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**PHYSICAL ACTIVITY COUNSELLING
ALONGSIDE PULMONARY
REHABILITATION IN PATIENTS WITH
COPD**

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PhD

2021

**PHYSICAL ACTIVITY COUNSELLING
ALONGSIDE PULMONARY
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COPD**

MATTHEW GEORGE ARMSTRONG

A thesis submitted in partial fulfilment of the requirements of the
University of Northumbria at Newcastle for the degree of Doctor of
Philosophy

Research undertaken in the Faculty of Health and Life Sciences,
Department of Sport, Exercise and Rehabilitation and in collaboration
with Newcastle Upon Tyne NHS Foundation Trust

2021

ABSTRACT

Background: In patients with Chronic Obstructive Pulmonary Disease (COPD) daily physical activity (PA) levels are significantly lower than in healthy age-matched individuals. PA counselling has been employed to address the complex behaviour of PA and was shown via a systematic review and meta-analysis to be effective in improving daily PA levels (steps/day) both as a standalone intervention and alongside pulmonary rehabilitation (PR). However, in patients reporting low baseline levels of PA (≤ 4000 steps/day), PA counselling alongside PR did not induce clinically important improvements in daily PA levels. A plausible reason involves the concept of a “low functional reserve”, indicating that these patients are less likely to become more physically active within their functional limits.

Objectives: 1) to perform a systematic review and meta-analysis on PA counselling as a standalone intervention and alongside PR in COPD, 2) to determine the criterion validity and test-retest reliability of a commercially available pedometer used by COPD patients to self-monitor and report daily PA levels, 3) to evaluate daily PA levels, muscle function, anxiety and depression in patients with COPD living in the North East of England in comparison to healthy age-matched individuals from the same region in a cross sectional study design, and 4) to investigate the feasibility, acceptability and efficacy of combining PR, designed to improve exercise capacity, with comprehensive PA behavioural modification interventions, designed to translate PR-induced improvements in exercise capacity into improved daily PA, in COPD patients with low baseline PA levels. .

Methods: To accomplish the latter objective a prospective, single centre, two parallel-group, RCT, compared the efficacy of a PR programme combined with PA behavioural modification interventions (PR+PA: incorporating motivational interviewing, face-to-face twice weekly goal setting, step count monitoring and feedback) to a PR programme alone in 48 patients with

COPD (FEV₁: 49±19 % predicted) exhibiting low baseline exercise capacity (6MWT: 289±85m) and daily PA levels (3293±2000 steps/day). In both groups (PR+PA and PA alone) patients with profound anxiety and depression (≥8 HADS score) received sessions of Cognitive Behavioural Therapy (CBT) by a specialist respiratory nurse.

Results: Compared to PR alone, PR+PA induced clinically important improvements in both PA levels (by 1016 steps/day; 95% CI 556 to 1474 steps/day, $p = 0.001$) and patients' PA experiences (by 7 points; 95% CI 4 to 11 points, $p= 0.001$) that were assessed by the European Medicines Agency qualified Clinical PROactive Physical Activity in COPD instrument (C-PPAC). Importantly, both groups reported clinically important improvements in the 6MWT (≥ 30 m) and CAT questionnaire (≥ -2 points), however improvements in upper and lower muscle strength were significantly greater in the PR+PA compared to PR group.

These findings were supported by evidence of adequate PR completion rates (80%) and high patient acceptability of the PA behavioural modification interventions, with 75% of patients indicating that they “liked taking part in the intervention a lot”, and 58% of patients claiming that the intervention “helped them a lot” regarding completing more PA outside of PR. Furthermore, patient adherence to the components of the behavioural modification interventions was high, including the weekly use of the pedometer (6.6±0.2 days) and interaction with the PA diary (93±17%) to self-monitor and report daily step counts.

Conclusions: The findings suggest that in COPD patients with low baseline exercise capacity and daily PA levels, improvements in exercise capacity following completion of a standard PR programme may translate into clinically important improvements in daily PA levels only when tailored PA behavioural modification interventions are added to PR. In addition, PA behavioural modification interventions were proven to be feasible to incorporate into a standard PR programme and were well accepted by patients with COPD.

PUBLICATIONS & CONFERENCE PROCEEDINGS ARISING FROM THIS THESIS

PUBLICATIONS

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TABLE OF ABBREVIATIONS

AATD	Alpha-1 Antitrypsin Deficiency
ATS	American Thoracic Society
BMI	Body Mass Index
CAT	COPD Assessment Test
CBT	Cognitive Behavioural Therapy
CCQ	Clinical COPD Questionnaire
CINAHL	Cumulative Index to Nursing and Allied Health Literature
COPD	Chronic Obstructive Pulmonary Disease
CPET	Cardiopulmonary Exercise Test
C-PPAC	Clinical PROactive Physical Activity in COPD Instrument
CV	Coefficient of Variance
D-PPAC	Daily PROactive Physical Activity in COPD Instrument
ERS	European Respiratory Society
ESWT	Endurance Shuttle Walk Test
EU-IMI	European Union Innovative Medicines initiative
FEV1	Forced Expiratory Volume in 1 Second
FVC	Forced Vital Capacity
GDPR	General Data Protection Regulations
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HADS	Hospital Anxiety and Depression Scale
HG	Hand Grip
HRA	Health Research Authority
ICC	Intraclass correlation coefficient
IRAS	Integrated Research Application System
LOA	Limits of Agreement

ISWT	Incremental Shuttle Walk Test
MID	Minimal Important Difference
MRC	Medical Research Council
MVPA	Moderate Vigorous Physical Activity
NuTH	Newcastle upon Tyne Hospital Foundation NHS Trust
PA	Physical Activity
PICOS	Participants, Intervention, Control, Outcomes, Study design
PR	Pulmonary Rehabilitation
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
QMVC	Quadriceps Maximal Voluntary Contraction
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
R&D	Research & Development
RVI	Royal Victoria Infirmary
SMD	Standard Mean Difference
SPO₂	Oxygen Saturation
SPSS	Statistical Package for Social Sciences
STS	Sit to Stand
V_{O₂}	Oxygen Uptake
WHO	World Health Organisation
6MWT	Six Minute Walk Test

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DECLARATION OF ORIGINALITY

Author's Declaration

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

Any ethical clearance for the research presented in this thesis has been approved.

Approval has been sought and granted by the Faculty of Health and Life Sciences Ethics committee (ref: 12928) for each study and from the Health Research Authority (ref: 248697 & 18/YH/0376; Appendix 4d & 4e).

I declare that the word count of this thesis is 48966 words

Name: Matthew Armstrong

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Date: 29th March 2021

CHAPTER 1

Chapter 1: Introduction

CHAPTER 1: INTRODUCTION

1.1 Background

Chronic Obstructive Pulmonary Disease (COPD) is a debilitating and progressive disease, primarily affecting the respiratory system (Global Initiative for Chronic Obstructive Lung Disease, 2021). In many patients, it may also have adverse extra-pulmonary effects, such as skeletal muscle dysfunction and weakness (Cooper, 2009). Combined, the pulmonary and skeletal muscle abnormalities exacerbate exercise-associated symptoms such as breathlessness and leg discomfort (O'Donnell & Gebke, 2014; Troosters et al., 2013). These symptoms make every day physical activity (PA) an unpleasant experience, which patients actively try to avoid (Pitta et al., 2005b; Troosters et al., 2010; Watz, Waschki, Meyer, & Magnussen, 2009). These recurring factors, alongside a depressive mood and associated fear factor, deteriorate patients physical state and increase the intensity of breathlessness. Thus, patients are forced into a vicious cycle of inactivity and worsening symptoms (Cooper, 2009; Shrikrishna et al., 2012; Troosters et al., 2013).

PA levels are therefore remarkably lower in patients with COPD than healthy age-matched individuals, associated with poor outcomes, including an increased risk of hospitalisation and mortality in these patients (Garcia-Aymerich, Lange, Benet, Schnohr, & Antó, 2006; Garcia-Aymerich et al., 2009; Garcia-Rio et al., 2012; Vaes et al., 2014; Waschki et al., 2011). Implementation of exercise training as part of Pulmonary Rehabilitation (PR) is an integral non-pharmacological component in COPD management that aims to reverse the systemic consequences of COPD (Bolton et al., 2013; Spruit et al., 2013). Currently PR programmes have shown substantial improvements in exercise capacity and health status; however, these findings have not consistently progressed into improvements in daily PA due to PA in COPD being a complex health behaviour (Cindy Ng, Mackney, Jenkins, & Hill, 2012; Spruit, Pitta, McAuley, ZuWallack, & Nici, 2015; Troosters et al., 2013; Watz et al., 2014).

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PA behavioural modification interventions, including the identification of barriers, goal setting, self-efficacy, motivation, self-monitoring and feedback, aim to impact upon the vicious cycle of inactivity in COPD (de Blok et al., 2006). Patients receive such interventions in order to modify their behaviour towards enhanced PA through the application of a pedometer, which allows patient monitoring and feedback of their daily steps along with frequently adjusted goal setting (Mantoani, Rubio, McKinstry, MacNee, & Rabinovich, 2016). Previous research has shown that PA counselling, a behavioural modification intervention, as a standalone intervention and alongside PR provided inconsistent improvements in steps/day in COPD, primarily due to diverse trial designs (Burge, Cox, Abramson, & Holland, 2020; Lahham, McDonald, & Holland, 2016; Mantoani et al., 2016). As a result, more research is needed to interpret the reasons for these inconsistencies and provide novel approaches that can promote effective and reliable improvements in PA.

Alongside the physical barriers influencing daily PA, the distressing nature of COPD has a significant impact on patients' psychological wellbeing, with major focusing points including the sense of feeling unwell, the inability to perform everyday activities and the emotional consequences of the condition (Pumar et al., 2014; Yohannes & Alexopoulos, 2014). These thoughts can often promote anxiety and depression, which are prevalent in patients with COPD and are associated with reduced PA and poorer treatment outcomes (Ng et al., 2007; Pumar et al., 2014; Tabak, Brusse-Keizer, van der Valk, Hermens, & Vollenbroek-Hutten, 2014). Cognitive behavioural therapy (CBT) is a psychological approach that focuses on understanding how experiences are interpreted, providing an interaction between thoughts, mood, behaviour and physical sensation (Heslop-Marshall et al., 2018). CBT has been shown to be effective in reducing elevated levels of anxiety and depression (Heslop-Marshall et al., 2018). However, it is yet to be investigated whether CBT incorporated into PR and PA

CHAPTER 1: INTRODUCTION

behavioural modification interventions can provide a combined approach to positively impact upon PA in patients with profound anxiety and depression.

CHAPTER 2

Chapter 2: Literature Review

CHAPTER 2: LITERATURE REVIEW

2.1 What is COPD?

COPD is a common, preventable and treatable disease that is characterised by persistent respiratory symptoms and airflow limitation that is due to airways and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases (Global Initiative for Chronic Obstructive Lung Disease, 2021).

2.2 Aetiology

COPD is primarily caused by long-term exposure to cigarette smoking, however exposure to biomass fuels, workplace dust and fumes exposure, history of respiratory-tract infections during childhood, chronic asthma and a history of pulmonary tuberculosis may influence or further cause COPD prevalence (Global Initiative for Chronic Obstructive Lung Disease, 2021; National Clinical Guideline, 2010).

2.2.1 *Cigarette smoking*

The most common cause of COPD is long-term exposure to tobacco smoking, with the majority of patients in primarily high-income countries reporting a history of tobacco exposure on diagnosis of COPD (Global Initiative for Chronic Obstructive Lung Disease, 2021). It is reasoned that tobacco smoking is responsible for nine in every ten cases, demonstrating an effective relationship between tobacco smoke exposure and a higher risk of developing COPD. Furthermore, COPD severity, based on a decline in Forced Expiratory Volume in 1 second (FEV₁), is related to a greater smoking history (Global Initiative for Chronic Obstructive Lung Disease, 2021). In addition, the inhalation of cigarette smoke through passive means, where non-smokers are exposed to cigarette smoke (passive smoking), can significantly increase the risk of developing COPD (Yin et al., 2007).

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2.2.2 Genetics

It has been shown that smokers with a family history of severe COPD are at an increased risk of airflow limitation and COPD development (Global Initiative for Chronic Obstructive Lung Disease, 2021). Alpha-1 antitrypsin deficiency (AATD) is a genetic disorder causing a reduction in the production of alpha 1-antitrypsin due to a mutation in the SERPINA1 gene on chromosome 14 (Chapman, Robinson, Stradling, West, & Wrightson, 2014; Thun et al., 2013). Those with AATD who are exposed to cigarette smoking or occupational exposures may have an increased likelihood of developing COPD (Global Initiative for Chronic Obstructive Lung Disease, 2021).

2.2.3 Occupational exposure and air pollution

The development of COPD from occupational exposures, including organic and inorganic dusts, fumes and chemical agents, are an under-appreciated risk factor for developing COPD (Eisner et al., 2010; Paulin et al., 2015). For example, a population-based study found several occupations including sculptors, gardeners and warehouse workers were at greater risk of developing COPD among never-smokers and never-asthmatics (De Matteis et al., 2019). Furthermore, a cross-sectional observational study highlighted that self-reported exposure to workplace dust and fumes was associated with increased airflow limitation, respiratory symptoms, emphysema and gas trapping, in both men and woman assessed by computed tomography scans (Marchetti et al., 2014).

Exposure to urban air pollution is extremely harmful to individuals with pre-existing lung disease, however its role as a risk factor for COPD remains unclear. One thing that is clear is that it appears to have a relatively small role compared to the role of cigarette smoking in the development of COPD (Eisner et al., 2010).

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2.2.4 Age and gender

COPD is well known to be more prevalent in the elderly population, however it is not clear whether age should be considered a risk factor for developing COPD or whether the long-term exposure to causative agents is to blame (Global Initiative for Chronic Obstructive Lung Disease, 2021). Previously, COPD prevalence and mortality rates were much greater among men than woman, although recent data from developing countries has begun reporting an almost equal prevalence of COPD in men and woman, which probably reflects the changing patterns of tobacco smoking in developing countries (Barnes, 2016; Landis et al., 2014).

2.2.5 Asthma

It remains unclear whether asthma plays a part in the development of chronic airflow limitation and COPD. An early report from a longitudinal cohort found that adults with asthma had a 12 fold higher risk of acquiring COPD over time compared to adults without asthma, following adjustment for smoking (Silva, Sherrill, Guerra, & Barbee, 2004). Around the same time, another longitudinal study of people with asthma found the development of irreversible airflow limitation and reduced transfer coefficient in around 20% of subjects (Vonk et al., 2003). In 2018, a meta-analysis documented that individuals reporting a history of asthma (childhood or adult onset asthma) were 7.2 times more likely to develop COPD (Asamoah-Boaheng et al., 2018).

2.3 Pathogenesis

The long-term exposure and inhalation of cigarette smoke and other noxious particles, such as biomass fuels and workplace exposures to dust and fumes, causes pathological changes in the airways, lung parenchyma and pulmonary vasculature (Hogg & Timens, 2009). Pathological changes characteristic of COPD includes chronic inflammation and structural changes due to

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repeated injury and repair of the lungs (Global Initiative for Chronic Obstructive Lung Disease, 2021). Lung inflammation is a common response that appears to be modified in patients who go on to develop COPD. This modified response “chronic inflammation” may induce parenchymal tissue destruction (Emphysema), mucous hypersecretion (Chronic Bronchitis) and disruption of the normal repair and defense mechanisms within the small airways, causing small airways inflammation and fibrosis (Bronchiolitis) (Global Initiative for Chronic Obstructive Lung Disease, 2021; Tudor & Petrache, 2012). These pathological changes do not always occur together and the relative contributions of which vary from person to person (Global Initiative for Chronic Obstructive Lung Disease, 2021).

The consequences of these pathological changes include a decline in lung elastic recoil, increased lung compliance, increased resistance to airflow in the small conducting airways, air trapping and progressive airflow obstruction. (Global Initiative for Chronic Obstructive Lung Disease, 2021).

Commonly, disease severity is associated with greater inflammatory and structural changes in the airways and continues following smoking cessation (Global Initiative for Chronic Obstructive Lung Disease, 2021). Alongside inflammation, both an imbalance between proteases and antiproteases (Stockley, 1999) as well as an imbalance between oxidants and antioxidants (Domej, Oettl, & Renner, 2014) within the lungs can impact the pathogenesis of COPD.

2.4 Prevalence and Incidence

The World Health Organisation (WHO) reported approximately 251 million cases of COPD worldwide in 2016 (World Health Organisation, 2017), with a prevalence varying between 1% and 4% of the overall population (Global Initiative for Chronic Obstructive Lung Disease,

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2021). In the UK, around 1.2 million people are diagnosed with COPD, with many more people living with undiagnosed COPD (British Lung Foundation, 2020).

In many countries, the prevalence of COPD has continued to increase in the latter part of the last century (Hurd, 2000), although recent data has begun reporting a stabilisation of COPD prevalence in several developed countries (Ford et al., 2013; Soriano et al., 2010; Vasankari et al., 2010). However, with an increased prevalence of smokers in developing countries, and an aging population in high-income countries, the overall prevalence of COPD is expected to rise over the next 40 years (Soriano et al., 2010).

In most developed countries, studies have demonstrated a greater prevalence in men than in woman, which is likely a result of historical smoking patterns (Gershon, Wang, Wilton, Raut, & To, 2010; Rosenberg, Kalhan, & Mannino, 2015). In addition, a greater prevalence of COPD was reported in older individuals, particularly over the age of 75 years old (Rosenberg et al., 2015). This relates to the knowledge that COPD is associated with aging and longer exposure to noxious particles and gases, as detailed earlier (Mercado, Ito, & Barnes, 2015).

2.5 Economic Burden

COPD is associated with significant economic burden which has a substantial impact on worldwide health care systems, with COPD treatment costing around \$2.1 trillion per annum (Global Initiative for Chronic Obstructive Lung Disease, 2021). The three most important factors that determine the level of economic and societal costs for COPD patients are disease severity, presence of comorbidities and exacerbations of disease (Mannino & Buist, 2007).

Specifically, in the UK, the annual cost of COPD is around £1.9 billion, with around 140,000 hospital admissions and one million bed days annually (British Lung Foundation, 2019). As a result, COPD is increasing the burden on the NHS, making research into COPD management essential.

2.6 Diagnosis and classification of COPD

To fully diagnose and understand the extent and/or severity of COPD, spirometry after the intake of bronchodilators is required and confirmed with post-bronchodilator FEV₁/Forced Vital Capacity (FVC) < 0.70 alongside the observation of relevant symptoms (dyspnea, sputum production or chronic cough) and a history of exposure to risk factors for the disease (i.e. tobacco smoking). The severity of COPD can be established using the Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages of COPD, outlined in Table 1 (Global Initiative for Chronic Obstructive Lung Disease, 2021).

Table 1. GOLD guidelines for COPD severity

COPD GOLD Stage	Severity of airflow obstruction	FEV ₁ (% predicted)
I	Mild airflow limitation	FEV ₁ ≥ 80%
II	Moderate airflow limitation	50% ≤ FEV ₁ < 80%
III	Severe airflow limitation	30% ≤ FEV ₁ < 50%
IV	Very severe airflow limitation	FEV ₁ < 30% or < 50% with respiratory failure

Abbreviations: GOLD: Global Initiative for Chronic Obstructive Lung Disease, FEV₁: Forced Expiratory Volume in one second.

2.7 Impact on mortality

Increasing evidence is available to suggest that COPD increases the risk of mortality across the general population and is one of the four main causes of death, with a recorded mortality of 3.2 million in 2015, equating to 5% of all deaths globally in that year (World Health Organisation, 2017). In this context, it is expected that COPD will become the third leading cause of death,

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with projections of up to 4.5 million deaths annually by 2030 (Global Initiative for Chronic Obstructive Lung Disease, 2021; May & Li, 2015). This increase in mortality has mainly been caused by a greater prevalence of smoking, reduced mortality from other common causes of death and the aging population in high-income countries (Global Initiative for Chronic Obstructive Lung Disease, 2021). The WHO suggests that respiratory death rates in the UK are almost double than the European Union average. Specifically, the UK ranked 12th for the number of COPD deaths per million per year between 2001-2010, with 29,776 people dying from COPD in 2012. Of these, 15,245 were males and 14,531 were females (British Lung Foundation, 2020).

