more likely to use LTOT and have previously completed PR than those in the 4MGS change ≥0.09 ms^{-1} group (table 6.4).

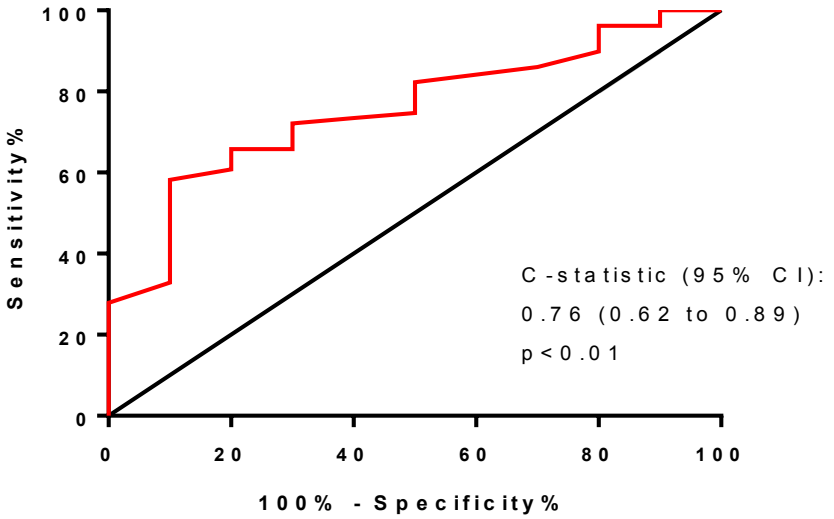

Figure 6.3: Receiver operating characteristic plot demonstrating the 4MGS change cut-off that best discriminated between patients who died and survived at one year post-PR.

Abbreviations: 4MGS: Four Metre Gait Speed.

Table 6.3: Baseline characteristics according to change in 4MGS: ≥0.09 ms^{-1} (n=59) versus <0.09 ms^{-1} (n=31).

Variable	**4MGS change ≥0.09 ms^{-1}**	**4MGS change <0.09 ms^{-1}**	**Between-group difference**	**p-value**
Gender: male (%)	69	74	5	0.61
Age (years)	74 (8)	73 (5)	-1 (-4 to 2)	0.55
MRC score	3 (1)	3 (1)	0.2 (-0.3 to 0.7)	0.36
BMI (kg/m^2)	27.3 (4.7)	27.2 (5.2)	-0.1 (-2.27 to 2.05)	0.92
FEV_1/FVC	0.78 (0.08)	0.82 (0.07)	0.04 (0.01 to 0.08)	0.01
FVC (L)	2.3 (0.7)	2.1 (0.7)	-0.2 (-0.5 to 0.1)	0.22
FVC (%)	76.2 (22.4)	66.4 (20.5)	-9.7 (-19.5 to 0.0)	0.050
Smoking status: never / former / current (%)	43 / 55 / 2	55 / 45 / 0	12 / -10 / -2	0.47
Age-adjusted Charlson Co-morbidity Index	2 (0, 4)	0 (0, 4)	-2 (0, 0)	0.91
Self-reported hospitalisations in past year	0 (0, 0)	0 (0, 0)	0 (0, 0)	0.43
Self-reported chest infections in past year	1 (0, 2)	0 (0, 2)	-1 (0, 0)	0.33
Oxygen: (%)				
Long-term	4	26	15	<0.01
Ambulatory	12	26	9	0.10
Walking stick: (%)	2	3	1	0.69
Pirfenidone: (%)	12	23	7	0.19
Nintedanib: (%)	0	0	0	NA

Prescribed anti-fibrotic medication during the study period: (%)	28	39	-11	0.28
4MGS (ms^{-1})	0.92 (0.24)	0.93 (0.27)	0.06 (-0.09 to 0.13)	0.76
ISW (m)	296 (182)	227 (142)	-69 (-145 to 7.2)	0.08
Handgrip strength (kg)	26.0 (7.0)	26.6 (8.6)	2.2 (-3.7 to 5.1)	0.76
QMVC (kg)	30.0 (11.0)	25.9 (9.2)	-4.1 (-10.8 to 2.5)	0.21
KBILD-Psychological domain	60.2 (17.2)	56.4 (16.3)	-3.8 (-12.1 to 4.6)	0.37
KBILD-Breathlessness and activities domain	44.3 (15.2)	37.1 (20.8)	-7.2 (-15.7 to 1.3)	0.09
KBILD-Chest and symptoms domain	67.2 (18.3)	67.0 (18.9)	-0.2 (-9.3 to 8.9)	0.96
KBILD-Total score	57.1 (9.7)	54.7 (11.7)	-2.5 (-7.6 to 2.7)	0.34
CRQ-Dyspnoea domain	16.4 (5.3)	16.8 (6.0)	0.4 (-2.1 to 2.9)	0.74
CRQ-Fatigue domain	15.8 (4.8)	14.5 (5.2)	-1.3 (-3.5 to 0.9)	0.24
CRQ-Emotion domain	34.2 (7.6)	32.4 (8.9)	-1.8 (-5.5 to 1.8)	0.31
CRQ-Mastery domain	19.2 (4.6)	20.3 (5.3)	1.1 (-1.1 to 3.3)	0.31
CRQ-Total score	85.6 (19.0)	84.0 (21.2)	-1.6 (-10.5 to 7.2)	0.72
Completed PR previously (%)	14	35	21	<0.01

Baseline data reported as mean (standard deviation) or median (25^{th}, 75^{th} centile) unless stated otherwise. Change data reported as mean (lower confidence limit to upper confidence limit) change or median (25^{th}, 75^{th} centile) change.

Abbreviations: 4MGS: Four Metre Gait Speed; BMI: Body Mass Index; CRQ: Chronic Respiratory Questionnaire; FEV_1: Forced Expiratory Volume in One Second; FVC: Forced Vital Capacity; ISW: Incremental Shuttle Walk Test; KBILD: King's Brief Interstitial Lung Disease questionnaire; MRC: Medical Research Council Dyspnoea score; NA: Not Applicable; PR: Pulmonary Rehabilitation; QMVC: Quadriceps Maximum Voluntary Contraction.

In the one year follow-up period, 5% of patients who improved their 4MGS by ≥0.09 ms^{-1} died in contrast to 23% in the <0.09 ms^{-1} group (p=0.01). The Kaplan–Meier curve demonstrated a significantly longer survival time with 4MGS change ≥0.09 ms^{-1} compared to <0.09 ms^{-1}, p=0.02 (figure 6.4).

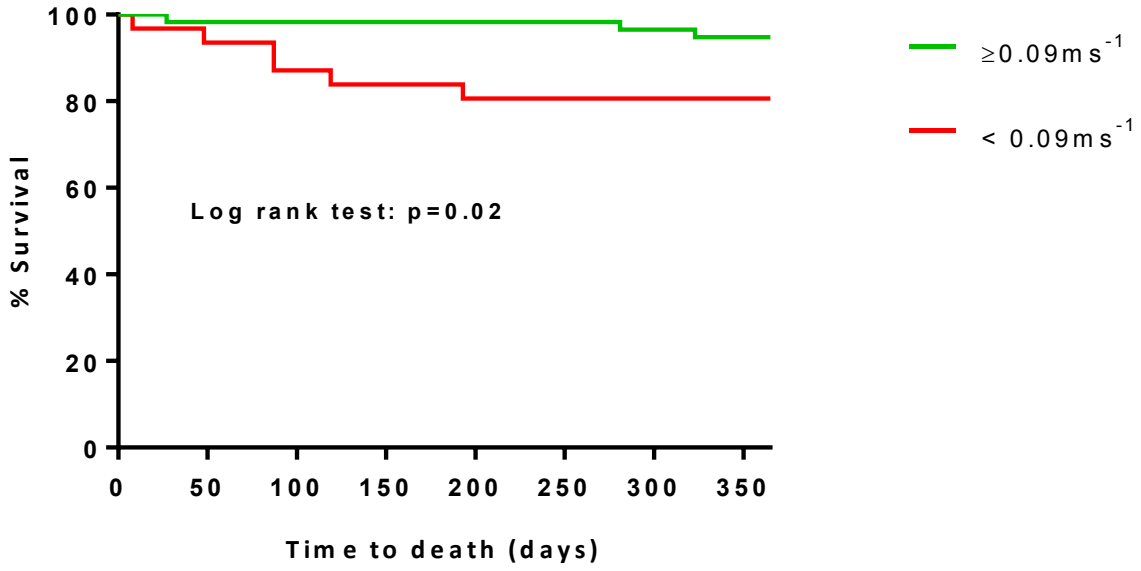

Table 6.4: Kaplan–Meier curve demonstrating improved survival time in patients with IPF who improved 4MGS by ≥0.09 ms^{-1} with PR.

Abbreviations: 4MGS: Four Metre Gait Speed; PR: Pulmonary Rehabilitation.

6.5.3 Prediction of hospital admission at one year

In total, 17% of patients (n=19) were hospitalised at least once within one year of completing PR. The univariable analysis for risk of all-cause, non-elective hospital admission at one year following PR is shown in table 6.5. The unadjusted hazard ratio (95% CI) for all-cause hospital admission for 4MGS change with PR was 0.50 (0.02 to 11.58) (table 6.5). With multivariable analysis, change in 4MGS with

PR was not an independent predictor of all-cause, non-elective hospital admission at one year (table 6.5).

Table 6.5: Univariable and multivariable Cox proportional regression analysis for time to all-cause, non-elective hospital admission at one year post-PR.

Covariates	**Univariable analysis**		**Multivariable analysis***	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**
Baseline 4MGS (ms^{-1})	0.18 (0.02 to 1.35)	0.10		
Change in 4MGS (ms^{-1})	0.50 (0.02 to 11.58)	0.66		
Age (years)	1.02 (0.94 to 1.10)	0.69		
Gender (reference: female)	2.08 (0.58 to 7.47)	0.26		
Smoking status (reference: never smokers)	1.69 (0.57 to 5.05)	0.35		
FVC (% predicted)	0.97 (0.94 to 1.00)	0.09	0.96 (0.93 to 1.00)	0.03
Prescribed anti-fibrotic medication during the study period (reference: no)	0.47 (0.11 to 2.09)	0.32	0.17 (0.02 to 1.37)	0.10
Number of respiratory hospital admissions in previous year	1.01 (0.96 to 1.07)	0.75		
Number of chest infections in previous year	1.16 (0.87 to 1.55)	0.32	1.36 (0.95 to 1.96)	0.10

*All of the variables in the univariable analysis were included in the multivariable analysis. Final model presented.

Abbreviations: 4MGS: Four Metre Gait Speed; CI: Confidence Interval; FVC: Forced Vital Capacity; HR: Hazard Ratio; PR: Pulmonary Rehabilitation.

6.6 Discussion

The main findings from this study are that change in 4MGS with PR predicts all-cause survival but not all-cause, non-elective hospital admission at one year following PR in patients with IPF. The results demonstrate that patients with a 4MGS change ≥0.09 ms^{-1} have increased survival at one year, compared to those with a 4MGS change <0.09 ms^{-1}. This cut-off requires external validation, *nonetheless*, it is within the range of the 4MGS minimum clinically important difference estimates (0.08 to 0.18 ms^{-1}) previously reported in Chapter 4. These data provide support for 4MGS to be considered a surrogate marker of survival, which may be of value for investigators conducting intervention trials in IPF.

Previous research

In other populations, a number of studies have demonstrated that improvements in gait speed are associated with improved prognosis (165, 172, 173) and conversely, that reductions in gait speed are associated with increased risk of adverse outcome (173-175, 179). These studies largely measured change in gait speed over time, not in response to an intervention, therefore findings are not directly comparable with the results of this study. In 439 community-dwelling elders, Hardy *et al* reported that improvements in 4MGS over one year, after adjusting for confounding variables, predicted reduced mortality over eight years (HR (95% CI): 0.42 (0.29 to 0.61) per 0.10 ms^{-1} increase in gait speed) (172). Sabia *et al* undertook a study involving 2,094 community-dwelling French elders and reported that patients who improved their fast gait speed measured over six metres had a longer time to death (HR (95% CI): 0.80 (0.71 to 0.90) per 0.10 ms^{-1} increase in gait speed) (173). In contrast, when change in fast gait speed was classified as a categorical variable, a 'substantial decline' (<-0.08 ms^{-1}) was associated with a greater risk of mortality compared to a 'normal change' (≥-0.04 ms^{-1}) in fast gait speed (HR (95% CI): 1.40 (1.02 to 1.92)) (173). However, as these cut-offs were obtained from a previous study that had measured usual, rather than fast, gait speed (287) the authors repeated the analysis using cut-offs based on the distribution of gait speed in their cohort: 'normal change': -0.14 to -0.06 ms^{-1}; 'substantial decline' group: <-0.17 ms^{-1}. They reported that

similar trends were observed but no data were provided to support this (173). Furthermore, neither the time period between gait speed measurements nor survival period were clearly described in the study methods. In a study involving 1,388 acutely unwell older male veterans, Purser *et al* demonstrated that increases in gait speed measured at hospital admission and at one year were associated with improved health status; physical function; fewer disabilities as well as lower healthcare utilisation and costs at one year (165). However, gait speed was measured over 15 metres and patients unable to complete the test in less than 90 seconds were assigned a gait speed of 0.17 ms^{-1} ($\frac{15\ metres}{90\ seconds} = 0.17ms^{-1}$). Seventy-four percent of patients were unable to complete the test within this timeframe at hospital admission. Furthermore, as gait speed was measured at hospital admission, not discharge, the care received during the admission may have been a determinant of outcome rather than the prognostic ability of gait speed. Perera *et al* reported that a 0.10 ms^{-1} reduction in 4MGS over one year, adjusted for confounding variables, was associated with increased risk of mortality at five years in 439 older patients (HR (95% CI): 2.23 (1.44 to 3.46)) (174). A study by White *et al* used cut-points to demonstrate that, compared to a small reduction in usual walking speed (20 metre course) in one year (-0.02 ms^{-1}), a large reduction (-0.03 ms^{-1}) was associated with a greater risk of all-cause death after adjusting for confounding variables (HR (95% CI): 1.9 (1.3 to 2.8) (175). Although this was a large study (n=2,364 community-dwelling adults aged 70 to 79 years), the results are difficult to extrapolate to clinical practice as the difference between the two gait speed categories (-0.02 ms^{-1} versus -0.03 ms^{-1}) is sufficiently small to be within the bounds of 4MGS measurement error. Gill *et al* undertook a study involving 586 adults living in retirement villages and measured fast gait speed back and forth over a three metre course, one year apart (179). Compared to no decline in fast gait speed, a large decline was associated with dependence with activities of daily living at one year (OR (95% CI): 5.3 (3.0 to 9.3)) but not three years (OR (95% CI): 0.9 (0.5 to 1.8)) (179).

Limitations and further studies

This is the first study to examine the association between the *change* in 4MGS and prognosis in patients with IPF or indeed any chronic respiratory disease. It also describes the response of one of the largest IPF-specific cohorts to undergo PR. However, there were limitations. First, the majority of the participants in this study (99%) were symptomatic patients recruited from the PR programme at the Royal Brompton and Harefield NHS Foundation Trust, a specialist cardiorespiratory centre. It is not known whether the results are generalisable to other PR programmes. Furthermore, the data need to be corroborated in other settings and other populations with IPF (for example, less or more symptomatic patients managed in primary care or the acute hospital setting respectively). Second, although 4MGS improved with PR it is not known for how long this is sustained. Third, the overall number of deaths and hospital admissions was low as duration of follow-up was only one year (chosen in order for the study to be completed within the time-frame of a PhD thesis). Furthermore, the sample size calculation for this study was based on demonstrating change in 4MGS with PR (as described in Chapter 4), and not the ability of 4MGS change to predict survival or hospital admission. The wide 95% confidence interval of the 4MGS change hazard ratio (95% CI: 0.00 to 0.42) to predict mortality reflects an imprecise estimate of prognostic risk due to the small number of deaths. A larger sample would be required to refine the precision of the hazard estimate, and extended follow-up would allow a better assessment of the relationship between improvement in 4MGS and longer-term survival. Fourth, although it requires external validation, this research identified a 4MGS change cut-point above which is associated with improved survival at one year a cut-point. Future research investigating a 4MGS change cut-point that predicts reduced survival would be of interest. Fifth, only all-cause mortality and non-elective hospital admissions were reported. It was not possible to ascertain a specific cause of death, or even whether the cause death or hospital admission was respiratory or non-respiratory related. Previous studies have suggested that it is not always possible to reliably discern if a death or hospital admission was IPF- or non-IPF related (75). Nonetheless, distinguishing between respiratory and non-respiratory related deaths and hospital admissions may have determined whether 4MGS change is a clinical indicator of overall multi-system

well-being or whether it represents a true surrogate of underlying disease progression. Sixth, in Chapter 5, DL_{CO} % predicted was a significant predictor of all-cause, non-elective hospital admission at one year. As DL_{CO} was not measured in this study, it was not possible to include it in the regression analysis but future studies should consider its inclusion.

Potential mechanisms

There are plausible reasons why an improvement in 4MGS with PR predicts better survival at one year in patients with IPF. Gait speed has been described as a 'clinical indicator of multi-system well-being' or the 'sixth vital sign' (138, 141). Walking ability and speed rely on many factors and the integration of multiple systems (140) including cardiac, respiratory, skeletal muscle, and psychological. PR has multiple benefits that impact on such systems (288) - it is likely that improvement in 4MGS with PR is a surrogate marker of improvement in these systems. Patients whose change in 4MGS was <0.09 ms^{-1} were more likely to use LTOT and have previously completed PR than those in the ≥0.09 ms^{-1} group. This may suggest that these patients had more advanced disease – which is supported by the trend towards significantly worse mean baseline FVC % predicted (66.4% versus 76.2%, p=0.050) – which in turn limited the capacity to improve their physical performance. In Chapter 3, it was demonstrated that 4MGS correlated with the six minute walk test; KBILD total score; MRC Dyspnoea score and the Gender, Age and lung Physiology (GAP) index and that stratification according to 4MGS phenotype identified large deficits in exercise capacity, respiratory disability, health status and multi-dimensional prognostic index in the 4MGS <0.80 ms^{-1} group. In this current study, there was a trend towards a lower baseline FVC % predicted in the 4MGS change <0.09 ms^{-1} group and although there was no correlation between change in 4MGS and FVC % predicted with PR it is plausible that disease severity limited the change in 4MGS with PR in this group. As spirometry, not full pulmonary function testing, was performed as part of a usual PR assessment, diffusing capacity of the lung for carbon monoxide (DL_{CO}) % predicted could not be included in multivariable analysis. Furthermore, DL_{CO} % predicted is a component of the Composite

Physiologic Index and GAP index which are established prognostic indices and as such it was not possible to compare the multivariable model in this study with either of these indices. Gait speed in older adults is considered an indicator of 'physiological reserve' (289) and a surrogate marker of frailty that reflects resilience and/or capacity to recover from a stressor (290, 291). Hence, the improvement in 4MGS with PR reflects not only improved physiology but also reduced frailty and better intrinsic capacity or resilience.

The reasons why an improvement in 4MGS with PR did not predict all-cause, non-elective hospital admissions are less clear. To date, no published studies have explored the relationship between change in gait speed and time to first hospital admission in any patient group. In the current study, the power calculation was not based on this research question and there were only a small number of hospital admissions which may have limited the identification of a meaningful 4MGS change cut-off that could predict first hospital admission. A standard eight-week outpatient PR programme has been shown to improve respiratory disease self-management skills (292). This may have influenced patients' decision on whether to go to hospital or self-manage a respiratory complaint but this requires verification.