2.8 COPD symptoms

Breathlessness is the hallmark symptom of COPD, alongside chronic cough, sputum production, wheeze and chest tightness (Global Initiative for Chronic Obstructive Lung Disease, 2021). In addition, many patients experience additional systemic features such as exertional fatigue, weight loss and skeletal muscle dysfunction and wasting (Global Initiative for Chronic Obstructive Lung Disease, 2021). The burden of these symptoms has a substantial detrimental impact on quality of life, health status and daily physical activities, and contributes to elevated levels of anxiety and depression, increased exacerbation risk and a worse disease prognosis (Doyle et al., 2013; Katajisto et al., 2012; Miravittles & Ribera, 2017; Tsiligianni, Kocks, Tzanakis, Siafakas, & van der Molen, 2011).

2.9 COPD symptoms and physical inactivity

Both clinical and functional determinants of COPD (including dyspnea, quality of life and exercise capacity) are consistently associated with physical inactivity (Gimeno-Santos et al., 2014), with symptoms found to have a negative impact on patients' levels of PA, irrespective

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of the time of day (Miravittles et al., 2014). Patients commonly perceive that symptoms cause a substantial limitation on their abilities to perform activities of daily living and can often impair sleep (Kessler et al., 2011).

Interestingly, patients have reported that the worst time for symptoms were during the morning, with both cough and sputum production reported as the most troublesome symptoms (van Buul, Kasteleyn, Chavannes, & Taube, 2017). Morning COPD symptoms are considered to be a key barrier towards performing daily physical activities, with a systematic review reporting that 37-91% of COPD patients experienced PA limitations associated with morning symptoms (van Buul et al., 2017). A range of daily activities including 'going shopping' and 'taking part in hobbies and sport' as well as morning chores (i.e., 'getting up', 'showering and dressing'), were cited by patients as key functional areas that were impacted by morning symptoms of COPD (Kessler et al., 2011; van Buul et al., 2017). Furthermore, it was noted that many routine activities took on average 10 minutes longer to complete compared to before morning symptoms occurred (van Buul et al., 2017). Some patients reported having to request assistance to successfully complete several daily activities, due to increased levels of impaired daily functioning. Therefore, many perceived themselves as a burden to others, and instead of seeking support, chose to avoid those daily activities (Kessler et al., 2011; van Buul et al., 2017).

Patients with COPD tend to reduce PA levels early in the disease progression to avoid elevated symptoms of dyspnea (Troosters et al., 2010; Watz et al., 2009). A reduction in levels of PA has been associated with limb muscle deconditioning, primarily found in the quadriceps muscles (Maltais et al., 2014). This is typically caused by muscle fiber atrophy and a shift in quadriceps fiber type distribution, from type I to type IIX fibers, a typical feature of advanced COPD (Caron, Debigaré, Dekhuijzen, & Maltais, 2009; Gosker, Zeegers, Wouters, & Schols, 2007; Kim, Mofarrahi, & Hussain, 2008; Whittom et al., 1998). Capillary density and the number of

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capillaries per muscle fiber are often diminished in the limb muscles of patients with COPD. Furthermore, mitochondrial functionality is altered and oxidative capacity within COPD limb muscles is reduced, consistent with the type I to type IIx fiber type shift (Gosker et al., 2007; Whittom et al., 1998). Based on the elevated symptoms of dyspnea and muscle deconditioning as a result of the above pathophysiological changes, patients are forced into a vicious cycle of inactivity (Figure 1) (Troosters et al., 2013).

The vicious cycle of inactivity is a widely accepted theory regarding the mechanisms of physical inactivity in patients with COPD, acknowledged by Troosters et al. (2013). Within this model, it is suggested that symptoms of both dyspnea and leg discomfort, that are associated with physical inactivity, are a result of both skeletal muscle wasting and airway remodelling that limit airflow and increase the requirements for minute ventilation. An increased severity of COPD brings a greater prevalence of symptoms, making conducting activities of daily living an unpleasant experience, creating fear of performing such activities. The associated fear factor naturally inclines those individuals to become more sedentary and depressed, subsequently causing an inactive lifestyle. This inactive lifestyle may further reduce cardiovascular function and promote skeletal muscle deconditioning, as well as deteriorating people's physical state and increasing the frequency of breathlessness.

As a result, patients are forced into a more sedentary lifestyle, creating a vicious cycle of inactivity and worsening symptoms (Troosters et al., 2013).

This cycle of inactivity is likely aggravated by acute COPD exacerbations. In an early study by Donaldson, Wilkinson, Hurst, Perera, and Wedzicha (2005), they found that time spent outdoors prior to an exacerbation and 5 weeks following the exacerbation were significantly reduced. Following admission to hospital with an acute exacerbation, PA levels dropped and failed to recover after a one month follow up. In addition, at one month, levels of PA were much lower in patients post exacerbation than in stable outpatients with equally severe COPD

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(Pitta et al., 2006b). Inevitably, muscle strength decreased in the first week of hospital admission following an exacerbation and was associated with the degree of immobility reported (Pitta et al., 2006b). Following the work of Donaldson et al. (2005), extensive research has been published regarding the influence of exacerbations on levels of PA in patients with COPD (Alahmari et al., 2016; Alahmari et al., 2014; Albarrati, Gale, Munnery, Cockcroft, & Shale, 2020; Crook et al., 2018; Demeyer et al., 2018; Ehsan et al., 2013; Pitta et al., 2006b). An acute reduction in PA at the onset of an exacerbation has been reported in exacerbations requiring both admission to hospital (Pitta et al., 2006b) and ambulatory treatment (Alahmari et al., 2014; Ehsan et al., 2013). Interestingly, sustained reductions in PA have been shown 1 month after hospital discharge following exacerbations (Pitta et al., 2006b) whereas following a community-treated exacerbation, PA levels almost returned to stable levels (Ehsan et al., 2013). A recently published research letter from (Demeyer et al., 2018) found that both moderate and severe exacerbations accelerated physical inactivity in COPD patients. Specifically, they detailed that the number of exacerbations experienced by patients was related to the decline in step count, with a mean change of 251, -144 and -797 steps/day observed in patients who presented no, one or two or more exacerbations, respectively (Demeyer et al., 2018). Furthermore, patients experiencing at least one severe exacerbation or two or more moderate exacerbations presented a larger decline in PA than those with no exacerbations (Demeyer et al., 2018).

Several hypotheses may explain the decrease in PA levels following exacerbations. Firstly, the decline may be a consequence of a loss in exercise capacity, although data from Demeyer et al. (2018) failed to demonstrate an association between changes in exercise capacity and exacerbations. Secondly, a more plausible hypothesis may be based on a worsening of symptoms during an exacerbation leading to increased inactivity, associated with the vicious cycle of symptoms and inactivity detailed earlier (Troosters et al., 2013). An explanatory

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et al., 2004). Importantly, several studies have consistently demonstrated that higher levels of PA and cardiorespiratory fitness are associated with lower all-cause and cardiovascular mortality in healthy individuals (Blair et al., 1989; McKinney et al., 2016; Myers et al., 2004) and can reduce disabilities (Berk, Hubert, & Fries, 2006; Shah, Buchman, Leurgans, Boyle, & Bennett, 2012; Warburton, Nicol, & Bredin, 2006) and the risk of falling in the older population (Chan et al., 2007; Graafmans, Lips, Wijnhuizen, Pluijm, & Bouter, 2003; Heesch, Byles, & Brown, 2008). Furthermore, regular PA is associated with improved health outcomes in relation to the prevention of several chronic diseases including cardiovascular disease, diabetes and several types of cancer (Warburton et al., 2006)

To remain physically active and sustain a healthy level of cardiorespiratory fitness, healthy adults aged 18-64 years are recommended to complete at least 150-300 minutes of moderate-intensity aerobic PA, or at least 75-150 minutes of vigorous-intensity aerobic PA (World Health Organization, 2020). Furthermore, all adults should include muscle-strengthening activities at moderate or greater intensity on 2 or more days, to facilitate greater health benefits (World Health Organization, 2020) Worryingly, even with these recommendations and the clear benefits of regular participation in PA, global estimates show that only one in four (27.5%) adults (World Health Organization, 2020) and more than three-quarters (81%) of adolescents (World Health Organization, 2020) do not meet the WHO recommendations.

2.11 COPD and physical inactivity

Based on the symptoms of COPD and the associated mechanisms that influence patients' abilities to undertake PA, knowledge regarding physical inactivity in patients with COPD has been extensively covered. This research began to accelerate following the early work of Schonhofer, Ardes, Geibel, Kohler, and Jones (1997), who assessed the feasibility of simple activity monitors to detect daily PA levels. Schonhofer et al. (1997) demonstrated that it was

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possible to obtain repeatable measurements of daily activities in patients with severe lung disease using a simple activity monitor. Based on this data, they documented that patients suffering from chronic lung disease's such as COPD, experienced significant reductions in daily movement compared to the average level in age and sex matched healthy individuals (Schonhofer et al., 1997).

Following these findings, research has continued to demonstrate that COPD patients conduct significantly lower quantities of PA on a daily basis than their healthy age-matched counterparts, with many also indicating reductions in movement intensity and time spent in moderate to vigorous PA (MVPA). (Hernandes et al., 2009; Pitta et al., 2005b; Singh & Morgan, 2001; Troosters et al., 2010; Vorrink, Kort, Troosters, & Lammers, 2011; Walker, Burnett, Flavahan, & Calverley, 2008; Waschki et al., 2012; Watz et al., 2009).

A detailed examination of PA in patients with COPD was undertaken by (Pitta et al., 2005b), using a validated triaxial accelerometer (DynaPort Activity Monitor; McRoberts BV) in 50 COPD patients (FEV₁%pred 43) and 25 healthy age-matched controls. Authors reported significant reductions in movement intensity; (1.8 vs 2.4 m/s²), standing time (191 vs 295 min) and walking time (44 vs 81 min, all $p < 0.001$) in COPD patients compared to healthy controls, respectively (Pitta et al., 2005b). Moreover, they discovered that 30% of COPD patients were unable to meet the WHO recommendations of PA (30 minutes of moderate intensity activity) (World Health Organization, 2020) and even in those patients who achieved the recommendations, the reported average movement intensity was 17% lower than healthy controls (Pitta et al., 2005b).

Watz et al. (2009) added to this research by measuring PA in a substantial number of COPD patients, investigating both the degree of inactivity compared to a control group and the relationships between clinical characteristics and PA. They found that steps/day and minutes of at least moderate PA all decreased compared to a control group that consisted of individuals

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with normal lung function reporting early symptoms of Chronic Bronchitis (Watz et al., 2009). Interestingly, significant limitations in PA were present in patients with COPD from GOLD stages II, with the most severe levels of physical inactivity found in very severe COPD patients (GOLD stage IV) (Watz et al., 2009).

Similar findings were shown by Troosters et al. (2010), however this time research was conducted across multi-centres, with investigations regarding the extent of physical inactivity highlighted across three different regions of the world. Regardless of the region of origin, significant reductions in steps/day were found following the analysis of 70 COPD patients (FEV₁%pred 54) and 30 healthy controls (5584 vs 9372 steps/day respectively). In agreement with Watz et al. (2009), authors demonstrated a gradual reduction in both steps/day and time spent in moderate intensity PA as the severity of COPD increased (Troosters et al., 2010). Moreover, it was clear that inactivity was present early in the course of the disease, with a similar pattern shown across all centres (Troosters et al., 2010).

As well as highlighting the impact of physical inactivity in COPD patients compared to healthy controls, research has begun investigating the longitudinal impact of COPD on PA levels and the influence of geographical area on PA variation among COPD patients. Boutou et al. (2019) analysed PA data over a 12-month period, comparing the impact of geographical location and associated factors on levels of PA. Based on a cohort of 157 COPD patients living across five European cities (Athens, Edinburgh, Leuven, London, and Groningen), there were significant time effects with a decline in almost every measure of PA over 12 months. In addition, major discrepancies in baseline PA levels were found, with steps/day ranging from 3338 to 5166 across the five European cities (Boutou et al., 2019). Plausible explanations for these findings included differences in climate (i.e., daylight hours, rainfall & temperature), socio-cultural and socio-economics within the area of living (Boutou et al., 2019). On analysis, variations in climate posed the greatest influence to PA levels, with hours of rainfall providing the largest

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negative effect on average steps/day (Boutou et al., 2019). The findings of Boutou et al. (2019) provide useful insight into PA levels across a wide spectrum of COPD patients, highlighting that interventions to improve PA may need to be modified to suit changing levels of PA based on geographic location and associated factors.

2.12 Physical inactivity, hospitalisation, and survival in COPD

The overall impact of physical inactivity on COPD patients is significant in terms of its association with increased risk for hospitalisation and all-cause mortality. Several longitudinal studies have assessed the association between PA and COPD related hospital admissions or readmissions as a result of COPD exacerbations (Benzo et al., 2010; Chen & Narsavage, 2006; Garcia-Aymerich et al., 2003; Garcia-Aymerich et al., 2006; Garcia-Aymerich, Lange, Serra, Schnohr, & Antó, 2008; Garcia-Rio et al., 2012; Pitta et al., 2006b). All of the above studies reported a statistically significant association between low levels of PA and increased risk for hospitalisation (Benzo et al., 2010; Chen & Narsavage, 2006; Garcia-Aymerich et al., 2003; Garcia-Aymerich et al., 2006; Garcia-Aymerich et al., 2008; Garcia-Rio et al., 2012; Pitta et al., 2006b). Specifically Garcia-Aymerich et al. (2006), found patients reporting levels of PA greater than “low” had a lower risk of COPD related hospital admission during a 20 year follow up than those who reported very low levels of PA, after adjusting for cofounders. Similar findings were reported by Benzo et al. (2010) with self-reported time ≥ 2 hours of PA per day associated with reduced hospitalisation. However, PA was assessed via self-reported questionnaires, limiting the robustness of the data. Importantly, the majority of studies have shown that PA equivalent to walking or cycling for a duration of 2 hours per week was associated with a significant reduction in risk for hospital admission due to COPD (Benzo et al., 2010; Chen & Narsavage, 2006; Garcia-Aymerich et al., 2003; Garcia-Aymerich et al., 2006; Garcia-Aymerich et al., 2008; Garcia-Rio et al., 2012; Pitta et al., 2006b).

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Regarding the effect of physical inactivity on survival in COPD patients, three longitudinal studies have demonstrated an association between low PA levels and greater all-cause mortality, over a follow-up period of 3-12 years (Garcia-Aymerich et al., 2006; Garcia-Aymerich et al., 2011; Garcia-Rio et al., 2012). The association was consistent across various patient characteristics, methods of PA measurement and settings. It's therefore plausible that patients who remain physically active should have a better prognosis compared to those who have a significant decline in PA. Therefore, treatment strategies to improve levels of PA in patients with COPD are essential to impact upon and lower the overall risk for hospitalisation and mortality in these patients.

2.13 Capturing physical activity in COPD

Prior to investigating treatment strategies to improve PA, understanding the available tools to capture levels of PA and their feasibility, validity and accuracy in a research setting are important. Capturing PA in COPD can include several tools from self-reported questionnaires, the doubly labelled water method, direct observations, and various motion sensors including step counters and accelerometers (Watz et al., 2014).

2.13.1 Self-reported questionnaires

The use of self-reported questionnaires and diaries to quantify activities of daily living has been implemented for numerous years and are specifically tailored to present subjective data regarding PA levels (Pitta et al., 2006a; Watz et al., 2014). This approach remains the most popular form of quantifying PA and is commonly implemented in large clinical trials and epidemiological studies due to their low cost and simplicity (Pitta et al., 2006a; Watz et al., 2014). Although most self-reported approaches are cost effective and convenient, they do have drawbacks, which cannot be overlooked. For instance, relying on memory and recall of the

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individual (Washburn, Heath, & Jackson, 2000), as well as variables such as questionnaire design and characteristics of both individuals and interviewer/researcher, can often affect the reliability of the results (Pitta et al., 2006a; Pitta, Troosters, Spruit, Decramer, & Gosselink, 2005a; Watz et al., 2014). Furthermore, many individuals often request guidance from a relative, friend or healthcare practitioner, introducing significant bias. Social desirability bias is often a concern for self-reported measures, with many individuals commonly over reporting levels of PA and underestimating the time spent in sedentary activities (Watz et al., 2014).

2.13.2 Pedometers

Pedometers are small, lightweight, portable devices, containing either a horizontal spring-suspended lever arm or piezo-electric cantilevered beam which detects vertical acceleration of the hips during walking (Crouter, Schneider, & David R Bassett, 2005). Primarily these instruments measure step counts but can also provide data on walking speed and burnt calories. The data derived from a pedometer can be used to provide information on distance walked, and an estimate of energy expenditure. Pedometers are low cost and easily worn, with easy to follow step counts on a digital screen, providing a simple but effective assessment of individual step targets or recommendations (Pitta et al., 2006a; Watz et al., 2014).

Disadvantages of using pedometers do exist, including the propensity to underestimate step counts and therefore energy expenditure at slow walking speeds, which in patients with COPD is a common phenomenon (Karpman & Benzo, 2014). Many of the devices are unable to store data, requiring individuals to periodically record the output of the assessment when multiple days of measurement are desired. These limitations may hinder the accuracy of pedometer recordings in certain interventions, however as a source of motivation to support the improvement of PA levels, this low burden instrument may be the most effective approach (Armstrong et al., 2019).

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2.13.3 Accelerometers

Accelerometers are portable electronic devices worn to detect acceleration and quantify activity counts that can be analysed to provide various PA variables including, an estimate of time spent above or below a pre-specified activity level (i.e. sedentary, light, MVPA), number of daily steps/day, movement intensity and energy expenditure (Pitta et al., 2006a; Van Remoortel et al., 2012b). As a result, accelerometers have received growing interest across research settings as they provide objective data that cannot be obtained from simple pedometers or questionnaires (Watz et al., 2014).

Several factors are known to influence the outcome of accelerometers. Firstly, artificial vibrations (i.e. vehicle vibrations), can falsely elevate activity counts in some devices. With growing research and greater technology, this issue can be reduced through several filtering options and by altering the technical aspects of wearing/analysing the accelerometer (Cohen et al., 2012). Secondly, the number of valid assessment days and hours used for PA assessment are important factors to consider as they often influence the reliability of these activity monitors (Demeyer et al., 2014; Hecht, Ma, Porszasz, Casaburi, & Network, 2009; Watz et al., 2009). For instance, Sundays were found to report the lowest amount of activity counts across a 7 day week in GOLD stage I to III COPD patients (Watz et al., 2009). Former studies in healthy individuals have also found that Sundays report the least amount of PA across a 7-day week (Matthews, Ainsworth, Thompson, & Bassett, 2002; Tudor-Locke et al., 2005). Within the study of (Watz et al., 2009), it was demonstrated that the reliability of accelerometer data varied depending on disease severity and the number of days used for analysis. It was indicated that the variability of PA was higher in less severe COPD patients (GOLD stage I), with 5 days of measurement required to reliably measure PA in those patients (Watz et al., 2009). In previous studies that have cited the intra-class correlation coefficient for accelerometer measurements

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in patients with COPD, early work from Steele et al. (2000) reported an intra-class correlation coefficient of 0.69 for statistical agreement of 3 days in patients with severe COPD. Meanwhile, Pitta et al. (2005a) reported that 2 days of weekday measurements were sufficient to achieve a ≥ 0.7 intra-class correlation coefficient.

For the assessment of PA over longitudinal changes, 3-4 days were shown to be sufficient to demonstrate a treatment effect following PR in moderate-severe COPD patients, with weekends either included (Watz et al., 2009) or excluded (Demeyer et al., 2014). Further details regarding the assessment criteria implemented for PA assessment in this thesis are provided in Chapter 4.

Although accelerometers present significant benefits to capturing PA levels over both step counters and questionnaires, they certainly present several limitations. For instance, little uniformity exist between types of accelerometers, making it difficult to compare studies that implemented difference devices (Butte, Ekelund, & Westerterp, 2012). Furthermore, slow walking speeds, often documented in patients with COPD, can influence the accuracy of activity counts and impede the estimation of energy expenditure (Troosters et al., 2010; Watz et al., 2009). Finally, purchase costs vary considerably between devices, many research projects with large sample sizes report difficulties purchasing sufficient numbers of accelerometer to meet research demands (Van Remoortel et al., 2012a).