Significance of findings

In Chapter 5, the prognostic ability of 4MGS to predict all-cause mortality and non-elective hospital admissions in patients with a new diagnosis of IPF was described, supporting a role for 4MGS as a stratification tool. The current chapter provides evidence that improving 4MGS with an intervention (in this instance, PR) is associated with improved survival but not reduced time to hospital admission. Nonetheless, this provides support for 4MGS to be considered a surrogate marker of survival, and may be of value for investigators conducting intervention trials in IPF. Other attractive properties of the 4MGS test include the low cost, little time or space to perform, and does not requires significant

operator training or expertise. These properties mean that 4MGS could be adopted in almost any clinical or research environment including the home (206) or hospital bedside (196). More studies are required to assess how the 4MGS test responds to other interventions (including pharmacological) and whether these are associated with prognosis in patients with IPF.

6.7 Conclusion

In summary, in patients with IPF who completed a standard outpatient PR programme, change in 4MGS with PR was independently associated with improved survival but not non-elective hospital admission at one year. A 4MGS change ≥0.09 ms^{-1} with PR was independently associated with improved survival, but this requires external validation.

Chapter 7 : Discussion and Future Work

7.1 Summary of findings

Several novel findings have arisen from the studies in this thesis.

1) The validity, responsiveness and minimum clinically important difference (MCID) of the incremental shuttle walk (ISW) was demonstrated in patients with idiopathic pulmonary fibrosis (IPF). There was a strong correlation between the ISW and the six minute walk test (6MWT), the best established measure of exercise capacity in IPF. Furthermore, the ISW was responsive to pulmonary rehabilitation (PR) with estimates of the MCID ranging between 31 to 46 metres. (Chapter 2)

2) The four metre gait speed (4MGS) test was reliable in patients with IPF with high inter-observer and test-retest reliability. (Chapter 3)

3) In two independent IPF cohorts, the 4MGS test shared moderate to strong correlations with established measures of walking exercise capacity, respiratory disability, health status and a multi-dimensional prognostic index (Gender Age and lung Physiology (GAP) index), supporting the concurrent validity of the 4MGS test. (Chapter 3)

4) When patients with IPF are stratified according to established gait speed cut-off recommended by gerontology expert consensus (4MGS <0.80 ms^{-1} versus ≥0.80 ms^{-1}) (143, 144), significant impairment in measures of exercise capacity, health status, dyspnoea and multi-dimensional prognostic index (GAP index) were observed in those with slow 4MGS despite similar lung function and radiological parameters. In contrast, when patients were stratified according to the six minute walk test (6MWT) prognostic cut-point (<250m versus ≥250m), only group differences in dyspnoea and gait speed were

observed. Accordingly, the 4MGS test appears to provide similar, perhaps supplementary, information to the 6MWT, the most widely used measure of exercise capacity in IPF. (Chapter 3)

5) The 4MGS test is responsive to PR and was equally responsive irrespective of baseline 4MGS. Furthermore, it was as responsive as an established field walking test used by the PR community, the ISW. (Chapter 4)

6) Using different methods, estimates of the MCID of the 4MGS following PR ranged from 0.08 ms^{-1} to 0.18 ms^{-1} with a mean of 0.14 ms^{-1}. (Chapter 4)

7) IPF patients with slow gait speed (4MGS <0.80 ms^{-1}) at diagnosis were shown to have a shorter time to all-cause death and increased all-cause, non-elective hospital admission at one year, compared to those with preserved gait speed (4MGS ≥0.80 ms^{-1}). After adjusting for confounding variables, 4MGS remained an independent predictor of both mortality and hospital admissions. (Chapter 5)

8) A multivariable model including 4MGS, age and forced vital capacity % predicted was a better predictor of all-cause death than established prognostic indices (the Composite Physiologic Index (CPI) and GAP index). Similarly, a model incorporating 4MGS, gender, CPI and number of chest infections in the previous year demonstrated greater discrimination for predicting all-cause, non-elective hospital admission than CPI or GAP index alone. (Chapter 5)

9) Improvement in 4MGS with PR predicted all-cause survival but not non-elective hospital admission at one year following PR in patients with IPF. Patients with a 4MGS change ≥0.09 ms^{-1} had reduced time to death, compared to those with a 4MGS change <0.09 ms^{-1}. (Chapter 6)

7.2 Significance of findings

As discussed in previous chapters, the rationale for this research was that surrogate endpoints or stratification tools are required to reduce the sample size requirements, follow up, duration and costs of clinical trials in IPF research. There is a developing therapeutic pipeline for IPF, but current dependence on slowing of decline in lung function or improved survival as primary endpoints have limitations. Forced vital capacity (FVC), for example, may be difficult to perform in highly symptomatic patients, and missing FVC data has been observed in clinical trials (76). Furthermore, slowing of the decline of FVC has not translated into improvements in outcomes that are meaningful to patients (such as increased exercise tolerance or better health-related quality of life) (33, 35, 36). Although mortality is a harder endpoint, and less susceptible to problems with missing data, there are difficulties elucidating the cause of death (75), and whether it is related to the underlying disease process. As discussed previously, in a randomized controlled trial where mortality is the primary endpoint, it may be difficult for both investigators and participants to accept a control treatment in the face of clear symptomatic deterioration and disease progression.

As discussed in Chapter 1, the 4MGS test is a simple assessment tool that has been extensively validated in the gerontology literature. It has been shown to be a consistent predictor of adverse prognosis in many population studies of community-dwelling older adults. Given that IPF primarily affects older adults, the hypothesis was developed that the 4MGS may have potential value in the stratification and prognostication in patients with IPF. Although it is acknowledged that IPF is a pulmonary disease and walking speed might not be considered a direct surrogate marker of lung fibrosis, it is important to point out that slowing of walking speed is a common end pathway for

deterioration in different physiological systems. The exemplar is the neurological disorder multiple sclerosis; in January 2010, the drug dalfampridine was approved by the Food and Drug Administration for patients with this disease, based on the demonstration of an increase in walking speed in two phase III randomized trials (148).

Only a limited number of studies have investigated the utility of 4MGS in patients with chronic respiratory disease, and none have involved IPF-specific populations. Data from this thesis has established the psychometric properties of the 4MGS in IPF. Specifically, I have demonstrated the reliability, validity, stratification ability, responsiveness and prognostic value of the 4MGS in patients with IPF. It has also been demonstrated that improvement in the 4MGS with PR is associated with increased survival; specifically, an improvement of $0.09ms^{-1}$ should be considered clinically important. The data from this thesis provides evidence to support the 4MGS test as a potential surrogate marker in patients with IPF, and justifies further work and evaluation.

7.2.1 Utility of the 4MGS test in the research and clinic environment

Although FVC and the 6MWT are the most commonly used surrogate endpoints of mortality in IPF, both have shortcomings that limit their utility in research and clinical settings. The data from this thesis indicate that the 4MGS test provides additional information to FVC and the 6MWT. However, given its simplicity, the 4MGS is potentially more acceptable and feasible to measure on a routine basis than the 6MWT in different healthcare settings.

7.2.1.1 Simple functional assessment tool

The 4MGS test reflects physical and functional performance. In Chapters 3 and 4, I demonstrated that 4MGS correlated strongly with established field walking tests, the 6MWT and ISW which

indicates that it has potential as a simple assessment tool of physical performance in this group. Furthermore, I showed that gait speed increases in response to PR, irrespective of baseline level of functional performance in Chapter 4; the ability to detect improvement is an essential trait in an assessment tool. In the clinical environment the 4MGS test may provide a simple way of objectively assessing functional performance in patients with IPF, particularly in settings where the 6MWT might not be feasible in terms of acceptability to patients, time or space restraints e.g. outpatient clinic setting, patient's home, primary care surgeries, hospital bedside. As slowing of gait speed and deterioration in physical performance represent the final common pathway of ageing and chronic disease, the 4MGS test is considered a 'marker of global well-being' or the 'sixth vital sign', which reflects biological rather than chronological age. Serial and contemporaneous measurement of 4MGS at routine clinic appointments may provide objective information on functional performance and monitor change over time, even in those with more severe functional impairment. Similarly, it may have a role as an outcome measure of functional performance in patients with IPF in observational studies and interventional clinical trials. Indeed it is already used routinely as an outcome measure in clinical trials of other disease groups (148) and is recognised by international expert working groups as the functional test closest to being ready for pharmacological trials in older adults with frailty or sarcopenia (146, 270).

7.2.1.2 Stratification tool

The 4MGS test may have a role in the stratification of patients with IPF. In Chapters 3 and 5, stratification according to the slow and preserved gait speed cut-off identified patients with greater symptom burden and poorer exercise intolerance - supplementing information provided by traditional pulmonary function tests and thoracic imaging. It was also demonstrated that using 4MGS cut-offs could identify those at highest risk of adverse outcomes such as all-cause mortality and non-elective hospital admission. Hence, it is conceivable that the 4MGS test may have a role in clinical trials either as a stratification tool or as an inclusion/exclusion criterion. Stratification of patients

using the 4MGS test may guide the individualisation of clinical management strategies (for example, referral to palliative care in those with particularly slow 4MGS) as well as providing clinicians with additional information to advise about likely prognosis to their patients. The results of Chapter 6 demonstrate that stratification according to increase in 4MGS with PR (≥0.09 ms^{-1} versus <0.09 ms^{-1}) was associated with improved survival at one year. Potential clinical implications include individualising the length and composition of the PR intervention, or perhaps offering repeat PR interventions according to patient 4MGS response.