2.14 Capturing patients' experiences of physical activity

Research regarding PA in COPD primarily focuses on the frequency, intensity, duration and type of PA, quantified by means of activity monitor and/or self-reported questionnaires as detailed above (Van Remoortel et al., 2012b). However, qualitative research has continued to highlight the importance of patients experience of symptoms while conducting PA, and the impact this has on their lifestyle habits (Dobbels et al., 2014). Thus, questions are being asked

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regarding why research studies have not incorporated a means of assessing patients qualitative experiences of symptoms while conducting PA, and the impact this has on their lifestyle habits (Dobbels et al., 2014). The primary reason for a lack of input regarding patients' experiences of PA in research to date is that such patient centred concepts are not quantifiable through activity monitors or via available self-reported questionnaires.

To overcome this issue, a novel approach from the "Framework of the European Union Innovative Medicines Initiative PROactive project", namely the PROactive PA in COPD instruments (clinical and daily visit versions, C-PPAC and D-PPAC) has been constructed (Gimeno-Santos et al., 2015). In brief, the C-PPAC instrument consists of 12-items that capture both the amount and difficulty of PA, completed at the day of each study visit (i.e., pre & post), either online using an electronic device or using pen and paper, with a one-week recall (Gimeno-Santos et al., 2015). The D-PPAC instrument has 7-items with a daily recall and needs to be completed every day for a week using an electronic device (Gimeno-Santos et al., 2015).

The majority of Randomised Controlled Trial's (RCT's) have used the C-PPAC instrument because it is easier to implement with patients only needing to complete the instrument twice (pre & post). In terms of the C-PPAC instruments effectiveness, a recently published article from Garcia-Aymerich et al. (2021), documented the response of the C-PPAC instrument in three non-pharmacological interventions in patients with COPD (Arbillaga-Etxarri et al., 2018; Demeyer et al., 2017; Louvaris et al., 2016). Firstly, a 12-week high intensity interval exercise training programme delivered by Louvaris et al. (2016) highlighted significant improvements in the difficulty, amount, and total scores of the C-PPAC instrument. The remaining two non-pharmacological interventions involved the use of PA counselling (Arbillaga-Etxarri et al., 2018; Demeyer et al., 2017). Demeyer et al. (2017) provided 12- weeks of PA tele-coaching, of which patients received weekly semi-automated goals via a smartphone app which provided

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encouragement to progressively undertake greater levels of PA. Following its completion, improvements in both the total and amount, but not in the difficulty dimension of the C-PPAC instrument were reported (Demeyer et al., 2017). Meanwhile Arbillaga-Etxarri et al. (2018) conducted a 12-month urban training programme that incorporated a behavioural and community-based exercise intervention in patients with COPD. The C-PPAC tool was able to detect significant improvements following the 12-month programme in both the amount and difficulty dimensions, although significant improvements between intervention and usual care groups was not documented (Arbillaga-Etxarri et al., 2018).

Based on findings of Garcia-Aymerich et al. (2021), the C-PPAC instrument was effective at documenting patients' experiences of PA and was responsive to both exercise training and PA counselling interventions. As a result, the C-PPAC instrument should be incorporated in future PA interventions to gauge an understanding of patients' experiences of PA alongside more common quantitative measures of PA.

2.15 Interventions to improve physical activity in COPD

With the availability of growing research, a clear trend has developed highlighting the severity of physical inactivity in patients with COPD compared to healthy age matched controls. The severity of physical inactivity has significant implications for COPD patient's health and wellbeing, with an increased risk of respiratory exacerbations, respiratory related hospitalisation, and overall mortality. As a result, the need for effective interventions to improve PA has never been greater.

2.15.1 Pulmonary rehabilitation

PR has now become a major tool for managing symptoms in COPD, with the latest American Thoracic Society and European Respiratory Society (ATS/ERS) statement defining PR as; “a

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comprehensive intervention based on a thorough patient assessment followed by patient-tailored therapies that include, but are not limited to, exercise training, education and behaviour change, designed to improve the physical and psychological conditions of people with chronic respiratory disease and to promote the long-term adherence to health-enhancing behaviours” (Spruit et al., 2013).

PR itself consists of a multidisciplinary program, including supervised exercise training, education that is relevant to the needs and requirements of the individual COPD patient, nutritional counselling, psychological and social support (Bolton et al., 2013; Spruit et al., 2013). Objectives of PR include reducing symptoms and improve both health-related quality of life and exercise capacity. In order to achieve these goals, PR covers a breadth of non-respiratory problems including cardiovascular and muscle de-conditioning, anxiety and depression, social isolation, skeletal muscle wasting and weight loss (Bolton et al., 2013; Spruit et al., 2013).

PR is well known to provide effective improvements to these outcomes (Egan et al., 2012; Ries et al., 2007; Verrill, Barton, Beasley, & Lippard, 2005). Specifically, a Cochrane review collating studies involving PR in COPD has shown both short- and long-term improvements in exercise capacity and health related quality of life (McCarthy et al., 2015). Moreover, there is significant evidence to show that PR is highly effective and safe intervention to reduce hospital admissions, mortality and health-related quality of life in patients who have recently suffered an exacerbation of COPD (Puhan, Gimeno-Santos, Cates, & Troosters, 2016; Rysør et al., 2018; Sahin et al., 2018; Seymour et al., 2010; Spruit et al., 2013).

With the benefits of exercise capacity and health related quality of life well documented following PR, it has often been proposed that such improvements should translate into improved levels of daily PA (Spruit et al., 2013). However, although there are effective improvements in measures of exercise capacity, improvements in daily PA are less convincing

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(Cindy Ng et al., 2012; Spruit et al., 2015; Watz et al., 2014). A number of review articles have taken a closer look at this, with both Cindy Ng et al. (2012) and Spruit et al. (2015) investigating the effects of exercise training on PA levels. Cindy Ng et al. (2012) reported 7 studies with a total sample size of 472 patients, however none were RCT's. Overall, they found limited effects of PR on PA levels, with significant heterogeneity amongst studies. The findings of Spruit et al. (2015) were similar, with the addition of 6 studies not included in the review of Cindy Ng et al. (2012). Again, results were inconsistent, with 3 studies reporting increased activity levels immediately following a PR programme (Mercken et al., 2005; Sewell, Singh, Williams, Collier, & Morgan, 2005; Walker et al., 2008), 5 studies documenting negative findings with no improvements in PA levels following PR (Coronado et al., 2003; Dallas et al., 2009; Mador, Patel, & Nadler, 2011; Saunders et al., 2015; Steele et al., 2003), and the remaining 3 reporting mixed results (Demeyer et al., 2014; Egan et al., 2012; Pitta et al., 2008b).

This discrepancy in findings highlights the extensive knowledge that although PR improves exercise capacity and health related quality of life in patients with COPD, such improvements do not consistently portray into improvements in PA (Spruit et al., 2013). The reasons for this are still relatively unknown, with many believing that because a comprehensive PR programme arguably includes all the relevant tools to improve PA in COPD, improvements should be seen more often. However due to the complexity of PA as a health behaviour, it is likely that the addition of specific strategies that incorporate theoretical constructs to support behaviour change for PA are required (Burge et al., 2020; Lahham et al., 2016; Mantoani et al., 2016).

2.15.2 Behaviour changes, feedback and physical activity counselling

As highlighted in the previous section on PR, increasing exercise capacity alone in patients with COPD may be insufficient to increase participation in daily PA (Coronado et al., 2003; Dallas et al., 2009; de Blok et al., 2006; Egan et al., 2012; Mador et al., 2011; Mercken et al.,

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2005; Pitta et al., 2008b; Probst et al., 2011; Sewell et al., 2005; Steele et al., 2003; Walker et al., 2008). Widespread acknowledgment of this problem has led researchers to identify behavioural factors related to patient participation in daily PA and develop several interventions targeting these behavioural factors (Burge et al., 2020; Mantoani et al., 2016; Watz et al., 2014).

Such interventions include combining self-monitoring of PA through activity monitors with behavioural counselling techniques in patient with COPD, which may have the potential to influence PA behaviour (Mantoani et al., 2016). Key components of behavioural interventions have been summarised and include mobilising social support using techniques of behaviour change and self-regulation (self-monitoring, problem solving, relapse prevention management, goal setting, self-reinforcement, performance feedback and developing action plans). Interestingly, although evidence is growing, the overall effectiveness of behavioural counselling interventions remain inconsistent, inhibiting its overall delivery across COPD (Burge et al., 2020; Lahham et al., 2016; Mantoani et al., 2016).

2.15.2.1 Physical activity counselling

PA counselling is a behavioural intervention employing several behavioural change interventions, including the identification of barriers, goal setting, self-efficacy, motivation, self-monitoring and feedback, to impact upon the vicious cycle of inactivity in COPD (de Blok et al., 2006). Patients receive counselling in order to modify their behaviour towards enhanced PA through the application of a pedometer, which allows patient monitoring and feedback of their daily steps along with frequently adjusted goal setting (Mantoani et al., 2016). This intervention can be delivered in several ways, including face-to-face contact between patients and clinicians, group contact during rehabilitation sessions and through electronic information and communication technologies ('tele coaching') (Demeyer et al., 2017). Several review

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articles and a meta-analysis have been published assessing the overall effectiveness of this intervention (Lahham et al., 2016; Mantoani et al., 2016). In the first systematic review from Mantoani et al. (2016), evidence was gathered from 14 studies that included either, advice on PA (n=3) or a coaching programme towards a more active lifestyle (n=11), compared to usual care in COPD patients. The majority of studies (n=11) reported some level of improvement in PA, however generic advice on improving PA was not effective (Mantoani et al., 2016). Interestingly, they found that PA coaching that incorporated the use of pedometers was successful for increasing PA levels, although the included studies provided small sample sizes. In addition, they suggested that an intervention of PA counselling in combination with PR may provide significant improvements, with further research needed to explore this concept (Mantoani et al., 2016).

Following this, a systematic review and meta-analysis from Lahham et al. (2016) was the first to incorporate studies that assessed PA counselling into a meta-analysis. Unlike Mantoani et al. (2016), they only included two studies assessing PA counselling compared to usual care. As a result, they found that providing individualised, pedometer-based counselling had no effect on improving PA levels (n=2 studies, SMD 0.23 [95% CI] [-0.26, 0.72]). However, they were the first to document a positive influence of PA counselling alongside exercise training as part of PR, with effective improvements in PA+PR compared to PR alone (n=4 studies, 0.47 [0.02, 0.92]) (Lahham et al., 2016).

Finally, a recent Cochrane review by Burge et al. (2020) collated the most up to date literature surrounding interventions for promoting PA in COPD. They found that the effectiveness of PA counselling to improve levels of PA remained widely inconsistent, highlighting that the identification of effective components of PA counselling was complex, with various programme durations, participant interfaces and intervention components used (Burge et al., 2020). Furthermore, components of PA counselling that provided beneficial effects on PA were

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not accompanied by improvements in health-related quality of life or exercise capacity, with further research needed to establish comprehensive improvements in PA, health-related quality of life and exercise capacity (Burge et al., 2020).

2.15.2.2 Physical activity counselling alongside pulmonary rehabilitation

One plausible solution was the incorporation of PA counselling to standard care PR programmes. Based on the recently published Cochrane review by Burge et al. (2020), the combination of PA counselling with PR has been the subject of numerous RCT's, with negative studies reporting a lack of improvement in PA and clinical outcomes including health-related quality of life and exercise capacity (Burtin et al., 2015; Nolan et al., 2017). Meanwhile positive studies, including two published abstracts, were variably accompanied by improvements in exercise capacity and health-related quality of life (Loeckx, Rodrigues, Demeyer, Janssens, & Troosters, 2018b; Mantoani et al., 2018) or unaccompanied by improvements in such clinical outcomes (Altenburg et al., 2015; Cruz, Brooks, & Marques, 2014; Kawagoshi et al., 2015).

Detailing the influence of PA counselling interventions combined with PR on PA levels, Lahham et al. (2016) was the first systematic review and meta-analysis to collate and report this variable. Specifically, Lahham et al. (2016) pooled together four RCT's regarding PA counselling alongside PR. Overall, they demonstrated that this combined approach provided clinically important improvements in steps/day compared to PR alone, although such improvements did not achieve statistical significance. This may have been a result of the four RCT's included in the meta-analysis consisting of small sample sizes that may have lowered statistical power (Lahham et al., 2016). However, the clinically important improvements in steps/day following PA counselling alongside PR reported by Lahham et al. (2016) were greater than alternative PA interventions (i.e. PA counselling alone, exercise training alone and health advise).

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Since the publication of Lahham et al. (2016), a large scale RCT from Nolan et al. (2017) has been published questioning the overall effectiveness of PA counselling alongside PR, with improvements in PA greater following PR alone. These findings are important because they provide novel data regarding PA counselling alongside PR in the UK and were the first research group to present a large scale RCT with sufficient statistical power. Further details regarding this novel RCT are provided in Chapter 3 of this thesis.

As detailed earlier, Burge et al. (2020) has provided the most up-to date analysis of interventions for promoting PA in people with COPD. Similar to PA counselling alone, they reported inconsistencies regarding the effectiveness of PA counselling alongside PR to improve levels of PA, suggesting that several areas were to consider. This included diversity in trial designs, delivery of PA counselling components and a lack of consistency in PA capturing tools.

Therefore, it remains important to continue investigating the impact of behaviour change techniques, feedback and PA counselling alongside PR, with an emphasis placed on designing an effective PA behavioural modification intervention that can support PR to comprehensively improve levels of PA, exercise capacity and health-related quality of life in patients with COPD. One novel approach yet to be fully investigated is the influence of psychological behavioural modification tools alongside PR and/or PA counselling interventions to support patients with COPD. The following section will discuss this in further detail.

2.15.3 Psychological behavioural modification tools

Alongside the physical barriers influencing daily PA, the distressing nature of COPD has a significant impact on patients' psychological wellbeing. Major focusing points for COPD patients are the sense of feeling unwell, the inability to perform everyday activities and the emotional consequences of the condition (Pumar et al., 2014; Yohannes & Alexopoulos, 2014).

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These symptoms can promote psychological difficulties including anxiety and depression, which are prevalent in patients with COPD and are associated with, poorer treatment outcomes, and reduced survival (Ng et al., 2007; Pumar et al., 2014; Yohannes & Alexopoulos, 2014). Furthermore, patients with psychological difficulties are less able to manage symptoms (Thew, MacCallam, Salkovskis, & Suntharalingam, 2017), and are less likely to improve levels of PA (Yohannes & Alexopoulos, 2014) or attend management sessions such as PR (Bolton et al., 2013).

CBT is a psychological therapy delivered to patients with a ≥ 8 Hospital Anxiety and Depression Scale (HADS) score, focusing on understanding how experiences are interpreted, through a combination of behavioural and cognitive theories of behaviour (Benjamin et al., 2011; Heslop & Foley, 2009). Specifically, the term ‘cognitive’ relates to people’s thoughts, emotions, feelings, ideas, beliefs and values, while ‘Behaviour’ relates to what a person does or chooses not to do. The main concept of ‘therapy’ involves a person’s emotional reactions being influenced by what they ‘think’ (cognitions) or indeed what they ‘do’ (behaviour) (Westbrook & Kennerley, 2011). A diagram of the CBT model can be found in Figure 2.

A core component of CBT is gaining an understanding that it is not the event, but what an individual makes of that event that is important (Heslop-Marshall & Burns, 2019). Patients may experience the same physical illness but interpret the experience in different ways. CBT provides an interaction between thoughts, mood, behaviour and physical sensations, which are intrinsically linked (Heslop-Marshall & Burns, 2019). Techniques used for **anxiety** included education on anxiety and COPD, distraction techniques, breathing control and relaxation. These techniques help to break the vicious cycle of anxiety and can reduce patients’ distress (Heslop-Marshall, 2018). Similar techniques for patients suffering mainly from **depression** included education about depression and inactivity and planning and recording activities each day, while rating these for achievement or pleasure. These techniques help to break patient

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inactivity, which can lead to improved mood and physical condition. A key treatment for depression can involve encouragement to increase activities within the patients' physical capabilities (Heslop-Marshall, 2018).

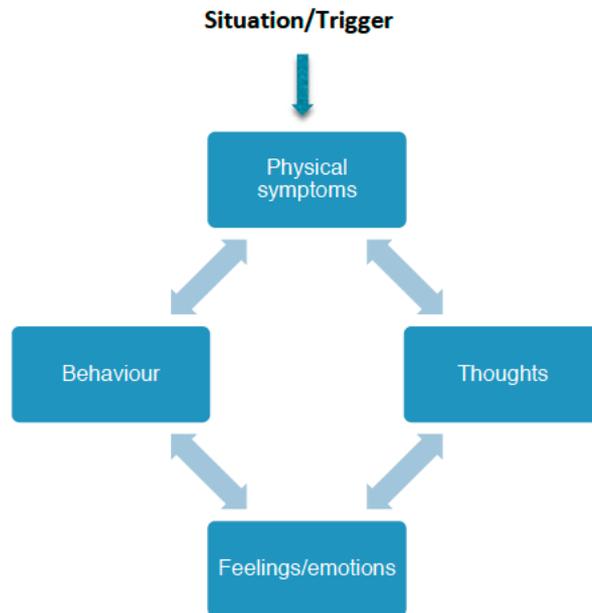


Figure 2. The CBT model, from (Westbrook & Kennerley, 2011)

Heslop-Marshall et al. (2018) designed a pragmatic RCT with sufficient power to address the hypothesis that one-to-one CBT sessions, delivered by respiratory nurses, could lead to a reduction in anxiety symptoms and could be a cost-effective intervention. A total of 236 patients completed the RCT, with 155 receiving one-to-one CBT sessions. Overall they reported clinically effective reductions in anxiety symptoms that were cost-effective, with reduced resource use, lower hospital admissions and reduced emergency department attendances (Heslop-Marshall et al., 2018).

However, the implementation of CBT strategies alongside PR and PA behavioural modification intervention is yet to be fully investigated, with only the influence of CBT and PR currently under investigation by the TANDEM COPD trial (Sohanpal et al., 2020). In more

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detail, the TANDEM group have developed a tailored, cognitive behavioural approach, which precedes and optimises the benefits of currently offered PR. They hypothesise that such a psychological intervention, delivered by training respiratory professionals, will provide improvements in mood in patients with mild to moderate anxiety and/or depression and encourage uptake and completion of PR. However, this investigation by the TANDEM COPD trial have failed to incorporate any assessment of PA, leaving the overall influence of CBT on PA open to further investigation.

2.16 Importance of this thesis

With the availability of growing research, a clear trend has developed highlighting the severity of physical inactivity in patients with COPD compared to healthy age matched controls. The severity of physical inactivity has significant implications for COPD patient's health and wellbeing, with an increased risk of respiratory exacerbations, respiratory related hospitalisation, and overall mortality.

Although PR has been extensively shown to provide improvements in both exercise capacity and health related quality of life, it often fails to have an influence on PA, due to PA being a complex health behaviour. Therefore, research has begun assessing the effectiveness of behaviour changes, feedback, and PA counselling as both an alternative intervention and in addition to PR to improve PA. The incorporation of PA behavioural modification strategies has provided the most effective avenues of success, especially alongside PR, but current findings remain inconclusive due to diversity in trial designs, leaving the true potential of this intervention poorly understood. The inclusion of psychological behavioural modification tools such as CBT, may have the potential to stimulate PA levels in specific patient groups alongside PR and PA counselling and hold the key to delivering consistent improvements in PA.

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To gauge a comprehensive understanding of PA behavioural modification interventions and its effectiveness towards improving PA, the purpose of this thesis is to expand the existing body of knowledge and provide novel data by investigating the role of PA behavioural modification interventions to improve PA in COPD, specifically focusing on the impact of combining PA behavioural modification techniques, exercise training as part of PR and psychological behavioural modification tools in the form of CBT in those with significant anxiety and depression. The specific focus of each subsequent chapter is as follows.