7.2.1.3 Prognostic ability and surrogate endpoint of adverse events

The results of Chapter 5 identified the 4MGS test as an independent predictor of all-cause mortality and non-elective hospital admission at one year in patients with a new diagnosis of IPF. Although the multivariable models to predict mortality and hospital admission require external validation, they had higher discrimination than current prognostic indices (CPI and GAP index). Previous validation studies of existing prognostic indices were based on retrospective data (82, 85), whereas this thesis used a prospective design to validate the prognostic value of the 4MGS. Further validation of the prognostic value of 4MGS was shown by demonstrating that *improvement* in 4MGS was associated with longer survival. These data suggest that the 4MGS test has potential as a surrogate endpoint for mortality.

7.3 Limitations and Future Work

The vast majority of patients participating in the research undertaken in this thesis were recruited from clinics at the Royal Brompton and Harefield NHS Foundation Trust; only one research patient was recruited from another hospital (Guy's and St. Thomas' NHS Foundation Trust in Chapters 4 and 6). The Royal Brompton and Harefield NHS Foundation Trust is a specialist cardiac and respiratory tertiary care centre. It has a dedicated interstitial lung disease unit to care for people with IPF. Furthermore, the Harefield PR team, which provided the intervention in Chapters 4 and 6, works

closely alongside clinical researchers and has an active research programme. Team members are trained (with continuous assessment) in the standard operating procedures for the physical and health status outcome measures described in this thesis. Accordingly, it is not known whether the results of this research are generalisable to other centres and healthcare professionals. Specifically, the findings need to be corroborated and externally validated in alternative settings (primary care, acute hospital, home-based care) as well as by other clinical and PR teams. This is particularly pertinent in settings where healthcare staff are not accustomed to making routine physiological measurements. For example, although the 4MGS test requires little operator training, nurses and healthcare assistants may be less familiar with performing functional outcome measures, compared with experienced physiotherapy and exercise rehabilitation staff. However, data from other chronic respiratory disease populations (e.g. chronic obstructive pulmonary disease (COPD)) suggest that the 4MGS can be easily implemented into clinical practice with high acceptability by non-rehabilitation healthcare assistants (191).

The patient population described in this thesis was recruited from outpatient and rehabilitation settings in a secondary/tertiary care setting. Therefore, primary care-based patients with few symptoms are not well-represented within the study cohorts described in this thesis. Further valuable work would include understanding whether the 4MGS has similar clinical and prognostic value in patients with IPF and either normal lung function indices or very few respiratory symptoms (for example, those where an incidental diagnosis of IPF might have been made from imaging studies organised for alternative medical reasons). Identifying patients with IPF who might benefit from early referral for secondary care may be of value for primary care health practitioners. Contrarily, the patient population in this thesis only included patients with IPF in the stable state, and did not comprise patients who were hospitalised or recovering from an acute exacerbation. Acute exacerbations are an important cause of death in IPF, and are associated with a very poor prognosis with an expected median survival of less than three months (293). Future work should include

identifying whether 4MGS, or recovery in 4MGS after exacerbation, is associated with prognosis in patients with acute exacerbations of IPF. Previous work, in patients hospitalised with acute exacerbation of COPD, has shown that 4MGS measured on the day of hospital discharge can predict short-term hospital readmission (196). This is particularly pertinent as the best established functional measure in IPF (the 6MWT) may not be acceptable to highly symptomatic patients with acute exacerbations; the prognostic value of the 6MWT in IPF has only been shown in patients without significant lung function impairment (FVC >55% predicted) (91, 94).

As the aims of the thesis were to evaluate the psychometric properties of the 4MGS (including responsiveness to an exercise intervention and association with existing exercise outcomes), participants who could not perform the 4MGS (defined as those unable to walk five metres), those who had co-morbidities that limited walking ability (e.g. neurological impairment) or patients where it was considered unsafe to exercise (e.g. unstable cardiac disease) were excluded. This potentially limits the value of the findings to selected populations. However, of the 350 patients approached as part of the research process, only ten patients were excluded for these reasons. This suggests that the 4MGS is acceptable and feasible in the majority of ambulatory patients with IPF. It is also possible that by excluding patients unable to perform the 4MGS, the prognostic value of the 4MGS may be underestimated as it would be expected that those unable to complete a 4MGS may be at particular risk for adverse prognosis. As explained previously, the 4MGS may be of particular value in those with very poor functioning (e.g. during an acute exacerbation or advanced disease with very poor lung function) where existing functional performance measures like the 6MWT are neither feasible nor acceptable to patients.

In chapter 4, the short-term responsiveness of 4MGS to PR is demonstrated. As expected, 4MGS increased with an eight-week outpatient supervised PR programme, but it is not known how long these improvements persist. Previous studies of patients with interstitial lung disease undergoing PR

have shown short-term improvements only, with a return to baseline by six months (24, 280). Whether a sustained, compared to short-term, improvement in 4MGS with PR is associated with better prognosis is worthy of further investigation. This might have implications regarding the design of individualised, disease-specific PR for patients with IPF, such as increasing the duration of the exercise intervention, the use of adjuncts to maximize the benefits of PR or the need for maintenance strategies to prolong the benefits. It has been speculated that the symptom burden associated with IPF may limit patients from undergoing whole-body exercise at a sufficient intensity to induce physiological change. Rehabilitation-like strategies that reduce ventilatory burden, such as the adjunctive use of non-invasive ventilation (294), neuromuscular electrical stimulation (295), whole body vibration (296), interval training (297) and single-legged cycling (298) have yet to be tested in patients with IPF; the 4MGS is a plausible and feasible outcome measure for such future trials.

Outside the rehabilitation setting, the data from this thesis might encourage collaborators from industry to incorporate the 4MGS as a functional outcome measure in future therapeutic trials. Given the simplicity of the test as well as feasibility and acceptability of the test to patients (191), this would not add a high financial or time burden to interventional trials, and would provide a deeper understanding of the mechanisms behind improvement (or deterioration) in 4MGS. Furthermore, the research studies within this thesis have focused either on baseline 4MGS or the immediate improvement in 4MGS with PR. Additional observational studies documenting the longitudinal change (presumably decline) of 4MGS with disease progression may provide useful prognostic information. This is very relevant to 4MGS as it is a simple test that can be performed frequently with patient acceptability, and is feasible in the home setting. An example comparator is daily home spirometry, where pilot data has shown that rates of decline in home daily measurements of FVC is associated with subsequent mortality (299). Such observational studies would also provide estimates of what constitutes a clinically significant deterioration in 4MGS; although the studies in this thesis

were able to provide an estimate of what is considered a clinically important improvement in the 4MGS, the PR study could not comment on clinically important deterioration as most patients improved their 4MGS with PR. It is perfectly plausible that patients may perceive the size of deterioration differently to the size of improvement.

In Chapter 5, 4MGS was shown to predict both all-cause mortality and all-cause, non-elective hospital admission at one year in patients with a new diagnosis of IPF. In Chapter 6, improvement in 4MGS with PR was associated with longer survival but not increased time to all-cause, non-elective hospital admission. A 4MGS change cut-off with predictive ability for survival was identified. As the study described in Chapter 6 did not have an *a priori* sample size calculation, future research should include an adequately powered sample which may refine the precision of the hazard estimate. The final multivariable models in both Chapters 5 and 6 and the cut-off described in Chapter 6 require external validation as well as corroboration in patients at different disease stages.

The period of follow-up was limited to one year follow-up in order for the longitudinal studies to be completed within the time constraints of a PhD thesis. Consequently, relatively few deaths were recorded. However, a longer duration of follow-up (with inevitably more deaths) would have enhanced estimates of prognostic risk, and be of greater value to healthcare staff caring for patients with IPF in providing additional information around prognosis, specifically survival. Additionally, it was not possible, due to the time constraints of a PhD thesis, to evaluate the predictive ability of change in 4MGS and to compare it with change in FVC, the most commonly used surrogate endpoint. Future studies should address this area as it would elucidate if 4MGS is superior, inferior or adds value to FVC.

A significant limitation of the prognostic studies described in this thesis (Chapters 5 and 6) was that the cause of death or reason for hospital admission were not elucidated. Although this was initially planned through ethically-approved requests to NHS Digital, the application process was lengthy, hampered by inconsistent administrative hurdles and not feasible within the thesis time-frame. Instead mortality and hospital admission data was collected through NHS Spine, primary care records, patient recall and corroboration from hospital records. Causes of death or hospital admission were not reliably recorded, but might have provided valuable insight into ascertaining whether 4MGS is a clinical indicator of multi-system well-being or provides some surrogate measure of underlying pulmonary function severity. As yet, it is not known whether 4MGS or change in 4MGS can predict acute exacerbation, future disability, institutionalisation, healthcare resource usage as well as long term outcomes in patients with IPF and this should be the subject for further research. Studies that evaluate a stratified management approach may help individualize and improve treatment strategies plans for patients (e.g. identify patients who might benefit from multi-system gerontology input such as comprehensive geriatric assessment, or referral for specialist management of symptom burden by palliative care).

7.4 Conclusion

At present, IPF is estimated to affect five million people globally and the occurrence of this disease is on the rise worldwide (7, 300, 301). Current treatment options for patients with IPF are limited and surrogate endpoints that can predict adverse outcomes are required to help develop and evaluate new management strategies, but existing options have limitations. A paradigm shift needs to be made in IPF research and clinical care, with particular attention to the extra-pulmonary manifestations of the disease. It is important for researchers, clinicians and policy makers to consider the multi-system, whole body impact of IPF and its associated comorbidities on patients with this heterogeneous disease. The 4MGS test is an easy and rapid measure of physical performance that is reliable, correlates with established outcome measures in IPF, is responsive to

intervention and provides prognostic information that can be measured in the majority of research and healthcare settings. In conclusion, the 4MGS test is a useful surrogate endpoint of adverse outcomes in IPF; I propose that other tools used in geriatric medicine may become increasingly relevant in IPF research and clinical care.

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Chapter 1: Introduction

Figure 1.1: The relationship between change in FVC % predicted over six months and mortality.