2.17 Chapter aims

Chapter Three: A systematic review and meta-analysis to collate and assess the current literature surrounding PA counselling as a standalone intervention and alongside PR and investigate the optimal way of using these intervention to effectively improve PA in COPD.

Chapter Four: Justification and rationale of general methods employed throughout this thesis.

Chapter Five: Investigate the criterion validity and test-retest reliability of a commercially available pedometer.

Chapter Six: Evaluate PA, muscular strength and endurance and levels of anxiety and depression in patients with COPD living in the North East of England compared with healthy age matched individuals from the same region of the United Kingdom and identify possible correlates associated with PA levels in these patients.

Chapter Seven: Investigate the feasibility, acceptability and efficacy of a novel intervention combining PA behavioural modification strategies, PR and CBT in patients with COPD.

Chapter Eight: An overall discussion interpreting and supporting the implications of the research findings.

CHAPTER 3

Chapter 3: Systematic Review and Meta-Analysis

3.1 Introduction

Research regarding effective interventions to promote PA have become important in the management of COPD due to compelling evidence surrounding physical inactivity and the associated risk of increased hospitalisation and mortality (Garcia-Aymerich et al., 2006; Garcia-Aymerich et al., 2009; Garcia-Rio et al., 2012; Pitta et al., 2005b; Vaes et al., 2014; Waschki et al., 2011; Watz et al., 2014).

It is well known that PR-induced improvements in exercise capacity often fail to translate into enhanced levels of PA in patients with COPD, leading many to identify alternative and adjunct interventions to PR to support the promotion of PA (Burge et al., 2020; Lahham et al., 2016; Mantoani et al., 2016; Qiu et al., 2018). PA counselling both as a standalone intervention and alongside PR has provided the most effective avenues of success, especially alongside PR. However, inconsistencies regarding diverse trial designs have left the true potential of this intervention poorly understood (Burge et al., 2020).

Therefore, the purpose of this systematic review and meta-analysis was to collate the most recent collection of studies documenting the effects of PA counselling, both as a standalone intervention and alongside PR, to elucidate on the design of specific aspects of PA counselling related to the ways in which the intervention can be used to optimise PA in COPD patients. Specifically, this review investigated the optimal frequency of goal setting, type of patient feedback, optimal length of intervention, type of instrument used for assessing PA, and associations between baseline activity levels and the magnitude of improvement in daily PA.

3.1.1 Review Objective

To systematically review and meta-analyse aspects of PA counselling, specifically how the interventions are used to optimise PA through the incorporation of pedometers as a key component for improving levels of daily PA in patients with COPD.

3.2 Methods

The Cochrane Handbook for Systematic Reviews of Interventions (Green & Higgins, 2005) and the preferred reporting items for Systematic Reviews and Meta-Analyses (Moher, Liberati, Tetzlaff, & Altman, 2009) guidelines for reporting systematic review and meta-analyses were followed when conducting and reporting this prospectively registered systematic review (CRD42018103893) <https://www.crd.york.ac.uk/prospero/>.

3.2.1 Eligibility criteria

The review team conducted a computerised literature search in the following databases, beginning in March 2018: Medline/PubMed, Cochrane Review, Web of Science and Cumulative Index to Nursing and Allied Health Literature (CINAHL). The original search of the literature ended on 18th January 2019, with an updated search of the literature commencing on 12th November 2020. Pre-piloted literature searches prior to the final search strategy were conducted based on two previously published systematic reviews on a related topic (Lahham et al., 2016; Qiu et al., 2018). An example search strategy can be found in Table 2. It included a wide range of modalities; using terms associated with “chronic obstructive pulmonary disease”, “physical exercise training”, “physical activity promotion, physical activity counselling” and “randomized controlled trial”. Bibliographic details of all articles from the different databases were stored in the reference software EndNote.

On completion of the literature search, all stored references were exported from EndNote to the systematic review management software program Covidence. Eligible studies published in the English language were included if they fulfilled the pre-determined criteria based on population, intervention, comparison, outcomes and setting/study design (PICOS);

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- Population: individuals with COPD defined by spirometry (i.e. $FEV_1/FVC < 0.7$).
- Interventions or exposures: COPD patients who have been enrolled onto a PA intervention which included the use of a tool that provides real-time feedback on steps/day (i.e. pedometer screen). This included standalone interventions or those incorporated into PR.
- Comparison or control groups: Patients not receiving any PA intervention.
- Outcomes of interest: The effect of PA counselling on steps/day as a measure of daily PA.
- Setting: certified research studies.
- Study design: RCT, pilot study and/or non-randomised.

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Table 2. Example search criteria for computerised literature search conducted in PUBMED

Search	Query
1	(Chronic obstructive pulmonary disease [Text Word] OR COPD [Text Word] OR Chronic Lung Disease [Text Word] OR Chronic Obstructive Lung Disease [Text Word] OR Emphysema [Text Word] OR Chronic Bronchitis [Text Word]).
2	("exercise" [Text Word] OR "rehabilitation" [Text Word] OR "exercise training" [Text Word] OR "pulmonary exercise training" [Text Word] OR "physical exercise training" [Text Word] OR "pulmonary rehabilitation" [Text Word] OR "exercise rehabilitation" [Text Word] OR "cardiopulmonary rehabilitation" [Text Word] OR "rehabilitation program*" [Text Word] OR "exercise program*" [Text Word] OR "physical activity advice" [Text Word] OR "physical activity counselling" [Text Word] OR "physical activity promotion" [Text Word] OR "accelerometer*" [Text Word] OR "Pedometer*" [Text Word] OR "activity monitor*" [Text Word] OR "step count*" [Text Word] OR "" [Text Word] OR "telerehabilitation" [Text Word] OR "e-Health intervention" [Text Word])
3	"Activity" [Text Word] OR "Motor activity"[Text Word] OR " OR "physical inactivity"[Text Word] OR "risk factor"[Text Word] OR "outcome assessment"[Text Word] OR "activity"[Text Word] OR step*[Text Word] OR walk*[Text Word] OR
4	(Randomised controlled trial OR clinical trial OR experimental study)
5	1 AND 2 AND 3 AND 4

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3.2.2 Data extraction

After removing the duplicates and based on the inclusion criteria, two authors (MA and NK) independently and blinded, reviewed the title and abstract of studies and assessed the full text of studies. Any possible disagreement between both authors during the study selection process was discussed with a third author (IV) for resolution.

For each eligible study, a predesigned standardised Excel (Microsoft, USA) form (Appendix 3a) was used to collect data by a single author (MA) on the following subheadings: author information (including name of first author and date of publication), blindness, participant characteristics (including age, FEV₁ % pred, FVC, 6MWD, baseline daily steps, Total Lung Capacity and Residual volume, intervention details, PA measurements, primary outcomes and results. Two blinded reviewers (MA and NK) screened all eligible studies independently, any disagreements were sent to a third independent author (IV) to make a majority agreement.

3.2.3 Quality assessment

Quality assessment was performed using the PEDro quality scale, which is an 11-item scale assessing internal and external validity of clinical trials (Maher, Sherrington, Herbert, Moseley, & Elkins, 2003). Two authors (MA and NK) independently reviewed the following domains employed by this scale: eligibility criteria, random allocation, concealed allocation, baseline similarity, blinding (subject, therapist, and assessor), and measures recorded from at least 85% of participants, full intention to treat, group comparison and point measure. The higher the given score, the better the quality. Cut points of the scale were excellent (9-10), good (6-8), fair (4-5) and poor (<3) (Maher et al., 2003).

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3.2.4 Data synthesis

Meta-analyses were undertaken using Review Manager (RevMan V5.3; Cochrane Collaboration, Oxford, UK). Change scores or end of intervention values with the corresponding pooled standard deviation for the outcomes of interest were used to obtain the overall effect size represented by standard mean difference with 95% confidence interval, with a threshold $p < 0.05$ considered as significant. Heterogeneity in this meta-analysis was assessed by I^2 value, as follows: 0%-40%, might not be important; 30%-60%, moderate heterogeneity; 50%-90% substantial heterogeneity; 75%-100% considerable heterogeneity (Higgins & Green, 2011). A fixed-effects model was used for the meta-analysis; however, if statistical heterogeneity was noted ($I^2 > 40\%$), meta-analyses were performed using the random-effects model. Sensitivity analysis was used if a substantial heterogeneity ($I^2 > 75\%$) was reported in meta-analyses.

The clinically important improvement in steps/day referred to throughout this thesis was based on the findings of Demeyer et al. (2016). A clinically important improvement is defined as the ‘smallest difference in score within a domain of interest which patients perceive as beneficial and which would mandate, in the absence of troublesome side effects and excessive costs, a change in patients’ management’ (Jaeschke, Singer, & Guyatt, 1989). Methods to determine clinically important improvements are typically divided into two well-defined categories: distribution-based and anchor-based approaches. However, distribution-based methods are often most effective when they are applied together with a meaningful external anchor (Wyrwich et al., 2005).

Demeyer et al. (2016) based their calculations on several distribution-based techniques including 1) standard error of measurement, 2) empirical rule effect size, 3) Cohen’s effect size and 4) 0.5 times the standard deviation of the baseline measurements. In terms of the anchors used, the 6MWT distance and CRDQ total and dyspnea domains were chosen as they were

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associated with levels of PA in cross sectional analyses (Gimeno-Santos et al., 2014) and related to changes in walking time after rehabilitation (Pitta et al., 2008b). Alongside anchors, a relevant clinical indicator, time for first hospital admission for an exacerbation of COPD following completion of PR, was included to assess the calculated clinically important improvement alongside a clinical outcome measure.

The calculated clinically important improvement in steps/day varied depending on the distribution-based technique used i.e., 1) 599 steps/day, 2) 1029 steps/day, 3) 1072 steps/day and 4) 1131 steps/day respectively). Therefore, it was deemed that a clinically important improvement in steps/day would range from 599 to 1131 steps/day. Furthermore, patients who exceeded the clinically important improvement reported a lower number of hospital admissions in the first two years after rehabilitation, deeming the proposed difference clinically valid (Demeyer et al., 2016).

3.3 Results

During the initial search strategy (commenced March 2018 to January 2019), 2582 potentially relevant studies were found. After removing 714 duplicates and screening 1868 abstract/titles, 55 studies remained for the full-text screening. On completion of full-text screening, 38 studies were excluded. Therefore, 17 studies were considered eligible for inclusion in this systematic review and meta-analysis. One study provided three different comparisons, resulting in three RCTs. An updated search strategy (commenced 12th November 2020) found a further 50 potentially relevant studies. After removing 4 duplicates and screening 46 abstracts/titles, 8 studies remained for the full-text screening. On completion of full-text screening, 6 studies were excluded. Therefore, 2 studies were added to the original pool of eligible studies included in this systematic review and meta-analysis. A full Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of the screening process is shown in

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Figure 3. Participants were individually randomised in all included trials (i.e. there were no cluster RCTs). Characteristics of included RCTs are summarised in appendix 3a and were all published between 2006 to 2020.

3.3.1 Characteristics of included subjects

All of the included trials (appendix 3a) comprised 1837 patients (53% female), with a median sample size of 72 (range 16-343). Included patients had a mean age of 67 years (range 54-75) and average FEV_{1%pred} ranged from 34 to 78 indicative of severe to moderate COPD (Vestbo et al., 2013). Patients were reported as physically inactive at baseline with an average mean value of 4450 steps/day (range 1557-7161 steps/day).

3.3.2 Characteristics of included/excluded trials

44 studies were excluded from this review on completion of full-text screening. The reasons for exclusion include the wrong intervention (n=17), duplicates (n=9), inappropriate study design (n=6), outcomes not meeting criteria (n=6), inappropriate comparators (n=2), no full text availability (n=2) and no reported data for daily steps (n=2).

3.3.3 Quality assessment

Table 3 provides a summary of the risk of bias decision made per category for the included studies. In line with the PEDro scale, quality of included studies ranged from good to excellent (mean PEDro score, [interquartile range] =7.3, suggesting a low risk of bias towards the main outcome measure (Maher et al., 2003).

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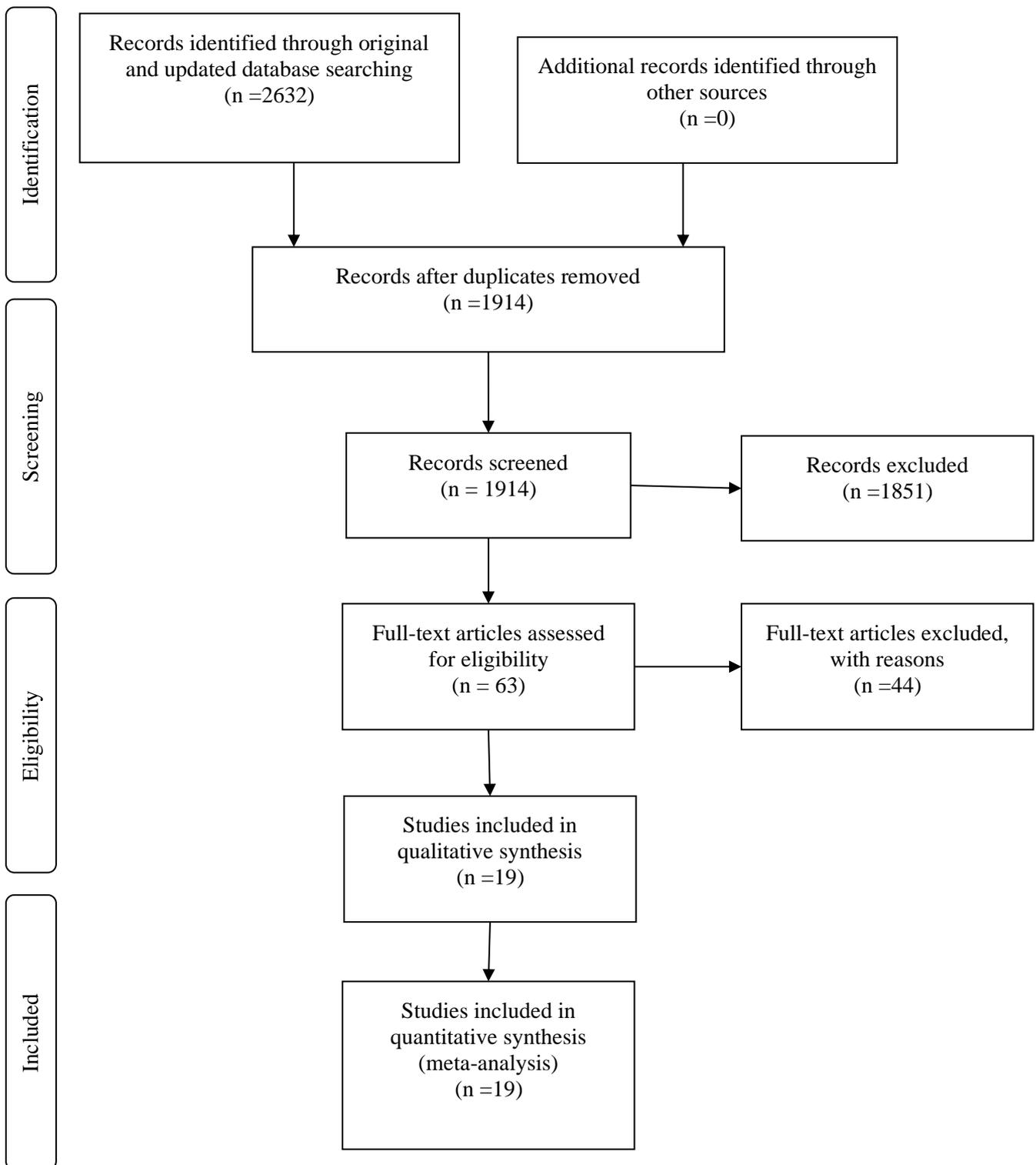


Figure 3. PRISMA flow diagram for original and updated database search and study selection process

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Table 3. Qualitative synthesis of included studies using PEDro scale for the quality of RCTs

Study name	Eligibility criteria	Random allocation	Concealed allocation	Baseline similarity	Blinding (subject)	Blinding (therapist)	Blinding (assessor)	Measure of >85%	ITT	Group comparison	Point measure	Quality score
^A Altenburg et al (2014)	*	*	*	*				*	*	*	*	7
^B Altenburg et al (2014)	*	*	*	*				*	*	*	*	7
^C Altenburg et al (2015)	*	*	*	*				*	*	*	*	7
Arbillaga-Etxarri et al (2018)	*	*	*	*	*	*			*	*	*	8
Bender et al (2016)	*	*		*				*	*	*	*	6
De Blok et al (2005)	*	*		*		*		*	*	*	*	7
Cruz et al (2016)	*	*	*	*	*		*	*	*	*	*	9
Demeyer et al (2017)	*	*	*	*			*	*	*	*	*	8
Holland et al (2016)	*	*	*	*			*	*	*	*	*	8
Hornix et al (2015)	*	*		*				*	*	*	*	6
Hospes et al (2009)	*	*		*				*	*	*	*	6

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Kawagoshi et al (2015)	*	*		*			*	*	*	*	*	7
(Kohlbrener, Sievi, Senn, Kohler, & Clarenbach, 2020)	*	*	*	*				*	*	*	*	7
Mendoza et al (2015)	*	*	*	*				*	*	*	*	7
Moy et al (2015)	*	*		*				*	*	*	*	7
Nolan et al (2017)	*	*	*	*		*	*	*	*	*	*	9
Tabak et al (2014)	*	*	*	*				*	*	*	*	7
Varas et al (2018)	*	*		*		*		*	*	*	*	7
Vornnik et al (2016)	*	*	*	*			*	*	*	*	*	8
Wan et al (2017)	*	*	*	*			*	*	*	*	*	8
Wootton et al (2019)	*	*	*	*			*	*	*	*	*	8

Abbreviations: ITT: Intention to treat. *: yes, score = 1. The higher the given score, the better the quality. Cut-off points of the scale were: excellent (9-10), good (6-8), fair (4-5) and poor (3).

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3.3.4 Meta-analyses of included studies

When observing the effects of PA counselling as a standalone intervention, there was a positive effect on steps/day compared to usual care (n=14 RCTs, standard mean difference [SMD] 0.49 [95% CI 0.31, 0.66], $p<0.00001$); Figure 4 (Altenburg et al., 2015; Arbillaga-Etxarri et al., 2018; Bender et al., 2016; Demeyer et al., 2017; Hornikx, Demeyer, Camillo, Janssens, & Troosters, 2015; Hospes, Bossenbroek, ten Hacken, van Hengel, & de Greef, 2009; Kohlbrenner et al., 2020; Mendoza et al., 2015; Moy et al., 2015; Tabak et al., 2014; Vorrink, Kort, Troosters, Zanen, & Lammers, 2016; Wan et al., 2017; Wootton et al., 2019) which equated to an improvement of 906 [536, 1277] steps/day. A positive effect on steps/day was also found when PA counselling was added to PR versus PR alone (n=7 RCTs, SMD 0.52 [95% CI 0.18, 0.86], $p=0.002$); Figure 4 (Altenburg et al., 2015; Cruz, Brooks, & Marques, 2016; de Blok et al., 2006; Holland et al., 2017; Kawagoshi et al., 2015; Nolan et al., 2017; Varas et al., 2018), which equated to an improvement of 1659 [506, 2811] steps/day. Both the pooled analysis of PA counselling compared to usual care and PA counselling alongside PR compared to PR alone reported moderate heterogeneity ($I^2=61\%$ & 58%) respectively.

Moreover, the SMD and improved steps/day induced by PA counselling were comparable among studies which provided: i) weekly or infrequent goal setting, ii) an intervention length less or more than 3 months, iii) remote or face-to-face contact, iv) accelerometer or pedometer measured PA (all $p<0.05$, Table 4). In contrast, studies reporting PA counselling alongside PR compared to PR alone were more effective in terms of SMD and steps/day in patients with greater baseline PA levels (>4000 steps/day) compared to those with lower baseline PA levels (≤ 4000 steps/day, Table 4). Specifically, only those with high baseline PA levels reported significant improvements in the SMD and steps/day of PA (n=3 RCTs, SMD 0.95 [95% CI 0.22, 1.67], $p<0.00001$) compared to those with low baseline PA levels (n=3 RCTs, SMD 0.20 [95% CI -0.02, 0.41], $p<0.135$). This equated to a clinically important improvement in

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steps/day of 3130 [95% CI 1957, 4303] steps/day in patients with higher baseline PA compared to 115 [95% CI -68, 379] steps/day in those with low baseline PA.