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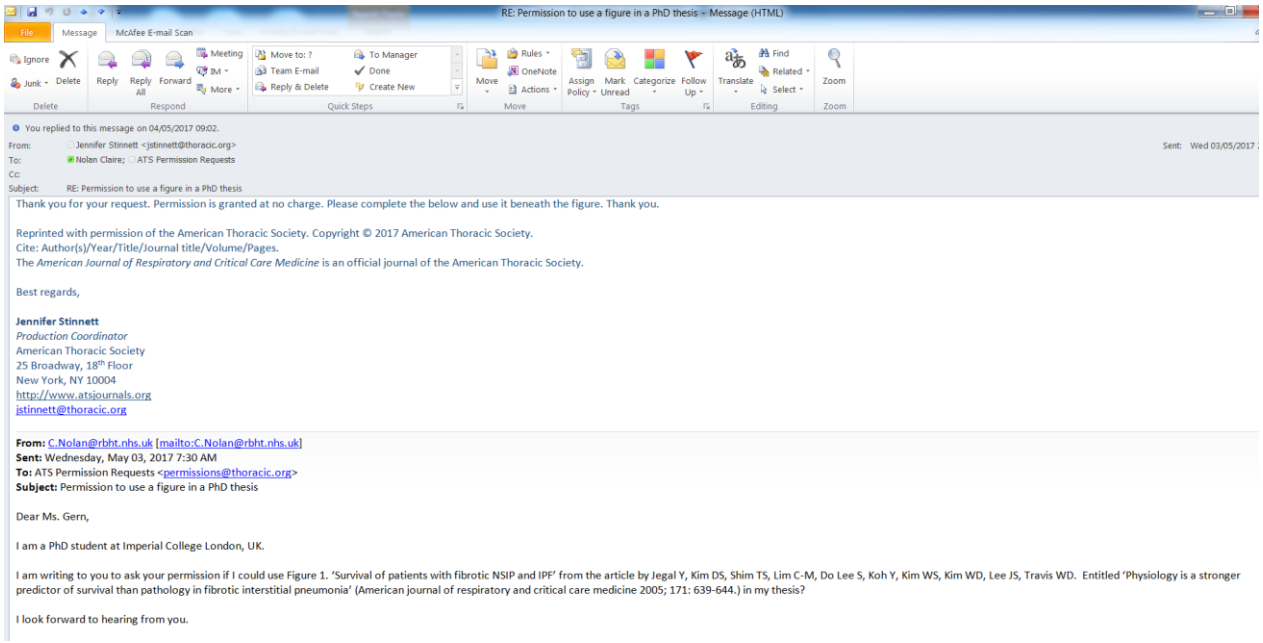

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I look forward to hearing from you.

Figure 1.3: Predicted median life expectancy by age and gait speed.

JAMA

Title: Gait Speed and Survival in Older Adults

Author: Studenski, Stephanie; Perera, Subashan

Publication: JAMA

Publisher: American Medical Association

Date: Jan 5, 2011

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Figure 1.4: Kaplan–Meier curve demonstrating time to 90-day all-cause, non-elective readmission in COPD patients according to 4MGS quartile (Q1: slowest gait speed; Q4: fastest gait speed).

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Figure 1.5: Change in 4 metre walk time following PR and 6 months after initiation of pulmonary rehabilitation.

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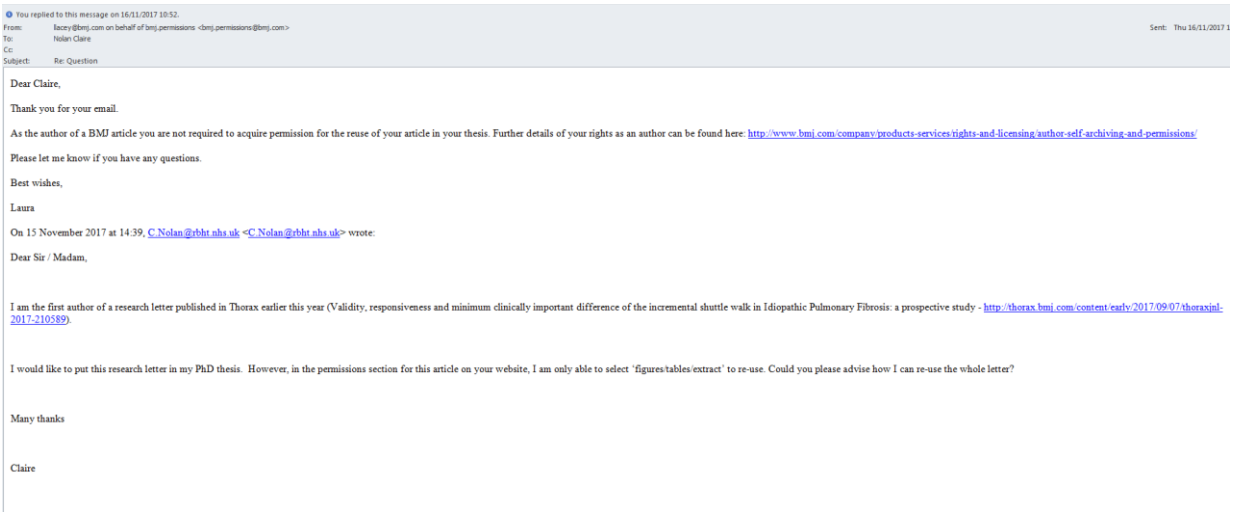

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Chapter 3: The reliability and validity of the four metre gait speed and the phenotypic characteristics of the slow gait speed phenotype in idiopathic pulmonary fibrosis

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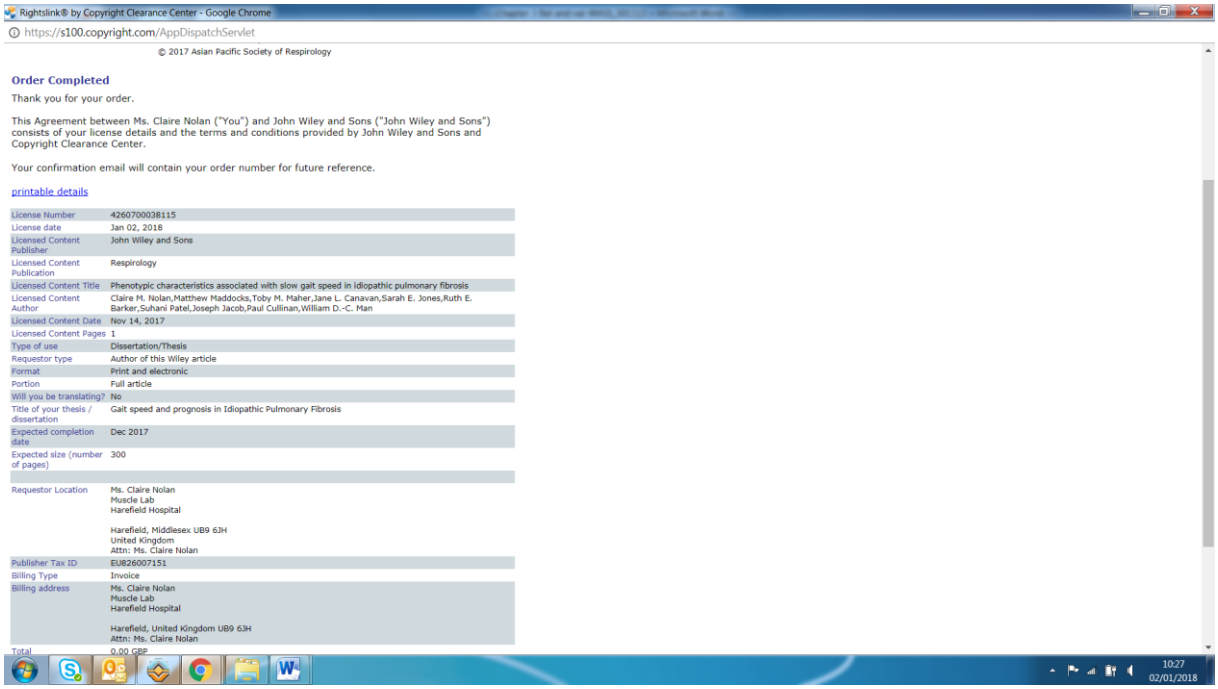

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Appendix 2: Description of the recruitment of patients to more than one study

A table showing the number of participants recruited to more than one study.

	Study 1: Reliability (n=46)	**Study 1: Validity (cohort 1: n=65)**	**Study 1: Validity (cohort 2: n=62)**	**Study 1: Phenotype (n=65)**	**Study 2 (n=95)**	**Study 3 (n=130)**	**Study 4 (n=90)**
Study 1: Reliability (n=46)					n=32		
Study 1: Validity (cohort 1: n=65)				n=65		n=65	
Study 1: Validity (cohort 2: n=62)							
Study 1: Phenotype (n=65)		n=65				n=65	
Study 2 (n=95)	n=32					n=26	n=90
Study 3 (n=130)		n=65		n=65	n=26		
Study 4 (n=90)					n=90		

Appendix 3: Study schemas for the study entitled 'Validity, responsiveness and minimum clinically important difference of the incremental shuttle walk in Idiopathic Pulmonary Fibrosis: a prospective study'.

This study was described in Chapter 2, section 2.12.2a-e.

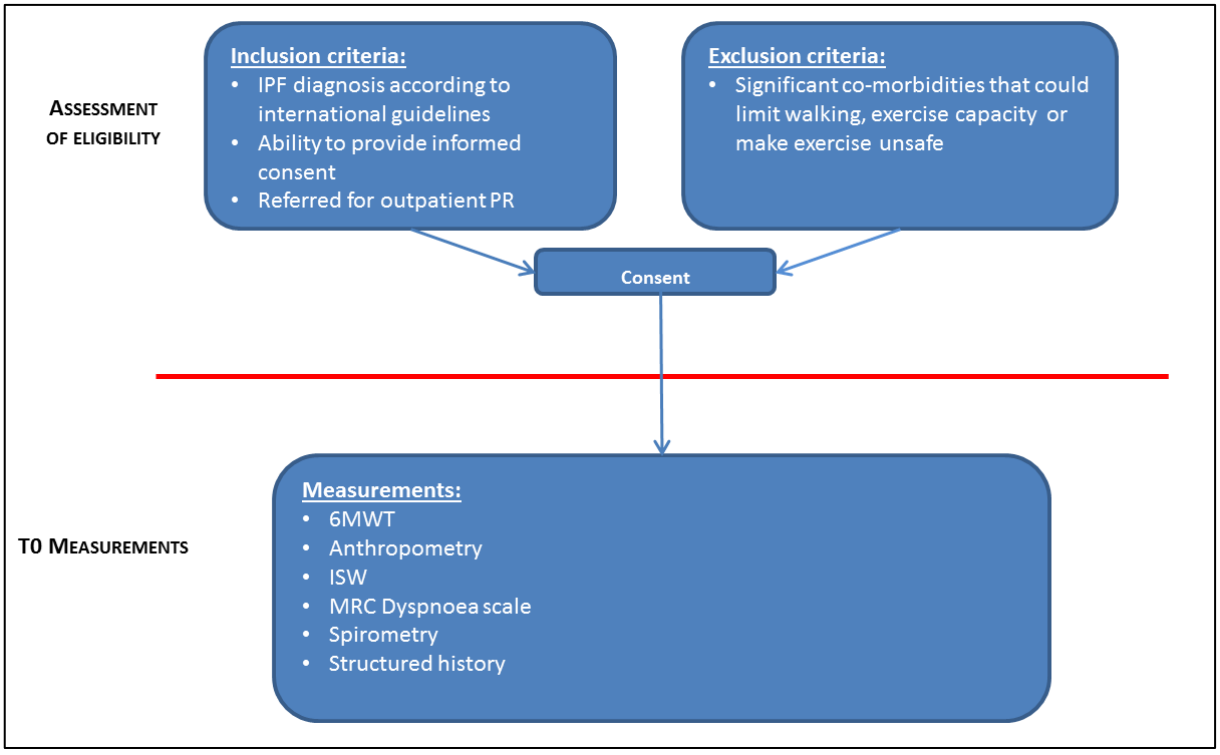

Figure 1: The study schema for study 1: Validation of the ISW in IPF.

Abbreviation: 6MWT: Six Minute Walk Test; IPF: Idiopathic Pulmonary Fibrosis; ISW: Incremental Shuttle Walk test; MRC: Medical Research Council Dyspnoea scale; PR: Pulmonary Rehabilitation.

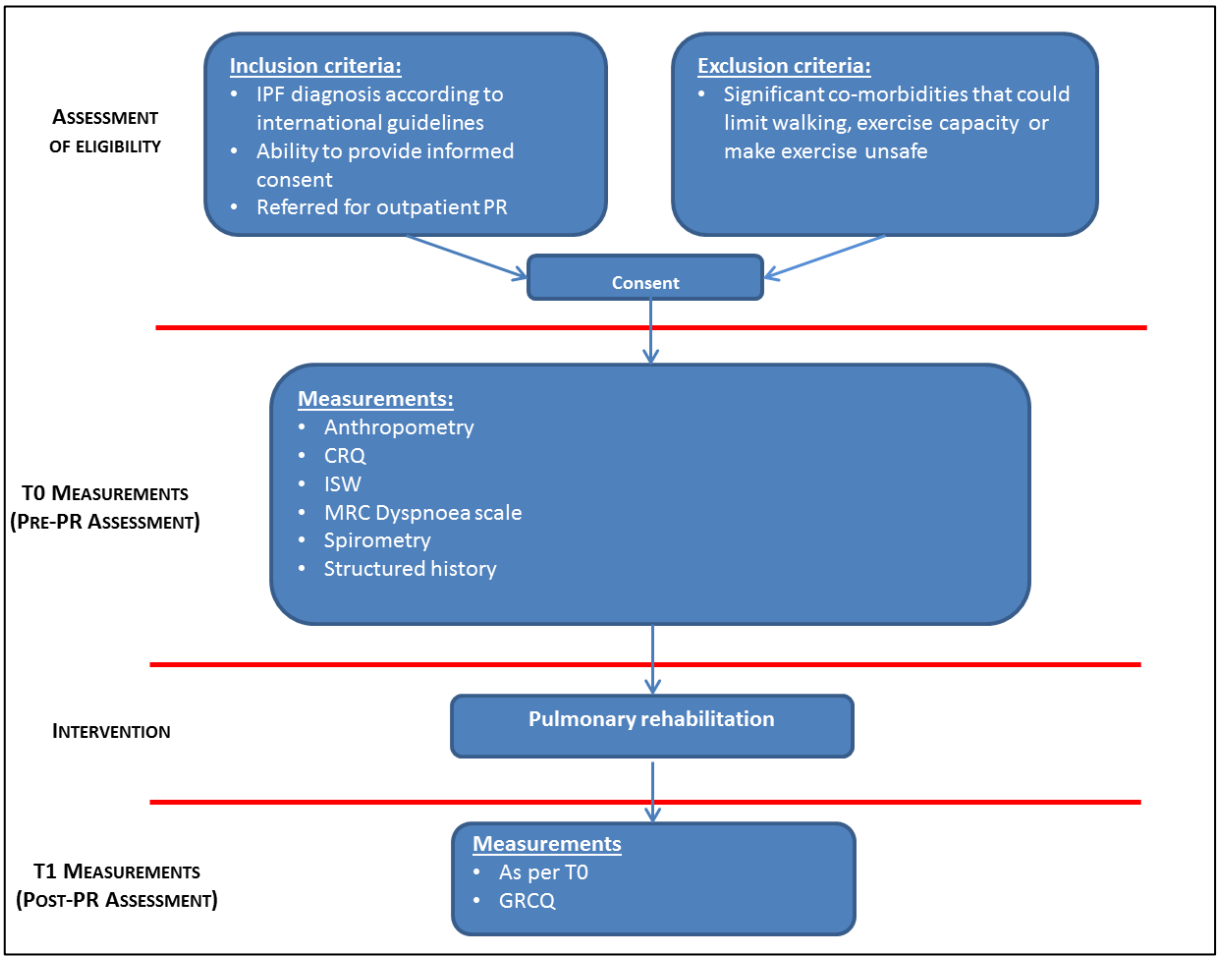

Figure 2: The study schema for study 2: The responsiveness of the ISW and estimation of the MCID.

Abbreviation: CRQ: Chronic Respiratory Questionaire; GRCQ: Global Rating of Change Questionnaire; IPF: Idiopathic Pulmonary Fibrosis; ISW: Incremental Shuttle Walk test; MCID: Minimum Clinically Important Difference; MRC: Medical Research Council Dyspnoea scale; PR: Pulmonary Rehabilitation.

Appendix 4: Questionnaires used in this thesis

The King's Brief Interstitial Lung Disease (KBILD) questionnaire

The King's Brief Interstitial Lung Disease Questionnaire (K-BILD)©2011 – Version 1

This questionnaire is designed to assess the impact of your lung disease on various aspects of your life. Please circle the response that best applies to you for each question

Name:_____ MRN:_____ Date:_____

1. In the last 2 weeks, I have been breathless climbing stairs or walking up an incline or hill:

1. Every time	2. Most times	3. Several Times	4. Some times	5. Occasionally	6. Rarely	7. Never

2. In the last 2 weeks, because of my lung condition, my chest has felt tight:

1. All of the time	2. Most of the time	3. A good bit of the time	4. Some of the time	5. A little of the time	6. Hardly any of the time	7. None of the time

3. In the last 2 weeks have you worried about the seriousness of your lung complaint?

1. All of the time	2. Most of the time	3. A good bit of the time	4. Some of the time	5. A little of the time	6. Hardly any of the time	7. None of the time

4. In the last 2 weeks have you avoided doing things that make you breathless?

1. All of the time	2. Most of the time	3. A good bit of the time	4. Some of the time	5. A little of the time	6. Hardly any of the time	7. None of the time

5.In the last 2 weeks have you felt in control of your lung condition?

1. None of the time	2. Hardly any of the time	3. A little of the time	4. Some of the time	5. A good bit of the time	6. Most of the time	7. All of the time

6.In the last 2 weeks, has your lung complaint made you feel fed up or down in the dumps?

1. All of the time	2. Most of the time	3. A good bit of the time	4. Some of the time	5. A little of the time	6. Hardly any of the time	7. None of the time

7. In the last 2 weeks, I have felt the urge to breathe, also known as 'air hunger':

1. All of the time	2. Most of the time	3. A good bit of the time	4. Some of the time	5. A little of the time	6. Hardly any of the time	7. None of the time

8. In the last 2 weeks, my lung condition has made me feel anxious:

1. All of the time	2. Most of the time	3. A good bit of the time	4. Some of the time	5. A little of the time	6. Hardly any of the time	7. None of the time

9. In the last 2 weeks, how often have you experienced 'wheeze' or whistling sounds from your chest?

1. All of the time	2. Most of the time	3. A good bit of the time	4. Some of the time	5. A little of the time	6. Hardly any of the time	7. None of the time

10. In the last two weeks, how much of the time have you felt your lung disease is getting worse?

1. All of the time	2. Most of the time	3. A good bit of the time	4. Some of the time	5. A little of the time	6. Hardly any of the time	7. None of the time

11. In the last 2 weeks has your lung condition interfered with your job or other daily tasks?

1. All of the time	2. Most of the time	3. A good bit of the time	4. Some of the time	5. A little of the time	6. Hardly any of the time	7. None of the time

12. In the last 2 weeks have you expected your lung complaint to get worse?

1. All of the time	2. Most of the time	3. A good bit of the time	4. Some of the time	5. A little of the time	6. Hardly any of the time	7. None of the time

13. In the last 2 weeks, how much has your lung condition limited you carrying things, for example, groceries?

1. All of the time	2. Most of the time	3. A good bit of the time	4. Some of the time	5. A little of the time	6. Hardly any of the time	7. None of the time

14. In the last 2 weeks, has your lung condition made you think more about the end of your life?

1. All of the time	2. Most of the time	3. A good bit of the time	4. Some of the time	5. A little of the time	6. Hardly any of the time	7. None of the time

15. Are you financially worse off because of your lung condition?

1. A significant amount	2. A large amount	3. A considerable amount	4.A reasonable amount	5. A small amount	6. Hardly at all	7. Not at all

CHRONIC RESPIRATORY QUESTIONNAIRE
SELF REPORTED (ASSESSMENT)

This questionnaire is designed to find out how you have been feeling during the last two weeks. You will be asked how short of breath you have been, how tired you have been feeling and how your mood has been.