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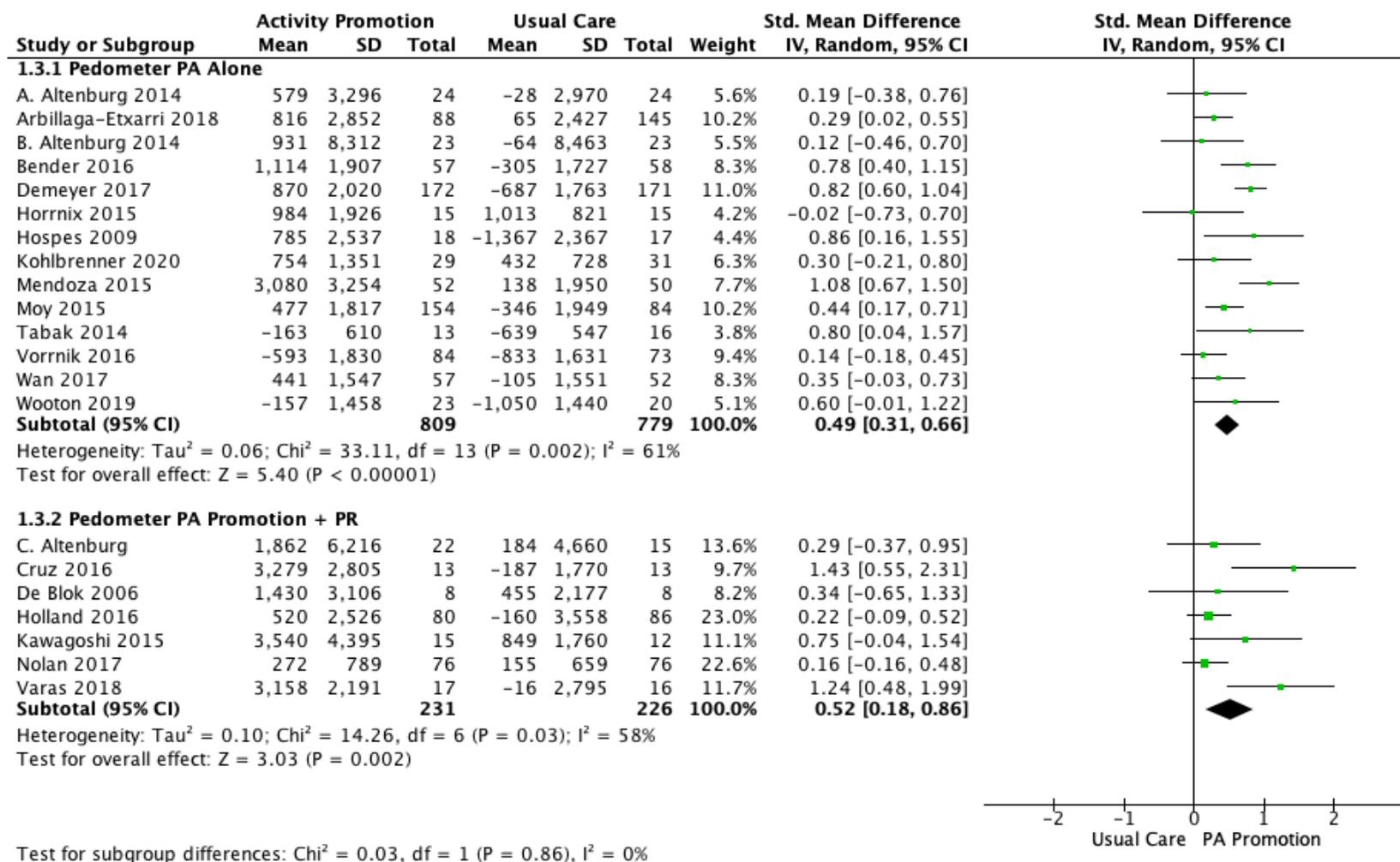


Figure 4. Effect sizes of physical activity counselling alone and alongside PR on steps/day. Abbreviations: SD, standard deviation; PA, physical activity; PR, pulmonary rehabilitation; CI, confidence interval

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Table 4. Subgroup analysis on components of PA counselling of included studies and the effect size of steps/day

Subgroups	Overall analysis					PA counselling alone					PA counselling + PR				
	No.	Effect Size		Steps/day		No.	Effect Size		Steps/day		No.	Effect Size		Steps/day	
		SMD	95% CI	MD	95% CI		SMD	95% CI	MD	95% CI		SMD	95% CI	MD	95% CI
Goal Setting															
Weekly	9	0.51**	0.25, 0.77	849**	348, 1350	6	0.44**	0.16, 0.71	663*	193, 1132	3	0.88	-0.03, 1.78	2137	-437, 4712
Duration															
Infrequent	12	0.48**	0.28, 0.67	1206**	684, 1728	8	0.53**	0.27, 0.78	1227**	582, 1872	4	0.29*	0.04, 0.54	980*	174, 1785
≤3 Months	16	0.53**	0.32, 0.73	1083**	616, 1550	1	0.55**	0.27, 0.83	999**	450, 1548	5	0.63	0.11, 1.16	184	6, 3683
>3 Months	5	0.36**	0.20, 0.51	835**	492, 1177	1 3	0.38**	0.20, 0.57	816**	443, 1189	2	0.35	-0.10, 0.80	5* 135	7 -505, 3220
Type of Feedback															
Remote	12	0.46**	0.28, 0.64	797**	459, 1136	1 0	0.46**	0.27, 0.64	730**	396, 1064	2	0.67	-0.32, 1.66	1818	-616, 4252
Face-to-face	9	0.55*	0.22, 0.87	1759**	526, 2993	4	0.57	-0.06, 1.09	2023**	850, 3196	5	0.51*	0.08, 0.94	1686	-44, 3416
Measure of PA															
Accelerometer	10	0.41**	0.18, 0.63	792*	291, 1293	6	0.39*	0.09, 0.68	664*	109, 1218	4	0.46	0.05, 0.87	1384*	76, 2692
Pedometer	11	0.58**	0.37, 0.79	1304**	755, 1854	8	0.57**	0.34, 0.80	1158**	601, 1715	3	0.63	0.00, 1.26	2373**	1005, 3741
Baseline PA Levels															
≤4000 steps	8	0.35**	0.20, 0.50	554*	192, 917	5	0.44**	0.24, 0.64	669*	253, 1085	3	0.20	-0.02, 0.41	155	-68, 379
>4000 steps	12	0.60**	0.36, 0.85	1411**	832, 1990	9	0.53**	0.27, 0.79	1116**	547, 1685	3	0.95**	0.22, 1.67	3130**	1957, 4303

Abbreviations: SMD: Standard Mean Difference, MD: Mean Difference, CI: Confidence Interval, PR: Pulmonary Rehabilitation, PA: Physical Activity

3.4 Discussion:

3.4.1 Summary of the main findings

This systematic review and meta-analysis, including 21 RCTs, provides updated evidence regarding the effectiveness of PA counselling as both a standalone intervention compared to usual care and alongside PR compared to PR alone, with significant improvements in steps/day that exceeded the clinically important improvement of 599-1100 steps/day (Demeyer et al., 2016). This increase in steps/day reported as a result of both PA counselling alone or alongside PR appears much larger than that from other methods including exercise training as part of PR, health monitoring, long term oxygen therapy or neuromuscular electrical stimulation (Lahham et al., 2016; Mantoani et al., 2016). In agreement with the findings of Lahham et al. (2016), PA counselling alongside PR was superior compared to PA counselling alone towards improving PA. However, important findings regarding the effectiveness of PA counselling in patients who report low baseline levels of PA were documented, with inferior improvements in steps/day documented in those studies that delivered PA counselling alongside PR in patients with baseline levels of PA ≤ 4000 steps/day.

3.4.2 Interpretation of the results

3.4.2.1 Physical activity counselling alone

The meta-analysis of PA counselling alone in this study is the first to incorporate two recently published RCTs (Kohlbrener et al., 2020; Wootton et al., 2019). The inclusion of these RCT's has reported no changes in PA compared to data from the most recent meta-analysis of Qiu et al. (2018). Interestingly, the findings of both the current study and the review of Qiu et al. (2018) do not support the findings of Lahham et al. (2016), who demonstrated that PA

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counselling was not an effective standalone intervention towards improving steps/day in patients with COPD. Several disparities are apparent between these review articles. Firstly, Lahham et al. (2016) based their analysis of PA counselling on a subgroup analysis of subjective and objectively derived PA (Lahham et al., 2016). In contrast, both the current meta-analysis and that of Qiu et al. (2018) only included studies that were able to demonstrate PA which was objectively measured due to limited validity and reliability when measuring PA subjectively (Pitta et al., 2005a; Watz et al., 2014). Secondly, the number of included studies varied across separate meta-analyses. In this meta-analysis, a total of fourteen studies with an average sample size of 120 were included in the pooled analysis of PA counselling as a standalone intervention. Meanwhile, Lahham and colleagues only reported two studies documenting objectively measured PA, with an average total sample size of 17 (Lahham et al., 2016). With the significant benefits of collecting and reporting objectively measured PA and a much greater sample size across pooled analyses, the current meta-analysis could be argued to have more valid findings than Lahham et al. (2016), therefore questioning the negative findings of their meta-analysis.

In terms of the subgroup analysis, which provided a breakdown of the various components involved in PA counselling, similar improvements in steps/day were found irrespective of the way the intervention was designed or implemented. Interestingly, previous meta-analyses in both outpatient adults and patients with type 2 diabetes have demonstrated that step diary use for recording steps/day was an important predictor of increased PA levels, however this is yet to be documented in patients with COPD and was not demonstrated in the current study (Bravata et al., 2007).

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3.4.2.2 *Physical activity counselling alongside pulmonary rehabilitation*

When observing the effects of PA counselling alongside PR, the majority of available literature supports its effectiveness in terms of improving levels of PA (Altenburg et al., 2015; Cruz et al., 2016; de Blok et al., 2006; Holland et al., 2017; Kawagoshi et al., 2015; Varas et al., 2018). Specifically, the present meta-analysis, that includes a recently published RCT (Varas et al., 2018), and the systematic review and meta-analyses of Lahham et al. (2016) and Qiu et al. (2018) have all shown statistically significant improvements in steps/day. Lahham et al. (2016), found that providing persistent and individualised feedback on activity levels in conjunction with PR, achieved significant effects that exceeded both PA counselling alone and PR alone. Furthermore, the present study was in agreement with Lahham et al. (2016) in that PA counselling alongside PR provided greater improvements in PA than PA counselling alone. Supporting those findings, Qiu et al. (2018) found that the addition of step counters as part of PA counselling alongside PR was able to enhance the effects of PR on both PA and exercise capacity.

The publication of Lahham et al. (2016), did not report an important RCT from Nolan et al. (2017), which incorporated a PA counselling intervention alongside PR based in the UK. Following this twice-weekly, supervised, 8-week, outpatient PR programme alongside PA counselling, patients observed minimal improvements in PA following the completion of both the PR+PA and PR alone interventions, with neither group able to achieve clinically important improvements in steps/day. Based on these findings, they determined that the routine use of PA counselling should not be included in standard care PR (Nolan et al., 2017). The findings of this study are important as they provide novel data regarding PA counselling alongside PR in the UK and were the first research group to document negative findings regarding PA counselling alongside PR. Interestingly, the findings of Nolan et al. (2017) were based on a sufficiently powered sample size to show statistical significance and scored highly on the

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PEDro scale, suggesting it had a low level of bias and a high quality of evidence (Nolan et al., 2017).

A major finding of this study is that patients with greater baseline PA levels (>4000 steps/day) reported greater improvements in steps/day compared to those with lower baseline PA (≤ 4000 steps/day) following PA counselling alongside PR in patients with COPD. Specifically, in studies that implemented PA counselling alongside PR, an improvement in steps/day was unable to reach the clinically important improvement of 599 steps/day in patients that documented baseline PA levels of ≤ 4000 steps/day (115 [-68, 379] steps/day, Table 4) (de Blok et al., 2006; Holland et al., 2017; Nolan et al., 2017). In comparison, significant improvements, greater than the clinically important improvement were reported following PA counselling alongside PR when patients had a baseline PA >4000 steps/day (3130 [1957, 4303] steps/day, Table 4) (Altenburg et al., 2015; Cruz et al., 2016; Varas et al., 2018). This finding may have significant implications for those with low baseline PA levels due to the increased risk of hospital admissions and mortality as a result of increased physical inactivity (Garcia-Aymerich et al., 2006; Garcia-Aymerich et al., 2009; Garcia-Rio et al., 2012; Vaes et al., 2014; Waschki et al., 2011). It must be recognised that there were only a small number of studies in this subgroup analysis with a small mean sample size, however such differences in steps/day warrants closer scrutiny. Within the meta-analysis of Qui and colleagues, they demonstrated similar findings, with severe COPD patients ($FEV_1 < 50\%$ Pred) more likely to see negative effects of pedometer PA counselling than with moderate severity patients ($FEV_1 > 50\%$ Pred) (Qiu et al., 2018). They speculate that this was a result of increased airflow limitation restricting the benefits of a pedometer. The choice to assess the severity of patients based on low and high baseline levels of PA instead of FEV_1 in the current study was due to the association between worsening FEV_1 and diminishing PA being only modest (Watz et al., 2014).

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A further potential reason for this finding was proposed by Osadnik et al. (2018), reporting that patients with COPD who exhibit greater exercise capacity prior to PR were more likely to achieve greater improvements in daily PA. They reported clinically important improvements in steps/day in patients reporting a 6MWT >350m compared to ≤ 350 m (707 ± 1780 vs 157 ± 1694 steps/day respectively). This higher likelihood of improvement in PA in those with a greater exercise tolerance may also provide an explanation for those patients exhibiting a higher baseline PA level (Osadnik et al., 2018). However in contrast to this, a recent study from Gulart et al. (2019) suggested that patients with a lower FEV₁ and baseline steps/day were more likely to achieve a clinically important improvement in steps/day. This finding was attributed to the belief that more severe patients have a greater potential for improvement as they are further from their “maximal” capacity, compared with patients with less severe disease (Gulart et al. (2019). However, this proposal requires further evidence before it can be considered a viable option. Future research may consider investigating the true effect of interventions to improve PA in patients with severe COPD vs moderate to low COPD and gauge a better understanding of the mechanisms associated with improved PA.

3.4.3 Quality of the evidence

The overall quality of evidence from included studies was good in line with the PEDro scale for quality assessment. The inability to blind subjects reduced the overall quality of evidence and increased the risk of bias towards the intervention procedure. Future research reporting the effects of PA counselling may improve quality scoring by blinding all subjects from the intervention procedure. However, a concern remains that blinding patients from the intervention would require a pedometer being issued to a control group, which may present the control group with a level of PA counselling as they are able to monitor their daily steps. A number of studies were unable to blind any members of the study from patient allocation

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(Altenburg et al., 2015; Bender et al., 2016; Hornikx et al., 2015; Hospes et al., 2009; Moy et al., 2015; Tabak et al., 2014). In any clinical trial, blinding of at least the researcher is desirable and the blinding of subjects warranted thus to decrease bias within the findings. When blinding is not used or the subject group status is easily detectable, subjects will generally try to fulfil the perceived expectation of the researcher (Clark & Mulligan, 2011).

3.4.4 Strengths and Limitations

This systematic review and meta-analysis is the first to include three recently published RCTs reporting PA counselling implemented either alone (Arbillaga-Etxarri et al., 2018; Kohlbrenner et al., 2020) or alongside a combined PR programme (Varas et al., 2018). Moreover, it is the first to report on the various components involved in PA counselling interventions, highlighting that improvements in PA can exceed clinically important improvements with several different intervention approaches. Several limitations should be noted. Firstly, considerable heterogeneity continues to exist in interventions of this nature, which was partially explained by the findings on the components of PA counselling. Secondly, it cannot be determined without knowledge, the specific improvement a pedometer intervention can have alongside PR without knowing the exact progression of exercise training for individual patients during PR. Finally, despite a comprehensive search of the literature using the main scientific search databases, there remains a possibility that studies eligible for inclusion may have been missed. The search restriction on English written studies and the failure to search for unpublished studies and/or abstracts/conference papers may have resulted in selection and publication bias.

3.4.5 Implications for future research

Several implications for future research should be considered following the findings of this study. Firstly, researchers may wish to further investigate the reliability and technical aspects

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of PA monitoring to measure changes in PA when designing future interventions both in COPD and other populations. A study from van Schooten et al. (2015) investigated the assessment of PA monitoring in older adults, demonstrating that several factors may influence the reliability of accelerometer derived PA monitoring, including different daily activities and investigating PA on an individual vs group level. Specifically, a minimum of two consecutive days of accelerometer measurements were required to reliably assess PA outcomes at a group level, including ‘the duration of locomotion, sitting, standing and shuffling and movement intensity’. Meanwhile for lying and median locomotion bout duration, three and five days were required, respectively. Furthermore, when investigating PA on an individual level, a minimum of four days of PA measurements were required to achieve the smallest detectable difference (van Schooten et al., 2015). Based on these findings, it’s important that future studies investigate PA monitoring beyond the limits of steps/day that are demonstrated in this chapter. Specific details regarding the technical aspects of accelerometry used throughout this thesis are provided in Chapter 4.

Secondly, considerations should be made prior to comparing any findings with a previously defined clinically important improvement. For example, if studies that define a clinically important improvement use a different PA device to monitor PA, this may have implications due to the validity and reliability of various PA monitoring devices. As a result, future research should only compare their findings to a clinically important improvement if a similar PA device is used to monitor PA levels.

Thirdly, standard mean difference and absolute mean difference in steps/day were used instead of relative mean difference throughout the meta-analysis and subgroup analysis of this chapter. These measures were chosen as they relate to previously administered meta-analyses and allowed for simple comparisons to be made (Burge et al., 2020; Lahham et al., 2016; Qiu et al., 2018). However, it should be noted that relative mean difference expresses the absolute

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change as a percentage of the baseline value and may support a better comparison of improvements in steps/day across different interventions and populations. Therefore, future meta-analyses should consider the use of relative mean difference as an alternative to standard mean difference and/or absolute mean difference.

3.5 Conclusion

In conclusion, this study has shown that PA counselling promotes steps/day when it is used as an intervention alone or alongside PR, with improvements in steps/day greater following PA counselling alongside PR. Evidence delivered in this study can be incorporated into future study designs aiming to implement a PA behavioural modification intervention, providing specific thought towards the design and implementation of such interventions.

Important evidence is provided in this study highlighting that patients benefit more from PA counselling when baseline levels of PA are greater than 4000 steps/day. This finding may have significant implications for those with low baseline PA levels due to the increased risk of hospital admissions and mortality as a result of increased physical inactivity (Garcia-Aymerich et al., 2006; Garcia-Aymerich et al., 2009; Garcia-Rio et al., 2012; Vaes et al., 2014; Waschki et al., 2011). Therefore, a greater emphasis on those with low levels of PA are urgently needed in order to suppress the decline in PA and promote a more physically activity lifestyle in these patients. Potential elements to this may include a greater understanding of patients baseline daily PA levels and/or exercise tolerance prior to designing and delivering future RCTs of this nature. In addition, future interventions of PA behavioural modification alongside PR, may wish to investigate the add-on effect of more complex psychological behavioural therapies (i.e. CBT) in those severe COPD patients who exhibit significant limitations in improving daily PA. Finally, this study has confirmed that only a single RCT (Nolan et al., 2017) reports on the effects of PA counselling alongside PR based in the UK. Intriguingly, it remains the only RCT

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to report negative effects on PA levels alongside PR. Therefore, more evidence to understand the effects of PA behavioural modification interventions alongside PR that is prescribed in the UK are needed. Chapter 7 reports the efficacy of combining a PA behavioural modification intervention alongside a PR programme (and CBT in those with high levels of anxiety and depression) compared to PR alone on daily PA levels in COPD patients living in the North East of England with low baseline PA levels.

METHODOLOGICAL CHAPTERS OF THIS THESIS

- ◇ **CHAPTER FOUR:** Justification and rationale of general methods employed throughout this thesis.

- ◇ **CHAPTER FIVE:** Investigate the criterion validity and test-retest reliability of a commercially available pedometer before its use in an intervention of PA behavioural modification alongside Pulmonary Rehabilitation.

CHAPTER 4

Chapter 4: General Methods

CHAPTER 4: GENERAL METHODS

4.1 Introduction

This chapter provides details on the general methods that were employed throughout this thesis with specific justification and rationale for the design and methods employed in:

- Chapter 5: A criterion validity and test-retest reliability study of a commercially available pedometer to capture levels of PA in COPD patients.
- Chapter 6: A case control and cross-sectional study assessing levels of PA in COPD patients compared to healthy age-matched controls and identifying correlates contributing to physical inactivity in patients with COPD.
- Chapter 7: An RCT assessing a novel intervention combining PA behavioural modification strategies, PR, and CBT in patients with COPD.

4.2 Ethical approvals

The principles of research ethics state that the individual taking part in the research study should not be harmed in any way by the procedures taking place (Aita & Richer, 2005). To ensure safety, all measures taken throughout the studies of this thesis were conducted by trained researchers and relevant risk assessments were always in place, complying with the current health and safety legislations including “The Health and Safety at Work Act 1974” and the “Management of Health and Safety at Work Regulations 1999”.

Research conducted as part of this thesis took place at both the University of Northumbria Newcastle and Newcastle upon Tyne Foundation NHS Healthcare Trust (NuTH), as such, ethical approval was required from both institutions and NHS committees.

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4.2.1 University ethical approval

Institutional ethical approval for Chapters 5 and 6 were submitted to Northumbria University Faculty of Health and Life Sciences Research Ethics Committee prior to the commencement of research (Appendix 4a). Given the nature of research, risk assessments were carried out and adhered to in line with ethical requirements. Ethical approval from Northumbria University Ethics Committee was provided (Ref: 12928) on 26/11/18.

4.2.2 NHS ethical approval

To begin the process of NHS ethical approval, the study protocol (Appendix 4b) was developed and submitted to the research and development (R&D) office within the NuTH (Ref no: 08968). An Integrated Research Application System (IRAS) project (Appendix 4c) was produced and applied for (IRAS ID: 248697) in order to begin the process for obtaining NHS ethical approval. Within the IRAS system, relevant documents were submitted and approved by the Health Research Authority (HRA) (Appendix 4d) and a favourable opinion received from the ‘Yorkshire and The Humber- Sheffield’ Research Ethics Committee (REC) on 7th September 2018 (Ref: 18/YH/0376) (Appendix 4e). Following ethical approval, the NuTH R&D department approved and granted permission for the study to commence and provided confirmation of capacity and capability (Appendix 4f). Given the nature of this research at an NHS site, a research passport and honorary contract/letter of access, was obtained (Appendix 4g) enabling the researcher to have access to the NHS site and identifiable patient information.

4.3 Data management

All relevant data collection throughout this thesis conformed to institutional guidelines, the EU General Data Protection Regulations (GDPR) and Data Protection Act (2018). In accordance with the principles of Good Clinical Practice, essential trial documentation was kept in a trial

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master file and investigator site file. All paper records including consent forms, clinical measurements and completed questionnaires were kept secure in a locked cabinet on the premises of the University of Northumbria campus. To conform with NHS research site regulations, a folder with relevant patient contact dates (i.e., date of interest shown, date of contact and date of consent), a copy of complete informed consent, a participant information sheet, a signed case report form, a complete GP letter (Appendix 4h) and an adverse events form were stored within the NHS Trust and relevant forms filed in medical records by the chief investigator.

To ensure the quality of data throughout this thesis, all outcome data (i.e. questionnaires) were checked manually by the study coordinator (MA) for completeness, clarity of answers and consistency before being entered electronically into Microsoft Excel. Any discrepancies with data entry were performed by the outcome assessor, with checks against the original questionnaires and clinical measurement sheets made.

Data saved electronically were stored on a password-protected computer and will be destroyed 2 years following the conclusion of the study. Any identifiable data was destroyed/deleted as soon as possible. A complete backup of electronic data was performed monthly, via a password protected hard drive, stored at both NHS and institutional sites.

4.4 Recruitment

4.4.1 COPD patients

A single cohort of COPD patients were recruited for this thesis from the NuTH Chest Clinic and PR waiting lists across both the Royal Victoria Infirmary (RVI) and Freeman hospital. Patients were initially approached by a healthcare professional (i.e., consultant respiratory physicians/specialist respiratory nurses/respiratory physiotherapists) who documented the study requirements and provided a participant information sheet (Appendix 4i) to patients who

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expressed initial interest. Upon this, patients provided contact details to the healthcare professional which were subsequently passed to a member of the research team. A researcher contacted interested patients at least 24 hours after initial contact from the healthcare professional via telephone and delivered a screening assessment.

The initial screening assessment was completed over telephone, with the nature and objectives of the study explained to the patient in more detail and an opportunity to ask any questions was given. Patients were asked to confirm eligibility to the study based on the inclusion/exclusion criteria outlined below. On confirmation of eligibility, patients were offered an invitation to attend a baseline assessment visit at either the RVI or the Freeman hospital depending on patient preference.

Inclusion criteria:

1. COPD confirmed by obstructive spirometry.
2. Clinically stable male or female COPD patients aged 40 years or older.
3. Optimised medical therapy.
4. Able to provide informed consent.

Exclusion criteria:

1. Orthopaedic, neurological, or other concomitant diseases that significantly impair normal biomechanical movement patterns, as judged by the investigator.
2. Moderate or severe acute exacerbation of COPD within 4 weeks.
3. Unstable ischaemic heart disease, including myocardial infarction within 6 weeks.
4. Moderate or severe aortic stenosis or hypertrophic obstructive cardiomyopathy.
5. Uncontrolled hypertension and another condition likely to limit life expectancy to less than one year (principally metastatic malignancy).

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Patients attended the physiotherapy department at either the RVI or Freeman hospital. On arrival, patients provided confirmation that they met the inclusion/exclusion criteria and written informed consent was obtained (Appendix 4j), conforming to the Medical Research Council (MRC) guidelines (Skivington, Matthews, Craig, Simpson, & Moore, 2018).

4.4.2 Healthy participants

Healthy participants were recruited for this thesis from a non-clinical population on a voluntary basis from around the University of Northumbria campus and local area. The recruitment of healthy participants was necessary to assess the validity and reliability of PA assessment tools (pedometer) via treadmill walking (Chapter 5) and compare PA levels with COPD patients from the same region (Chapter 6).

A number of recruitment methods were used including (1) a recruitment database of people who previously expressed interest in participating in research studies within the university, (2) advertisements via recruitment posters (Appendix 4k), (3) Word of mouth around the University campus. These recruitment methods were performed to generate a cross sectional representative selection of individuals living in the North East of England with diverse demographical and clinical characteristics.

Following a response of interest from individuals, a participant information sheet (Appendix 4l) was provided with at least 24 hours to consider the information given. Once verbal consent was received, the first visit to the Northumbria University laboratory was scheduled. During the first visit, individuals were fully informed of the study requirements and were screened for eligibility using the below inclusion/exclusion criteria:

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Inclusion criteria:

1. Normal spirometry results ($FEV_1/FVC > 0.70$ & $FEV_1 > 80\%$ predicted).
2. Sedentary males and females aged 50-75 years old.
3. Stable condition with no comorbidities which would affect levels of daily physical activity/ability to walk on a treadmill.
4. Able to provide informed consent.

Exclusion criteria:

1. Orthopaedic, neurological or other concomitant diseases that significantly impair normal biomechanical movement patterns, as judged by the investigator.
2. Unstable ischaemic heart disease, including myocardial infarction within 6 weeks.
3. Moderate or severe aortic stenosis or hypertrophic obstructive cardiomyopathy.
4. Uncontrolled hypertension and another condition likely to limit life expectancy to less than one year (principally metastatic malignancy).

Upon meeting the inclusion/exclusion criteria, patients signed an informed consent form (Appendix 4m) before being entered into the study and the data collection schedule planned. As per the consent form, all patients were free to withdraw from the study at any time.

4.5 Study Design

To establish sufficient evidence, several study designs were developed throughout this thesis, with the purpose of addressing the research aims and hypotheses outlined in Chapter 1. Below is a description of the study designs implemented for each chapter with a rationale of why they were conceived.

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4.5.1 Chapter 5: Criterion validity and test-retest reliability.

The effectiveness of pedometers to assess and promote PA in COPD is dependent on these devices being validated as an accurate and reliable measure of PA. Previous literature has confirmed the validity and reliability of several pedometers at walking speeds more commonly associated with healthy individuals (Kooiman et al., 2015; Takacs et al., 2014). However, at slower walking speeds, commonly found in COPD patients, pedometers often underestimate step counts (Crouter, Schneider, Karabulut, & Bassett Jr, 2003). As a result, it was important to determine the criterion validity and reliability of the pedometer (Fitbug, Fitbug Corporation, London, United Kingdom) used in this thesis to determine its ability to record PA at slower walking speeds.

Criterion validity, which measures how well one measure predicts an outcome for another measure, was assessed by comparing the step count of the pedometer with visual step counts measured through a tally counter or video camera in line with previous validation studies (Kooiman et al., 2015; Takacs et al., 2014). Several statistical tests based on the same previous validation studies (Kooiman et al., 2015; Takacs et al., 2014) were used, including (1) paired sample T-Test to assess systematic differences, (2) mean percentage error, (3) Bland Altman plots to assess the level of agreement and (4) Deming regression. Unlike previous validation studies, Deming regression was used as a tool to assess validity in Chapter 5 as both measurement tools (pedometer and visual counts) were subject to a degree of random error. Specifically, Deming regression is a term used to refer to linear regression analysis in which the random error of both methods of assessment are taken into account (Martin, 2000).

Test-retest reliability, testing consistency over time, was assessed by comparing pedometer step count measurements at two time points. Two statistical tests based on previous literature (Kooiman et al., 2015; Takacs et al., 2014) were used, including (1) Intra-class correlation

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coefficient (ICC) to assess inter-rater reliability and (2) Coefficient of variance to assess the stability of the pedometer across repeated trials.

4.5.2 Chapter 6: Case control and Cross-sectional study

As detailed in Chapter 2, levels of PA are significantly lower in patients with COPD compared to healthy age-matched individuals, with the severity of inactivity varying depending on study geographical location and study population (Boutou et al., 2019; Troosters et al., 2010).

Several studies have highlighted the severity of physical inactivity in COPD patients compared to healthy age-matched controls in mainland Europe and North/South America (Pitta et al., 2005b; Troosters et al., 2010), however, to our knowledge this has yet to be assessed in the UK, particularly on a regional basis. Therefore, it was necessary to gain an understanding of PA levels in both COPD patients and healthy age-matched controls living specifically in the North East of England. As a result, a case control design was undertaken.

It is acknowledged that case control studies generate a high level of evidence and have the potential for a high external validity, enabling the data to be extrapolated to the wider COPD population (Schulz & Grimes, 2002). To control for confounding factors between the COPD and healthy populations, the principles of a matched case-control study were used (Dey, Mukherjee, & Chakraborty, 2020). Specifically, healthy controls were selected in a manner that matched for age (+/- 3 years) based on a previous study of a similar design in COPD patients (Troosters et al., 2010).

Furthermore, it was important to gauge a consideration of baseline daily PA levels in COPD patients prior to their inclusion in Chapter 7, since earlier in this thesis it was detailed that patients were found to benefit more from PA counselling interventions when baseline levels of PA were greater than 4000 steps/day (Armstrong et al., 2019). Prior knowledge of patient's baseline PA levels supported the design and delivery of the RCT in Chapter 7.

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To identify factors that are associated with PA in patient with COPD, Spearman's correlation coefficient and multiple linear regression analysis using a stepwise model were constructed based on a previous study in COPD patients (Troosters et al., 2010). Within these analyses, lung function, BMI, exercise capacity, health-related quality of life, anxiety and depression and symptoms of breathlessness were included as independent variables. In considering potential factors that may be related to PA, variables that have already been linked to the development of physical inactivity in COPD, as highlighted in both cross-sectional and longitudinal studies and the ERS statement on PA in COPD (Boutou et al., 2019; Pitta et al., 2005b; Troosters et al., 2010; Watz et al., 2014) were used.

4.5.3 Chapter 7: RCT

To date, previous literature has yet to explore the potential for a combined PA behavioural modification intervention, alongside PR and CBT in patients with COPD who report profoundly low baseline PA. To explore the effectiveness of this combined intervention, outcome measures (detailed below) were assessed within group (from baseline to post PR), and between groups (PR+PA vs PR alone), with differences assessed using a two-way repeated measures ANOVA. To support these findings, assessment of the feasibility of recruitment, randomisation and completion rates to patients assigned either to PR+PA or the PR alone groups, as well as the acceptability and adherence to the PA behavioural modification intervention was conducted.

To define feasible rates of recruitment, randomisation and completion, a consultation with health care professionals involved in the delivery of PR and consideration of previous literature were held (Leon, Davis, & Kraemer, 2011; Ward et al., 2018). Following discussions, the following criteria were set (1) Recruitment of at least 30% of eligible patients, (2)

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Randomisation of at least 80% of patients following informed consent, (3) At least 80% of randomised patients should complete the intervention period and post assessment visit.

Assessing the acceptability is essential in the development, evaluation and implementation of interventions and may have a significant impact on the effectiveness of the intervention (Sekhon, Cartwright, & Francis, 2017). The acceptability of the PR+PA intervention was assessed through a qualitative project-tailored questionnaire. The project-tailored patient questionnaire administered was based on a previous questionnaire by Loeckx et al. (2018a) and specifically tailored to the PA behavioural modification intervention delivered (Appendix 4n). Adherence was assessed by examining the degree which components of the intervention were used by patients (Donkin et al., 2011). Specifically, actual usage was assessed by (1) The number of weekly goal setting targets met, based on a percentage of the 8 weekly step targets provided throughout the intervention, (2) Weekly completion of the step count diaries based on researcher's observation of the patient's diary twice weekly, (3) Pedometer wear time, based on a minimum of 70 steps for a valid day of wearing, in line with a previous study (Loeckx et al., 2018a) (4) Accelerometer wear time was based on a minimum of 8 hours recording time for a valid day of wearing (Demeyer et al., 2014). Furthermore, patients subjectively reported their usage of the step counter and step count diary using the project-tailored questionnaire.

To gauge a better understanding of CBT added to a PA behavioural modification intervention, a subgroup analysis was undertaken in patients with HADS ≥ 8 who were provided with a session of CBT alongside their allocated group (PR+PA+CBT vs PR+CBT).

4.6 Outcome measures

All demographic and outcome assessment tool data for this thesis were collected between November 2018 and February 2021. A trained research team collected all data from the RVI and Freeman hospital NuTH sites and Northumbria University laboratories. Ethical approvals

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and participant written informed consent were all confirmed before assessment measures were taken. Outcome measures are identified in Table 5 and described below.

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Table 5. Outcome measures assessed throughout this thesis

Outcome measures	Validity and reliability study (Chapter 5)	Case control study (Chapter 6)	RCT (Chapter 7)
Accelerometer derived PA		✓	✓
Pedometer derived PA	✓		✓
Patient experience of PA (C-PPAC)			✓
Exercise capacity (6MWT)			✓
Lower body muscle strength (QMVC)		✓	✓
Upper body muscle strength (HG)		✓	✓
Lower body muscle endurance (STS)		✓	✓
CAT			✓
CCQ			✓
HADS		✓	✓
MRC dyspnea scale			✓

Abbreviations: 6MWT: Six Minute Walk Test, CAT: COPD Assessment Test, CCQ: Clinical COPD Questionnaire, HADS: Hospital Anxiety and Depression Scale, MRC: Medical Research Council, C-PPAC: Clinical Visit of Proactive Physical Activity in COPD, QMVC: Quadriceps muscle voluntary capacity.

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4.6.1 Assessment of Anthropometrics Measures

Stature was measured to the nearest 0.1 cm in both COPD patients (Seca Ltd, Seca 220 Stadiometer, Birmingham, UK) and healthy participants (stadiometer, SECA 217). Both populations followed the same instructions; individuals were asked to remove items of footwear, position themselves with their back and heels against the stadiometer. The research team member measuring would inform the individual to take a deep breath in and a measurement would be taken.

Body mass was measured in COPD patients (Seca Ltd, Seca Scales 709, Birmingham, UK) and healthy participants (Avery scales, SECA 711) to the nearest 0.1 kg. All individuals were asked to remove any items from their pockets, remove all items of footwear and asked to stand in the centre of the scales. Body mass index (BMI) was calculated using the validated calculation (BMI = body mass [kg]/Stature [m²]).

4.6.2 Pulmonary function testing

An objective measure of pulmonary function was performed in every COPD patient at the RVI Chest Clinic prior to inclusion in the study and was carried out by respiratory nurses/physiologists according to the latest guidelines from The Association for Respiratory Technology & Physiology (Sylvester et al., 2020).

4.6.3 Recording of oxygen saturation

Oxygen saturation (SpO₂) was reported in several Chapters across this thesis using a pulse oximeter (Nonin, Palm SAT 2500, USA), placed on a finger of preference. Literature surrounding the placement of pulse oximetry found that measurements taken from the finger were more accurate than those taken from the ear (Jensen, Onyskiw, & Prasad, 1998). A meta-analysis consisting of 21 oximeters found a correlation coefficient ranging from $r = 0.986$ to r

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= 0.591. When SpO₂ was measured within the range of 70-100%, the accuracy of most devices were found to be within 2-5% of in vitro oximetry (Jensen et al., 1998).

4.6.4 Capturing physical activity

Within this thesis, PA was captured using both a pedometer (Fitbug, Fitbug Corporation, London, United Kingdom, Figure 5) and a triaxial accelerometer (Actigraph wGT3X, Actigraph LLC, Pensacola, FL, USA, Figure 5). The Fitbug pedometer was used to record PA and self-motivate patients as part of the PA behavioural modification intervention in Chapter 7. The validity and test-retest reliability of the Fitbug pedometer in both COPD patients and healthy controls is detailed in Chapter 5.



Figure 5. Fitbug pedometer and Actigraph triaxial accelerometer

The Actigraph wGT3X (Actigraph LLC, Pensacola, FL, USA) is a triaxial accelerometer used to objectively capture daily PA throughout this thesis (Table 8) in both COPD patients and healthy individuals. Outcomes of the Actigraph wGT3X included step counts, vector magnitude units (to calculate movement intensity) and time spent in different intensities of activity (Table 6). The Actigraph wGT3X accelerometer was positioned above the anterior spine of the iliac crest in line with the anterior axillary line of the dominant hip. This placement

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location has been reported to result in the highest accuracy (Swartz et al., 2000). All participants throughout this thesis were provided with a thorough description of the Actigraph accelerometer prior to initiation. This included information on i) correct positioning of the device; ii) the wearing period (e.g., wear the device from the moment you wake up until the moment you go to bed “wakefulness hours”), with instructions to keep on wearing the device even during sedentary time and illness; iii) when to take off the device (e.g. during bathing and showering) iv) date of when to stop assessment. A detailed explanation of the accelerometry data collection and processing conducted in this thesis is outlined below and condensed in Table 7.

Table 6. MET Intensity Threshold and Cut Points

	MET Intensity	Cut Points
	Thresholds (METs)	(Activity Counts)
Sedentary PA	<1.5	≤100
Light PA	≥1.5 and <4	>100 and <2296
Moderate PA	≥4 and <6	≥2296 and <4012
Vigorous PA	≥6	≥4012

Abbreviations: MET: Metabolic Equivalent Threshold.

4.6.4.1 Sampling period

Throughout this thesis individuals were required to wear the Actigraph accelerometer during waking hours (i.e. 07:00 to 22:00 hours) for 7 days. The Actigraph accelerometers were given to individuals in delay mode on day 0 and commenced logging on day one at 07:00 with a seven day stop time indicated. Previous research documents that PA measurements during

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waking hours optimise the compliance between the individual and device, lower the burden and help to standardise the sampling period (Demeyer et al., 2014). Research into accelerometer derived PA most often use sampling periods of 24-hour assessment or waking hours (Demeyer et al., 2014; Furlanetto et al., 2017; Mesquita et al., 2017; Pitta et al., 2005b). In COPD patients, activities are typically performed between 7am and 8pm, with 90% of total daily steps taken by 8pm. This timeframe was found to be comparable in apparent healthy individuals of a similar age and was not affected by disease severity (Doherty et al., 2017; Mesquita et al., 2017).