NAME_____

DATE_____

We would like you to think of ways in which your shortness of breath limits your life. We are particularly interested in activities, which you still do, but which are limited by your shortness of breath. Listed below are some activities, which can make people with lung problems feel short of breath.

If you have felt **short of breath** doing any of the **activities** listed below **during the last two weeks** then please tick each relevant activity. If you have **not** done the activity during the last two weeks or it does **not** make you short of breath then leave it blank.

1. BEING ANGRY OR UPSET ☐
2. HAVING A BATH OR SHOWER ☐
3. BENDING ☐
4. CARRYING - SUCH AS GROCERIES ☐
5. DRESSING ☐
6. EATING ☐
7. GOING FOR A WALK ☐
8. DOING YOUR HOUSEWORK ☐
9. HURRYING ☐
10. MAKING YOUR BED ☐
11. MOPPING OR SCRUBBING A FLOOR ☐
12. MOVING FURNITURE ☐
13. PLAYING WITH CHILDREN/GRANDCHILDREN ☐
14. PLAYING SPORTS ☐
15. REACHING OVER YOUR HEAD ☐
16. RUNNING - SUCH AS FOR A BUS ☐
17. SHOPPING ☐
18. WHILE TRYING TO SLEEP ☐
19. TALKING ☐
20. VACUUMING ☐
21. WALKING AROUND YOUR OWN HOME ☐
22. WALKING UPHILL ☐
23. WALKING UP STAIRS ☐
24. WALKING WITH OTHERS ON LEVEL GROUND ☐
25. PREPARING MEALS ☐

Please list **any other activities** that you have done during the last two weeks, which have made you feel short of breath. These should be activities, which you do frequently and which are important in your day-to-day life.

Other Activities:
1.
2.
3.

HOW SHORT OF BREATH HAVE YOU BEEN DURING THE LAST TWO WEEKS WHILE PERFORMING THESE ACTIVITIES?

We would now like you to identify the most important activities in which you have been limited by your shortness of breath in the last two weeks. Using the list you have made on the previous page, write down the five most important activities that have made you short of breath on the lines below. We would then like you to tell us how short of breath you have been while performing each activity by ticking the box which best describes how you feel.

THE ACTIVITIES ARE:

	Extremely short of breath	Very short of breath	Quite short of breath	Moderate shortness of breath	Some shortness of breath	A little shortness of breath	Not at all short of breath
1							
2							
3							
4							
5							

6. In general, how much of the time during the last 2 weeks have you felt frustrated or impatient?
Please indicate how often during the last 2 weeks you have felt frustrated or impatient by ticking one of the following options from the list below.

1. ALL OF THE TIME ☐
2. MOST OF THE TIME ☐
3. A GOOD BIT OF THE TIME ☐
4. SOME OF THE TIME ☐
5. A LITTLE OF THE TIME ☐
6. HARDLY ANY OF THE TIME ☐
7. NONE OF THE TIME ☐

7. How often during the past 2 weeks did you have a feeling of fear or panic when you had difficulty getting your breath?
Please indicate how often you had a feeling of fear or panic when you had difficulty getting your breath by ticking one of the following options from the list below.

1. ALL OF THE TIME ☐
2. MOST OF THE TIME ☐
3. A GOOD BIT OF THE TIME ☐
4. SOME OF THE TIME ☐
5. A LITTLE OF THE TIME ☐
6. HARDLY ANY OF THE TIME ☐
7. NONE OF THE TIME ☐

8. What about fatigue? How tired have you felt over the last 2 weeks?
Please indicate how tired you have felt over the last 2 weeks by ticking one of the following options from the list below.

1. EXTREMELY TIRED ☐
2. VERY TIRED ☐
3. QUITE A BIT OF TIREDNESS ☐
4. MODERATELY TIRED ☐
5. SOMEWHAT TIRED ☐
6. A LITTLE TIRED ☐
7. NOT AT ALL TIRED ☐

9. How often during the last 2 weeks have you felt embarrassed by your coughing or heavy breathing?
Please indicate how much of the time you felt embarrassed by your coughing or heavy breathing by ticking one of the following options from the list below.

1. ALL OF THE TIME ☐
2. MOST OF THE TIME ☐
3. A GOOD BIT OF THE TIME ☐
4. SOME OF THE TIME ☐
5. A LITTLE OF THE TIME ☐
6. HARDLY ANY OF THE TIME ☐
7. NONE OF THE TIME ☐

10. In the last 2 weeks, how much of the time did you feel very confident and sure that you could deal with your illness?
Please indicate how much of the time you felt very confident and sure that you could deal with your illness by ticking one of the following options from the list below.

1. NONE OF THE TIME ☐
2. A LITTLE OF THE TIME ☐
3. SOME OF THE TIME ☐
4. A GOOD BIT OF THE TIME ☐
5. MOST OF THE TIME ☐
6. ALMOST ALL OF THE TIME ☐
7. ALL OF THE TIME ☐

11. How much energy have you had in the last 2 weeks?
Please indicate how much energy you have had by ticking one of the following options from the list below.

1. NO ENERGY AT ALL ☐
2. A LITTLE ENERGY ☐
3. SOME ENERGY ☐
4. MODERATELY ENERGETIC ☐
5. QUITE A BIT OF ENERGY ☐
6. VERY ENERGETIC ☐
7. FULL OF ENERGY ☐

12. In general, how much of the time did you feel upset, worried or depressed during the past 2 weeks?
Please indicate how much of the time you felt upset, worried or depressed during the past 2 weeks by ticking one of the following options from the list below.

1. ALL OF THE TIME ☐
2. MOST OF THE TIME ☐
3. A GOOD BIT OF THE TIME ☐
4. SOME OF THE TIME ☐
5. A LITTLE OF THE TIME ☐
6. HARDLY ANY OF THE TIME ☐
7. NONE OF THE TIME ☐

13. How often during the last 2 weeks did you feel you had complete control of your breathing problems?
Please indicate how often you felt you had complete control of your breathing problems by ticking one of the following options from the list below.

1. NONE OF THE TIME ☐
2. A LITTLE OF THE TIME ☐
3. SOME OF THE TIME ☐
4. A GOOD BIT OF THE TIME ☐
5. MOST OF THE TIME ☐
6. ALMOST ALL OF THE TIME ☐
7. ALL OF THE TIME ☐

14. How much of the time during the last 2 weeks did you feel relaxed and free of tension?
Please indicate how much of the time you felt relaxed and free of tension by ticking one of the following options from the list below.

1. NONE OF THE TIME ☐
2. A LITTLE OF THE TIME ☐
3. SOME OF THE TIME ☐
4. A GOOD BIT OF THE TIME ☐
5. MOST OF THE TIME ☐
6. ALMOST ALL OF THE TIME ☐
7. ALL OF THE TIME ☐

15. How often during the last 2 weeks have you felt low in energy?
Please indicate how often during the last 2 weeks you have felt low in energy by ticking one of the following options from the list below.

1. ALL OF THE TIME ☐
2. MOST OF THE TIME ☐
3. A GOOD BIT OF THE TIME ☐
4. SOME OF THE TIME ☐
5. A LITTLE OF THE TIME ☐
6. HARDLY ANY OF THE TIME ☐
7. NONE OF THE TIME ☐

16. In general, how often during the last 2 weeks have you felt discouraged or down in the dumps?
Please indicate how often during the last 2 weeks you felt discouraged or down in the dumps by ticking one of the following options from the list below.

1. ALL OF THE TIME ☐
2. MOST OF THE TIME ☐
3. A GOOD BIT OF THE TIME ☐
4. SOME OF THE TIME ☐
5. A LITTLE OF THE TIME ☐
6. HARDLY ANY OF THE TIME ☐
7. NONE OF THE TIME ☐

17. How often during the last 2 weeks have you felt worn out or sluggish?
Please indicate how much of the time you felt worn out or sluggish by ticking one of the following options from the list below.

1. ALL OF THE TIME ☐
2. MOST OF THE TIME ☐
3. A GOOD BIT OF THE TIME ☐
4. SOME OF THE TIME ☐
5. A LITTLE OF THE TIME ☐
6. HARDLY ANY OF THE TIME ☐
7. NONE OF THE TIME ☐

18. How happy, satisfied or pleased have you been with your personal life during the last 2 weeks?
Please indicate how happy, satisfied or pleased you have been by ticking one of the following options from the list below.

1. VERY DISSATISFIED, UNHAPPY MOST OF THE TIME ☐
2. GENERALLY DISSATISFIED, UNHAPPY ☐
3. SOMEWHAT DISSATISFIED, UNHAPPY ☐
4. GENERALLY SATISFIED, PLEASED ☐
5. HAPPY MOST OF THE TIME ☐
6. VERY HAPPY MOST OF THE TIME ☐
7. EXTREMELY HAPPY, COULD NOT HAVE BEEN MORE SATISFIED OR PLEASED ☐

19. How often during the last 2 weeks did you feel upset or scared when you had difficulty getting your breath?
Please indicate how often during the past 2 weeks you felt upset or scared when you had difficulty getting your breath by ticking one of the following options from the list below.