4.6.4.2 Number of assessment days

In order to achieve a valid assessment of PA, a wearing period of 7 days was deemed appropriate throughout this thesis. Rabinovich et al. (2013) documented that patients with COPD were almost entirely willing to wear an accelerometer for a minimum of 7 days.

4.6.4.3 Defining a valid day of assessment

A valid day of assessment throughout this thesis was defined as a minimum of 8 hours of activity counts (480 minutes). In patients with COPD, previous literature has suggested the use of at least 8 hours of wearing time in order to gauge a clear representation of PA levels (Demeyer et al., 2014). Adjustments should be made on an individualised basis if night shift working, or variable sleeping patterns affected the sampling period. It is important to validate the assessment of PA based on the wear time of the device being used (Actigraph wGT3X), in order to ensure the results are representative of patients' actual PA levels.

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4.6.4.4 Type of days for analysis

The type of days (weekdays vs weekends) used to assess PA vary depending on the precise aims of relevant Chapters in this thesis. To assess the PA levels of COPD patients in Chapter 7, weekday levels of PA were analysed (Demeyer et al., 2014). Meanwhile when assessing PA levels of both COPD patients and healthy participants in Chapter 6, both weekdays and weekends were analysed. When measuring PA across numerous populations, studies have typically reported lower levels of PA during the weekend than during weekdays' (Demeyer et al., 2014; Rabinovich et al., 2013; Watz et al., 2009). Importantly, when analysing these methods, adding weekend days has been found to increase the variability, but not the observed effect of outcomes (Demeyer et al., 2014). Therefore, excluding weekends when analysing the effect of an intervention on PA outcomes will support a smaller sample size and a greater observed effect (Demeyer et al., 2014). In contrast, when the aim of a study is to characterise the PA of a patient cohort with another disease or healthy comparator, including both weekdays and weekend days can present a more comprehensive analysis (Demeyer et al., 2014).

4.6.4.5 Number of valid days for inclusion in analysis

Likewise, with the types of days assessed (outlined above) the number of valid days required for inclusion vary across Chapters. In Chapter 7, the highest four weekday step counts were taken for the analysis. Demeyer et al. (2014) reported that more weekdays (up to 4) resulted in a decreased variability of outcome measures and a smaller sample needed to obtain statistical power (Demeyer et al., 2014). Therefore, in clinical trials, 4 weekdays of PA assessment were considered as the ideal assessment (Demeyer et al., 2014). In Chapter 6, five valid days including weekdays and weekends were required for analysis. Choosing to assess 5 valid days provides a greater overview of PA behaviour and increases the variability of data (Demeyer et al., 2014).

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4.6.4.6 Validity and reliability

Several studies have outlined the validity of the Actigraph wGT3X device for detecting levels of daily PA in patients with COPD (Rabinovich et al., 2013; Van Remoortel et al., 2012b). Using both ‘lab based’ and ‘real life’ approaches, the Actigraph GT3X was found to be one of two most valid and responsive monitors for use in COPD, when correlated with the gold standard assessment of energy expenditure (doubly labelled water) (Rabinovich et al., 2013; Van Remoortel et al., 2012b). In addition, monitors worn closer to the centre of mass of an individual (e.g. belt) provide higher validity compared to wrist worn monitors (Rabinovich et al., 2013; Van Remoortel et al., 2012b)

Table 7. Details surrounding accelerometer data collection and processing

Information	Details
Accelerometer model	Actigraph wGT3X Version 5
Piezosensor orientation	Tri-axial
Data collection sample rate	100 Hz
Deployment method	Example of fitting provided by researcher (baseline)
Location worn	Dominant hip
Days of wear	7 days (starting the day after visit 1)
Initialisation	Deployed in delay mode during day 0 and commenced logging at 07:00 hrs with a 7 day stop time indicated.
Wear instructions	Wear during hours of wakefulness
Valid day criteria	≥ 8 hours of valid wear time (480 minutes)
Valid recording	At least 4 valid weekdays
Epoch length	60 seconds

Abbreviations: Hz: Hertz, hrs: Hours.

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4.6.4.7 *Capturing patients' physical activity experiences*

The C-PPAC instrument (Appendix 4o) was administered to capture patients' experiences of PA in this thesis. Developed by the framework of the European Union Innovation Medicines Initiative (EU-IMI) PROactive project following recommendations from the US food and Drug administration, the C-PPAC instrument combines subjective questionnaire items and activity monitor variables to measure the amount of PA, difficulty completing PA and total PA experience (Gimeno-Santos et al., 2015). The C-PPAC instrument consisted of 12 subjective questions with a 7-day recall and was completed using paper and pen. Activity monitor data (steps/day and VMU) were taken from the Actigraph wGT3X accelerometer, which has been validated to be part of the C-PPAC instrument (Actigraph wGT3X, Actigraph LLC, Pensacola, FL, USA) (Gimeno-Santos et al., 2015). Overall C-PPAC scores were calculated by combining the 12 subjective questions regarding difficulty and amount of PA with two objective variables from the accelerometer (steps/day and VMU). Three scores were generated (amount of PA, difficulty of PA and total PA experience) ranging from 0 to 100, where higher numbers indicated a better score (Gimeno-Santos et al., 2015).

A validation study found the C-PPAC instrument to be simple, reliable, and valid for measuring patients experiences of PA in COPD (Gimeno-Santos et al., 2015). Furthermore the C-PPAC instrument was reported as valid and reliable across sexes, age groups, COPD severity, countries, and languages (Gimeno-Santos et al., 2015).

A recent study from Garcia-Aymerich et al. (2021) was the first to provide data on the responsiveness (response to intervention and ability to detect change) and minimal important difference following non-pharmacological interventions. Based on this data, authors suggested a minimum important difference of 6 for the amount and difficulty scores and 4 for the total scores of the C-PPAC instrument (Garcia-Aymerich et al., 2021).

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Table 8. Instruments used to capture PA

Instrument used to capture PA	Validity and reliability study (Chapter 5)	Case control study (Chapter 6)	RCT (Chapter 7)
Actigraph wGT3X triaxial accelerometer (Actigraph LLC, Pensacola, FL, USA)		✓	✓
Fitbug pedometer (Fitbug Corporation, London, United Kingdom)	✓		✓
Clinical Visits of PROactive Physical Activity tool (C-PPAC)			✓

4.6.5 Exercise capacity

The exercise capacity of COPD patients was assessed using the 6MWT throughout this thesis (Table 5). The 6MWT is a self-paced test of exercise capacity, with patients required to walk as far as possible in six minutes along a 30-metre flat corridor (Holland et al., 2014). The test was performed at both hospital sites (RVI and Freeman hospital) over a marked 30 metre corridor in accordance to the ATS/ERS technical standards (Holland et al., 2014). Prior to the test, a respiratory physiotherapist recorded measurements of SpO₂ and measures of dyspnea and leg discomfort using the Modified Borg 1-10 Scale (Appendix 4p). Patients were then advised to walk the 30-metre corridor for six minutes at their own pace, taking rests when

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required. Measurements of SpO₂, dyspnea and leg discomfort were taken throughout the walk test and on its completion. The 6MWT has demonstrated a moderate-to-strong relationship (ICC 0.4 to 0.8) with peak VO₂, measured using a cardiopulmonary exercise test (CPET) (Singh et al., 2014). Furthermore, a moderate to strong relationship has been documented between the 6MWT and objectively measured PA (ICC: 0.64-0.75) (Garcia-Rio et al., 2009; Hernandez et al., 2009; Pitta et al., 2005b).

The 6MWT has been reported as a reliable measure of exercise capacity, with good to excellent correlation coefficients across a number of studies in COPD (ICC range: 0.72-0.99) (Singh et al., 2014). Despite the excellent reliability, there is strong evidence to suggest a learning effect can occur when two or more tests are conducted in close proximity of each other. Specifically, the percentage of COPD patients who walked further on the second 6MWT ranged from 50%-87%, with 15% of those reporting a clinically significant improvement on their second walk (Sciurba et al., 2003). To reduce the influence of a learning effect on 6MWT outcomes, patients were required to perform a second 6MWT within 7 days of the first 6MWT at both pre- and post-PR assessments, with the best distance from the two pre and post 6MWT's recorded (Holland et al., 2014).

Available evidence suggests a clinically important improvement of 30 m for adult patients with chronic respiratory disease (Singh et al., 2014). Although some variability across studies and methods to determine the clinically important improvement exists, available evidence reports that it lies between 25 and 33 m (Singh et al., 2014).

4.6.6 Lower body muscle strength

Lower body muscle strength (QMVC) was measured using isometric maximal volitional limb muscle strength assessment, using a calibrated Myometer (MIE Medical Research Ltd., Leeds, UK) throughout this thesis (Table 5). Quadriceps muscle dysfunction has been recognised as a

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major systemic manifestation of COPD (Barreiro & Gea, 2015), and therefore, it has been recommended that quadriceps muscle strength is assessed in COPD (Nyberg, Saey, Martin, & Maltais, 2018).

Individuals sat in a purpose-built chair with an inextensible strap connecting the ankle of their dominant leg to a Myometer (MIE Medical Research Ltd., Leeds, UK). Care was taken to ensure that the participants knee was flexed to 90°, and that the strain gauge and coupling were aligned to ensure an isometric contraction occurred. Participants performed three sustained maximal isometric quadriceps contractions of between a 3- and 5-seconds duration, with vigorous encouragement given throughout. A resting period of 30-60 seconds between each contraction was given to allow time to recover from each effort. The highest of three attempts was recorded (Edwards, Young, Hosking, & Jones, 1977).

Isometric measurements of quadriceps muscle strength using a strain-gauge have been recommended over alternative strategies, due to its simplicity, availability and the quality of data outputs (Maltais et al., 2014). The test-retest reliability of isometric quadriceps muscle maximal strength in patients with COPD were high satisfactory, evident by high ICC (0.97 [95% CI, 0.92-0.99]) and low coefficient of variance (3.2%) (Nyberg et al., 2018).

A recently published article from Oliveira et al. (2021) has detailed an updated minimal clinically important difference for quadriceps muscle strength in people with COPD following completion of PR. The pooled minimal clinically important differences were 5.7kg and 26.9% of change for quadriceps one repetition maximal based on the pre-post PR difference (Oliveira et al., 2021).

4.6.7 Upper body muscle strength

Upper body muscle strength assessment was obtained by assessment of handgrip strength using a calibrated hand-dynamometer (Camry EH101, Camry Electronic CO. Ltd., Zhongshan,

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China) throughout this thesis (Table 5). Upper body muscle strength has been associated with a higher risk of mortality in COPD patients (Puhan, Siebeling, Zoller, Muggensturm, & Ter Riet, 2013). As a result, handgrip strength assessment is recommended in this patient population (Puhan et al., 2013). Practice attempts and demonstrations were allowed for individuals to make them feel more comfortable about the procedure. Individuals were asked to position their elbow at a 90° angle from the side of their body, with the base of the handgrip dynamometer placed in the palm of the individuals' hand. Researcher informed the individual to grip the handle with maximum isometric effort for 5 seconds, with 30 seconds rest between attempts.

Evidence reports good to excellent ($r=0.80$) test-retest reproducibility and excellent ($r=0.98$) interrater reliability in healthy volunteers (Mathiowetz, Weber, Volland, & Kashman, 1984; Peolsson, Hedlund, & Öberg, 2001). In addition the reliability of hand grip strength in COPD patients was identified as excellent, with a mean difference between tests of -0.05 ± 5.97 kg and an ICC (0.81) (O'Shea, Taylor, & Paratz, 2007).

4.6.8 Lower body muscle endurance

The ability to get up from a seated position is essential to several everyday tasks and is necessary for autonomy, especially in older people and those with chronic disease (Hansen, Beyer, Frølich, Godtfredsen, & Bieler, 2018). The 30 second sit to stand test was therefore used to measure lower body muscular endurance across this thesis (Table 5). A straight-backed chair with a hard seat was stabilised by placing it against a wall. Floor to seat height was approximately 45-47 cm. Individuals were instructed to start in a seated position with their feet flat on the floor, back straight, with their upper limbs across the chest (Jones, Rikli, & Beam, 1999). Prior to the test, a demonstration was given and then a practice attempt was provided to the participant to ensure a valid technique was being performed. Individuals started in the

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seated position and, upon command, stood up and returned to sitting as many times as possible in a 30-second time period. The number of fully standing positions were recorded and if the individual was over halfway to standing when the 30 seconds had elapsed, this repetition was recorded (Jones et al., 1999).

The 30 second sit to stand test was selected due to its extensive use throughout literature in COPD and its efficient nature in assessing lower body muscle endurance in a short period of time (Hansen et al., 2018; Zanini et al., 2015; Zanini et al., 2018). The 30 second sit to stand test was found to have good levels of agreement ($ICC > 0.70$) with other sit to stand protocols (5 rep test & 1 minute test) in COPD patients (Morita et al., 2015). Furthermore, the reproducibility of the 30 second sit to stand test was found to be excellent in COPD patients with high ICC (0.94) (Hansen et al., 2018). The minimum clinically important difference calculated for the 30 second sit to stand was a change of at least 2 repetitions following completion of a PR programme (Zanini et al., 2019).

4.6.9 Hospital Anxiety and Depression Questionnaire

The HADS questionnaire (Appendix 4q) is a patient-reported measure that examines the anxiety and depression of individuals and was used throughout this thesis (Table 5). Both depression and anxiety are highly prevalent in patients with COPD and should be assessed and treated in order to improve patient's health related quality of life (Puhan, Frey, Büchi, & Schünemann, 2008). The scale consists of two distinct subscales assessing anxiety and depression across 7 specific items (Zigmond & Snaith, 1983). Each item is rated on a 0-3 Likert scale, with 0 representing 'absence of that trait' to 3 representing 'extreme presence of that trait'. The overall scoring of the scale is defined as 0-7 normal; 8-10 borderline anxiety/depression; and 11-21 representative of clear anxiety and/or depression (Snaith, 2003). An updated systematic review reported on the validity and internal consistency of the HADS

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questionnaire from studies assessing elderly patients with various chronic diseases. Based on 15 studies, the Cronbach's alpha coefficient of internal consistency varied from 0.67 to 0.93 (mean 0.83), showing good consistency (Bjelland, Dahl, Haug, & Neckelmann, 2002). Recently published literature on the minimum clinically important difference for the HADS questionnaire proposes a decrease of between -1.8 and -1.3 points for HADS-Anxiety, and between -1.7 and -1.5 points for HADS-Depression (Smid et al., 2017).

4.6.10 COPD Assessment Test

The COPD Assessment Test (CAT) was administered at baseline and post-PR in Chapter 7 (Table 5) to quantify the impact of COPD on patient's health related quality of life (Appendix 4r). This questionnaire was developed as a shorter tool which would be easier and quicker to complete and therefore more applicable in clinical settings than the St Georges Respiratory Questionnaire (Jones et al., 2009). It is a self-reported questionnaire taking around 5 minutes to complete, consisting of eight items that include; cough, phlegm, chest tightness, breathlessness, going up hills/stairs, activity limitation, confidence leaving home, sleep and energy. All points are scored from 0 to 5 giving a total score in the range of 0 to 40 (Jones et al., 2009). The development and validity of this questionnaire was assessed with very good validity ($r=0.80$) compared to the St Georges Respiratory Questionnaire in stable COPD patients (Jones et al., 2009). Recently published literature on the minimum clinically important difference for the CAT questionnaire proposes a decrease of between -3.0 and -2.0 points (Smid et al., 2017).

4.6.11 Clinical COPD Questionnaire

Likewise, with the CAT questionnaire, the Clinical COPD Questionnaire (CCQ) was developed as a shorter, easier tool for implementation in a clinical setting, and was

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implemented at baseline and post-PR in Chapter 7 (Table 5, Appendix 4s). It provides a reflection of patient's physical symptoms, emotional response and activity limitation to the disease. Based on a Likert scale (0 to 6), 10 questions are asked, reflecting symptoms, functional state and mental, with a maximum score of 15 indicating severe disability (Van der Molen et al., 2003). The reliability of the CCQ questionnaire was good across all domain levels; total (ICC) (0.85), symptoms (0.74), functional state (0.86) and mental state (0.83) (Ställberg, Nokela, Ehlers, Hjemdal, & Jonsson, 2009). Good intra-class correlations with the SGRQ was also reported, regardless of COPD severity (Ställberg et al., 2009). Recently published literature on the minimum clinically important difference for the CCQ total proposes a decrease of between -0.5 and -0.3 (Smid et al., 2017).

4.6.12 Medical Research Council Dyspnea Scale

The MRC Dyspnea scale (Appendix 4t) is a subjective measure used to quantify disability attributable to breathlessness in COPD patients and was implemented at baseline and post-PR in Chapter 7 (Table 5) (Fletcher, Elmes, Fairbairn, & Wood, 1959). It is based on five grades of increasing severity, rating the type and magnitude of dyspnea experienced. The five grading categories encompass the whole range of respiratory disability (from non to almost complete incapacity). It can be self-administered, and the score is the number that best fits the patient's levels of activity. The MRC scale cannot quantify breathlessness itself, but the disability associated with activities of daily living. The MRC has been previously validated for use in COPD patients (Bestall et al 1999).

CHAPTER 5

Chapter 5: Validity and Test Re-Test Reliability

CHAPTER 5: VALIDTY AND RELIABILITY

5.1 Introduction

Subjective methods of PA assessment (e.g. recall questionnaires and diaries) are the most popular instruments for quantifying levels of PA in COPD patients, however, many are prone to recall bias, limiting the validity and reproducibility of these tools to assess and promote levels of PA (Watz et al., 2009). Objective methods, including pedometers and accelerometers are now becoming optimal for the quantification of the amount and intensity of PA (Reilly et al., 2008). Previous literature has documented the benefits of accelerometers to provide an objective, practical, accurate and reliable means of quantifying PA in various populations (Rabinovich et al., 2013; Van Remoortel et al., 2012b). Unfortunately, the vast majority of accelerometer devices are unable to provide patients with direct feedback of PA levels, making these devices difficult to incorporate into PA counselling interventions (Armstrong et al., 2019; Qiu et al., 2018).

Unlike accelerometer devices, pedometers provide more limited PA measurements, with step/day and calorie counts often the only information collected. Benefits of pedometer devices include their simplicity of use and cheap shelf price, with many having the beneficiary of a visual display, rendering them more accessible and user friendly. This has led to their increased use in interventions to promote PA, as the visual display provides direct feedback of activity levels, acting as a motivational tool to self-monitor PA behaviour (Armstrong et al., 2019; Burge et al., 2020; Mantoani et al., 2016). As detailed in Chapter 3, pedometers are an effective tool for promoting PA, either as a standalone intervention or alongside PR, inducing meaningful improvement in steps/day in patients with COPD (Armstrong et al., 2019).

The effectiveness of pedometers to assess and promote PA in COPD patients is dependent on them being validated as an accurate and reliable measure of PA. Previous literature has confirmed the validity and reliability of numerous pedometers at walking speeds more commonly associated with healthy individuals (≥ 1.11 m/s) (Crouter et al., 2003; Feito, Bassett,

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& Thompson, 2012; Hasson, Haller, Pober, Staudenmayer, & Freedson, 2009; Kooiman et al., 2015; Takacs et al., 2014). However, at slower walking speeds (<1.0 m/s) pedometers often underestimate step counts as a result of less prominent vertical accelerations, limiting the ability to quantify movement (Crouter et al., 2003). In patients with COPD, it is common to ambulate at slower speeds than healthy individuals, therefore it is important to determine the validity and reliability of pedometers at slower walking speeds prior to their use in patients with COPD (Ilgin et al., 2011).

Accordingly, the purpose of this study was to assess the criterion validity and test-retest reliability of the Fitbug pedometer (Fitbug Corporation, London, United Kingdom) in a controlled environment, prior to its inclusion in a PA behavioural modification intervention (Chapter 7), in patients with COPD and apparent healthy individuals, compared to direct observations of PA.

5.2 Methods

5.2.1 Study design

This cross-sectional investigation was conducted as two separate sub studies: (1) assessment of criterion validity in COPD patients while in a controlled hospital environment; (2) assessment of criterion validity and test re-test reliability in a group of apparent healthy individuals while in a controlled laboratory environment.

5.2.2 Study participants

A convenience sample of 24 healthy adults and 14 patients moderate to severe COPD were recruited to this study. Apparent healthy adults were recruited from a database of people who previously expressed interest in participating in research studies, and from advertisements within

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the University of Northumbria at Newcastle. Meanwhile COPD patients were recruited as part of the RCT detailed in Chapter 7 (detailed in Chapter 4).

5.2.3 Measurement Tools

5.2.3.1 Step counter

The Fitbug pedometer (Figure 6) is a small device containing a piezo-electric model to detect body movement. It can be carried on the waist using an adjustable strap or detachable clip and has a 2x3 cm LCD display to illustrate step counts, distance, calorie, and time functions. In addition, internal memory of the pedometer supports 14 days of step count history, limiting the amount of data lost and the expected battery life is 18-24 months making the device sustainable for long periods of time.



Figure 6. Fitbug pedometer

5.2.3.2 Visual step counts

Depending on the sub-study, direct observations of PA were recorded through (1) a video camera (Sony, Handycam HDR-CX240) attached to a tripod (Hama) in healthy participants or (2) tally counter manually operated by a researcher in COPD patients. Further details are provided below.

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5.2.4 Study Protocol 1: COPD Patients

To examine the criterion validity of the Fitbug pedometer in a controlled environment, patients with COPD were asked to wear the pedometer during a 6MWT at the conclusion of PR. The 6MWT was performed by a respiratory physiotherapist according to the instructions of the ATS/ERS technical standards (Holland et al., 2014). Patients were required to walk repeatedly along a 30-metre corridor for 6 minutes, with the aim of walking as far as possible (detailed in Chapter 4). Data regarding stature, body mass and gender were entered into the pedometer prior to the start of the 6MWT. Following approval from the respiratory physiotherapist and patient, the pedometer was attached on the dominant hip at the mid-clavicular line using an elasticated waist band. Visual step counts were recorded by two researchers using a hand tally device. Pedometer step counts were recorded on completion of the 6MWT and compared to the visual step counts. To gain an understanding of the average walking speed of a COPD patient living in the North East of England, the following calculation was used: (Walking speed (m/s) = 6MWT distance (m) / walking time (s)). For example, a 6MWT distance of 300 m during which a patient has an unintended stop (s) of a total duration of 40s, the 6MWT speed would be 0.94 m/s (e.g. 300/320) (Cesari et al., 2005; Studenski et al., 2011).

5.2.5 Study Protocol 2: Healthy participants

To examine the criterion validity and test-retest reliability of the Fitbug pedometer in a controlled environment, healthy adults visited Northumbria University's exercise laboratory on two separate occasions to perform a walking treadmill protocol. Upon arrival, demographic data was collected and stature, body mass and gender were entered onto the pedometer. Participants received verbal instruction on how to use the treadmill, followed by a 5-minute familiarisation/warm-up period to enable the participant to experience the different speeds during the protocol. In an identical manner to study protocol 1, the pedometer was attached on

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the dominant hip at the mid-clavicular line using an elasticated waist band. The walking protocol consisted of four pre-defined speeds (0.69/0.83/0.97/1.11m/s), reflecting those commonly undertaken by patients with COPD both during the 6MWT (study protocol 1) and based on previous literature (Louvaris et al., 2013).

Each speed was performed at a 0% gradient for a 2-minute duration. Participants received a 5 second warning prior to completion of each speed and adequate rest was provided between speeds. Researchers recorded pedometer step counts between speeds and devices were reset to zero before proceeding to the next speed. Throughout the protocol, a video camera was focused on the participants lower limbs to visually record steps. Visit 2 was undertaken approximately 8 days later, with the walking protocol repeated.

5.2.6 Statistical analysis

All statistical analyses were conducted using SPSS v26 (IBM Statistics) or GraphPad 5.03 with descriptive statistics used to characterise the sample. The criterion validity of the pedometer was calculated using several statistical tests; (1) Deming regression was employed to assess the agreement between Fitbug step counts and visual step counts. Agreement was confirmed if the 95% confidence interval for the slope contained 1 and the intercept contained 0 (Deming, 1943); (2) Bland-Altman plots with associated limits of agreement (LOA) were constructed to visually inspect the data and to assess the agreement with the criterion measure (Bland & Altman, 1986). In the Bland-Altman plot, an average of the criterion measure and Fitbug were plotted against the difference between both measures to give an indication of agreement between the Fitbug and visual step counts; (3) Mean percentage errors between the Fitbug and criterion measure was also calculated using the following equation, “Fitbug step count-visual count / visual count x 100”, with values closer to zero indicating more accurate pedometer results. A percentage relative error exceeding 5% was considered as a practically relevant

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difference (Middleton, Fritz, & Lusardi, 2015; Musto, Jacobs, Nash, DelRossi, & Perry, 2010).

(4) The mean difference between two measures of step counts was measured using a paired sample T Test, with the Wilcoxon test used for non-normally distributed data. A rationale for the criterion validity statistical tests used are detailed in Chapter 4. The test-retest reliability of the Fitbug in healthy participants were calculated using ICC (two-way mixed, absolute agreement, average measures with a 95% confidence interval) between visit 1 and visit 2. Common cut-off points for the ICC assessment were used; $>.90$ (excellent), $.75-.90$ (good), $.60-.75$ (moderate), and $< .60$ (low) (Koo & Li, 2016). Using the ICC as a measure of relative reliability is well-accepted, however it is difficult to interpret ICC values due to their high dependence on the variable of the group being assessed. Therefore, to assess the absolute reliability, typical error expressed as a percentage of Coefficient of Variance (CV) was also calculated. A rationale for the test re-test reliability statistical tests used are detailed in Chapter 4.

5.3 Results

5.3.1 Baseline characteristics

Baseline characteristics of COPD patients and healthy adults are summarised in Table 9. A total of 14 COPD patients and 24 healthy adults volunteered to participate, 18 of whom were males and all of whom were of white ethnicity. A mean age of 73 ± 7 and 58 ± 17 years and a mean BMI of 26.5 ± 5 and 26.2 ± 8 were reported in COPD patients and healthy adults, respectively. All participants were right leg dominant.

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Table 9. Baseline characteristics

	Healthy adults (n=24)	COPD patients (n=14)	<i>p-value</i>
Age (years)	58±17	73±4	0.002
Gender (M/F)	14/10	5/9	0.188
Stature (cm)	171±9	161±13	0.001
Body Mass (kg)	78±16	69±17	0.103
BMI (kg/m ²)	26.5±5	26.2±8	0.882
FEV ₁ (litres)	3.3±0.9	1.1±0.4	0.001
FEV ₁ (% predicted)	110±10	50±20	0.0001
FVC (litres)	4.0±1.1	2.3±0.7	0.001
FEV ₁ /FVC (%)	80±10	48±14	0.001

Abbreviations: M: Male, F: Female, cm: Centimetre, kg: Kilograms, BMI: Body Mass Index, m²: Metres squared, FEV₁: Forced Expiratory Volume in 1 second, FVC: Forced Vital Capacity.

Mean ± S.D are indicated for all columns unless stated.

5.3.2 Criterion validity in COPD patients

During the 6MWT, step counts were deemed consistent between the pedometer (566±66 step counts) and visual (566±65 step counts), with no significant differences ($p>0.05$). Bland-Altman plot analysis were conducted to visually inspect the agreement between the pedometer and visual counts, upper and lower LOA were -33.41 to 32.41 and bias -0.50. Most of the points fall between the 95% LOA suggesting a normal distribution of differences (Figure 7). Deming regression analysis revealed no systematic [13.10 (-77.8 to 104.1) steps] or proportional bias [0.97 (0.82 to 1.13) steps] between the pedometer and visual step counts (Figure 10). The pedometer criterion validity was analysed further based on the average walking speed of COPD patients calculated during the 6MWT (0.85±0.17 m/s), with the analysis stratified by slower (≤ 0.85 m/s) and faster (> 0.85 m/s) walking speeds. Step count recordings were deemed valid

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between the pedometer and visual counts at ≤ 0.83 m/s (531 ± 51 and 611 ± 58) and > 0.85 m/s (529 ± 53 and 614 ± 46) respectively, with no significant differences ($p > 0.05$). LOA were -13.06 to 15.81, with a bias of 1.38 at slower walking speeds (Figure 8) and -52.74 to 46.74, with a bias of 0.83 at faster walking speeds (Figure 9). All data points fall between the 95% LOA suggesting a normal distribution of differences. Deming regression analysis revealed no systematic [-22.02 (-97.48 to 53.43) and 145.6 (-157.9 to 449.1) steps] or proportional bias [1.04 (0.90 to 1.18) and 0.77 (0.27 to 1.16) steps] between the pedometer and visual step counts at slower and faster walking speeds respectively (Figures 11 and 12).

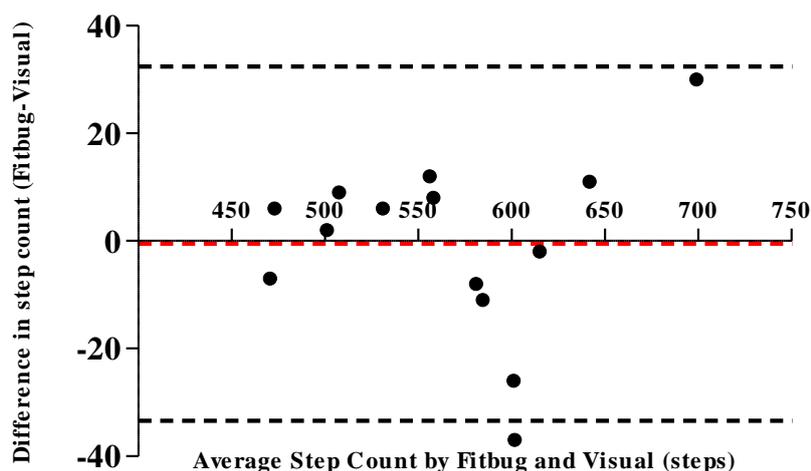


Figure 7. Bland Altman limits of agreement for all COPD patients (red line indicating the mean and dotted lines denoting the upper and lower limits of agreement)

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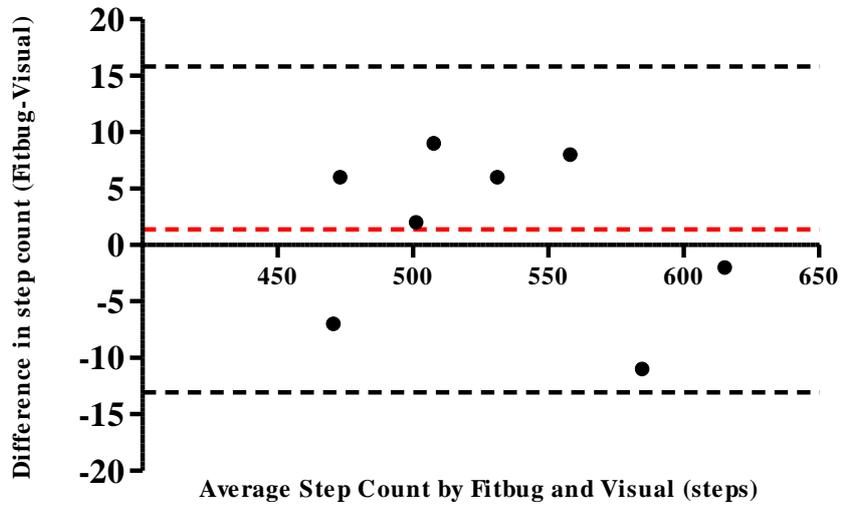


Figure 8. Bland Altman limits of agreement for COPD patients with slower walking speed (≤ 0.85 m/s), red line indicating the mean and dotted lines denoting the upper and lower limits of agreement)

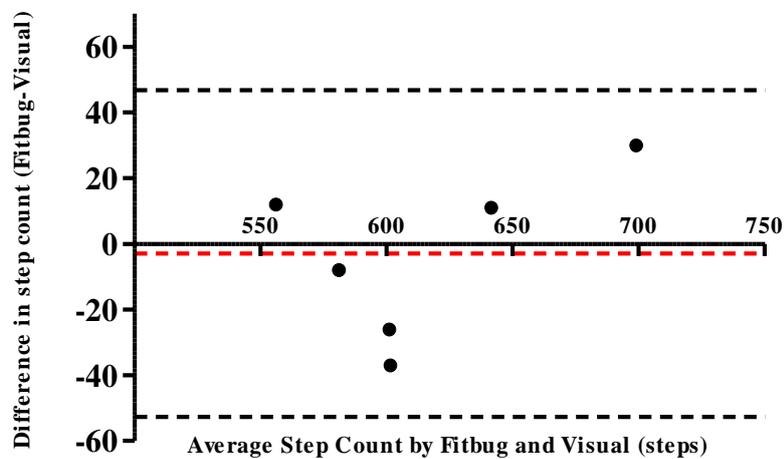


Figure 9. Bland Altman limits of agreement for COPD patients with faster walking speed (> 0.85 m/s), red line indicating the mean and dotted lines denoting the upper and lower limits of agreement)

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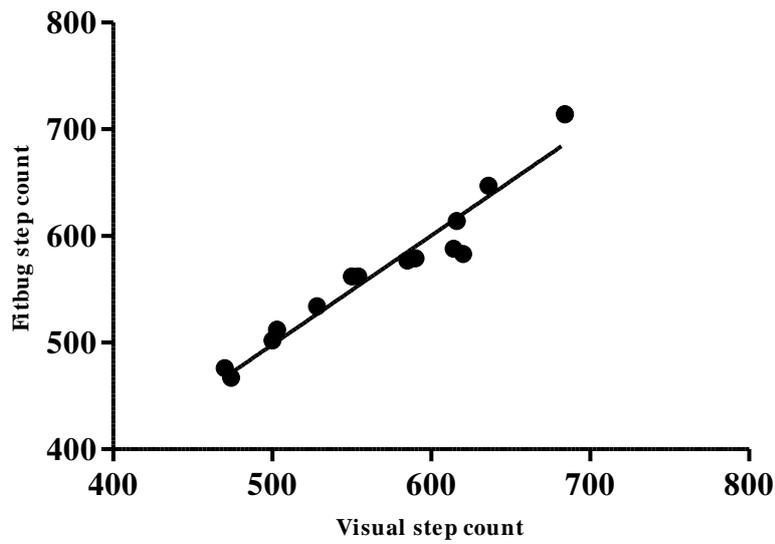


Figure 10. Deming regression analysis for all COPD patients (solid line represents the line of identity)

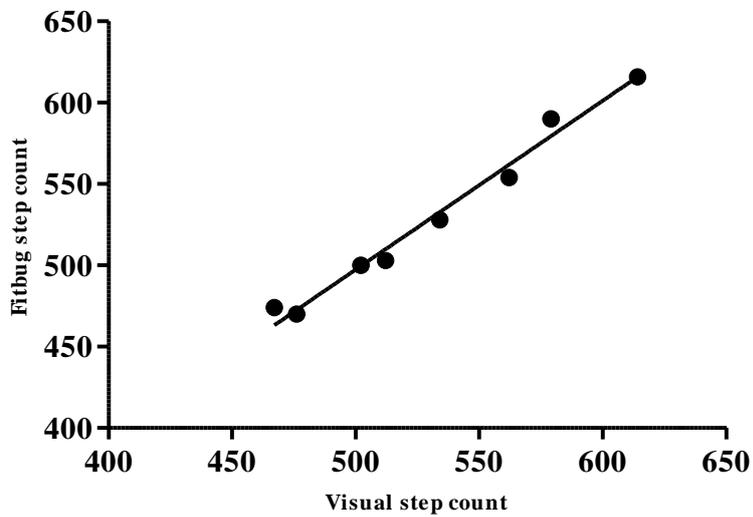


Figure 11. Deming regression analysis for COPD patients with slower walking speed (≤ 0.85 , solid line represents the line of identity)

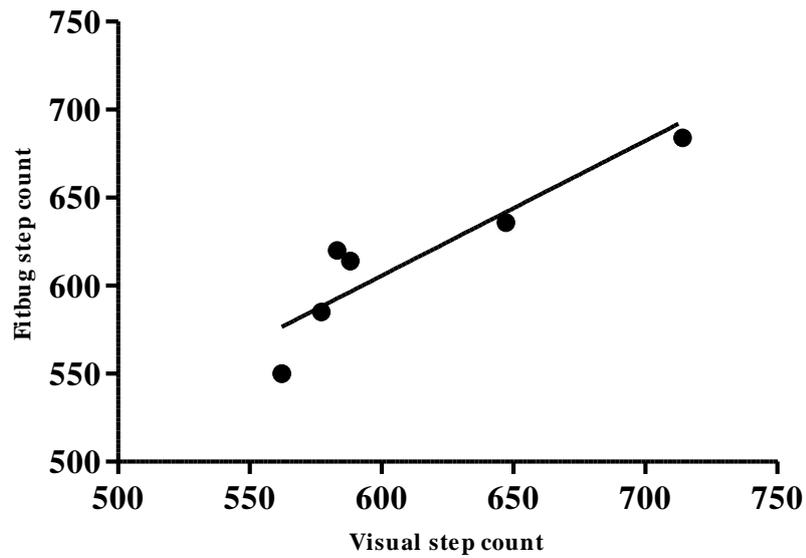


Figure 12. Deming regression analysis for COPD patients with faster walking speed (>0.85, solid line represents the line of identity)

5.3.3 Criterion validity in Healthy Participants

The pedometer was deemed valid, with no significant differences ($p>0.05$) in step counts between the pedometer and visual counts across all four pre-defined treadmill speeds (0.69, 0.83, 0.97 and 1.11m/s) (Figure 13). The mean percentage error of the pedometer at all treadmill walking speeds were less than 5.0% (Figure 14).

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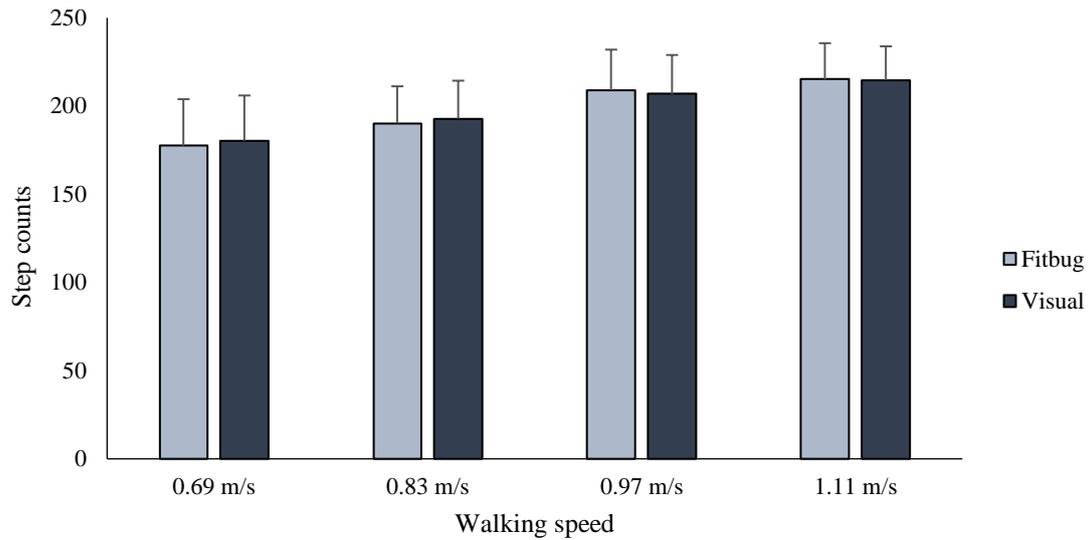


Figure 13. Difference between Fitbug and visual step counts at four pre-defined treadmill speeds in healthy participants. Error bar represents SD