1. ALL OF THE TIME ☐
2. MOST OF THE TIME ☐
3. A GOOD BIT OF THE TIME ☐
4. SOME OF THE TIME ☐
5. A LITTLE OF THE TIME ☐
6. HARDLY ANY OF THE TIME ☐
7. NONE OF THE TIME ☐

20. In general how often during the last 2 weeks have you felt restless , tense or uptight?
Please indicate how often you have felt restless , tense or uptight by ticking one of the following options from the list below.

1. ALL OF THE TIME ☐
2. MOST OF THE TIME ☐
3. A GOOD BIT OF THE TIME ☐
4. SOME OF THE TIME ☐
5. A LITTLE OF THE TIME ☐
6. HARDLY ANY OF THE TIME ☐
7. NONE OF THE TIME ☐

Thank you very much for taking the time to complete this questionnaire.

FOR PR TEAM:

D	1 to 5	
F	8, 11, 15, 17	
E	6, 9, 12, 14, 16, 18, 20	
M	7, 10, 13, 19	

SCORED BY:
DATE:

CHRONIC RESPIRATORY QUESTIONNAIRE

Self Reported - FOLLOW UP (END OF COURSE)

You have previously completed a questionnaire telling us about how you have been feeling and how your lung disease has affected your life. This is a follow-up questionnaire designed to find out how you have been getting on since then.

NAME_____

DATE_____

We asked you previously to identify the five most important activities in your life which were limited by shortness of breath. Listed below is the list of activities which you selected. Please could you tell us how short of breath you have been in the last two weeks while performing each activity by ticking the box which best describes how you feel.

HOW SHORT OF BREATH HAVE YOU BEEN DURING THE LAST TWO WEEKS WHILE PERFORMING THESE ACTIVITIES?

	Extremely short of breath	Very short of breath	Quite short of breath	Moderate shortness of breath	Some shortness of breath	A little shortness of breath	Not at all short of breath
1							
2							
3							
4							
5							

6. In general, how much of the time during the last 2 weeks have you felt frustrated or impatient?
Please indicate how often during the last 2 weeks you have felt frustrated or impatient by ticking one of the following options from the list below.

1. ALL OF THE TIME ☐
2. MOST OF THE TIME ☐
3. A GOOD BIT OF THE TIME ☐
4. SOME OF THE TIME ☐
5. A LITTLE OF THE TIME ☐
6. HARDLY ANY OF THE TIME ☐
7. NONE OF THE TIME ☐

7. How often during the past 2 weeks did you have a feeling of fear or panic when you had difficulty getting your breath?
Please indicate how often you had a feeling of fear or panic when you had difficulty getting your breath by ticking one of the following options from the list below.

1. ALL OF THE TIME ☐
2. MOST OF THE TIME ☐
3. A GOOD BIT OF THE TIME ☐
4. SOME OF THE TIME ☐
5. A LITTLE OF THE TIME ☐
6. HARDLY ANY OF THE TIME ☐
7. NONE OF THE TIME ☐

8. What about fatigue? How tired have you felt over the last 2 weeks?
Please indicate how tired you have felt over the last 2 weeks by ticking one of the following options from the list below.

1. EXTREMELY TIRED ☐
2. VERY TIRED ☐
3. QUITE A BIT OF TIREDNESS ☐
4. MODERATELY TIRED ☐
5. SOMEWHAT TIRED ☐
6. A LITTLE TIRED ☐
7. NOT AT ALL TIRED ☐

9. How often during the last 2 weeks have you felt embarrassed by your coughing or heavy breathing?
Please indicate how much of the time you felt embarrassed by your coughing or heavy breathing by ticking one of the following options from the list below.

1. ALL OF THE TIME ☐
2. MOST OF THE TIME ☐
3. A GOOD BIT OF THE TIME ☐
4. SOME OF THE TIME ☐
5. A LITTLE OF THE TIME ☐
6. HARDLY ANY OF THE TIME ☐
7. NONE OF THE TIME ☐

10. In the last 2 weeks, how much of the time did you feel very confident and sure that you could deal with your illness?
Please indicate how much of the time you felt very confident and sure that you could deal with your illness by ticking one of the following options from the list below.

1. NONE OF THE TIME ☐
2. A LITTLE OF THE TIME ☐
3. SOME OF THE TIME ☐
4. A GOOD BIT OF THE TIME ☐
5. MOST OF THE TIME ☐
6. ALMOST ALL OF THE TIME ☐
7. ALL OF THE TIME ☐

11. How much energy have you had in the last 2 weeks?
Please indicate how much energy you have had by ticking one of the following options from the list below.

1. NO ENERGY AT ALL ☐
2. A LITTLE ENERGY ☐
3. SOME ENERGY ☐
4. MODERATELY ENERGETIC ☐
5. QUITE A BIT OF ENERGY ☐
6. VERY ENERGETIC ☐
7. FULL OF ENERGY ☐

12. In general, how much of the time did you feel upset, worried or depressed during the past 2 weeks?
Please indicate how much of the time you felt upset, worried or depressed during the past 2 weeks by ticking one of the following options from the list below.

1. ALL OF THE TIME ☐
2. MOST OF THE TIME ☐
3. A GOOD BIT OF THE TIME ☐
4. SOME OF THE TIME ☐
5. A LITTLE OF THE TIME ☐
6. HARDLY ANY OF THE TIME ☐
7. NONE OF THE TIME ☐

13. How often during the last 2 weeks did you feel you had complete control of your breathing problems?
Please indicate how often you felt you had complete control of your breathing problems by ticking one of the following options from the list below.

1. NONE OF THE TIME ☐
2. A LITTLE OF THE TIME ☐
3. SOME OF THE TIME ☐
4. A GOOD BIT OF THE TIME ☐
5. MOST OF THE TIME ☐
6. ALMOST ALL OF THE TIME ☐
7. ALL OF THE TIME ☐

14. How much of the time during the last 2 weeks did you feel relaxed and free of tension?
Please indicate how much of the time you felt relaxed and free of tension by ticking one of the following options from the list below.

1. NONE OF THE TIME ☐
2. A LITTLE OF THE TIME ☐
3. SOME OF THE TIME ☐
4. A GOOD BIT OF THE TIME ☐
5. MOST OF THE TIME ☐
6. ALMOST ALL OF THE TIME ☐
7. ALL OF THE TIME ☐

15. How often during the last 2 weeks have you felt low in energy?
Please indicate how often during the last 2 weeks you have felt low in energy by ticking one of the following options from the list below.

1. ALL OF THE TIME ☐
2. MOST OF THE TIME ☐
3. A GOOD BIT OF THE TIME ☐
4. SOME OF THE TIME ☐
5. A LITTLE OF THE TIME ☐
6. HARDLY ANY OF THE TIME ☐
7. NONE OF THE TIME ☐

16. In general, how often during the last 2 weeks have you felt discouraged or down in the dumps?
Please indicate how often during the last 2 weeks you felt discouraged or down in the dumps by ticking one of the following options from the list below.

1. ALL OF THE TIME ☐
2. MOST OF THE TIME ☐
3. A GOOD BIT OF THE TIME ☐
4. SOME OF THE TIME ☐
5. A LITTLE OF THE TIME ☐
6. HARDLY ANY OF THE TIME ☐
7. NONE OF THE TIME ☐

17. How often during the last 2 weeks have you felt worn out or sluggish?
Please indicate how much of the time you felt worn out or sluggish by ticking one of the following options from the list below.

1. ALL OF THE TIME ☐
2. MOST OF THE TIME ☐
3. A GOOD BIT OF THE TIME ☐
4. SOME OF THE TIME ☐
5. A LITTLE OF THE TIME ☐
6. HARDLY ANY OF THE TIME ☐
7. NONE OF THE TIME ☐

18. How happy, satisfied or pleased have you been with your personal life during the last 2 weeks?
Please indicate how happy, satisfied or pleased you have been by ticking one of the following options from the list below.

1. VERY DISSATISFIED, UNHAPPY MOST OF THE TIME ☐
2. GENERALLY DISSATISFIED, UNHAPPY ☐
3. SOMEWHAT DISSATISFIED, UNHAPPY ☐
4. GENERALLY SATISFIED, PLEASED ☐
5. HAPPY MOST OF THE TIME ☐
6. VERY HAPPY MOST OF THE TIME ☐
7. EXTREMELY HAPPY, COULD NOT HAVE BEEN MORE SATISFIED OR PLEASED ☐

19. How often during the last 2 weeks did you feel upset or scared when you had difficulty getting your breath?
Please indicate how often during the past 2 weeks you felt upset or scared when you had difficulty getting your breath by ticking one of the following options from the list below.

1. ALL OF THE TIME ☐
2. MOST OF THE TIME ☐
3. A GOOD BIT OF THE TIME ☐
4. SOME OF THE TIME ☐
5. A LITTLE OF THE TIME ☐
6. HARDLY ANY OF THE TIME ☐
7. NONE OF THE TIME ☐

20. In general how often during the last 2 weeks have you felt restless, tense or uptight?
Please indicate how often you have felt restless, tense or uptight by ticking one of the following options from the list below.

1. ALL OF THE TIME ☐
2. MOST OF THE TIME ☐
3. A GOOD BIT OF THE TIME ☐
4. SOME OF THE TIME ☐
5. A LITTLE OF THE TIME ☐
6. HARDLY ANY OF THE TIME ☐
7. NONE OF THE TIME ☐

Thank you very much for taking the time to complete this questionnaire.

FOR PR TEAM:

D	1 to 5	
F	8, 11, 15, 17	
E	6, 9, 12, 14, 16, 18, 20	
M	7, 10, 13, 19	

SCORED BY:
DATE: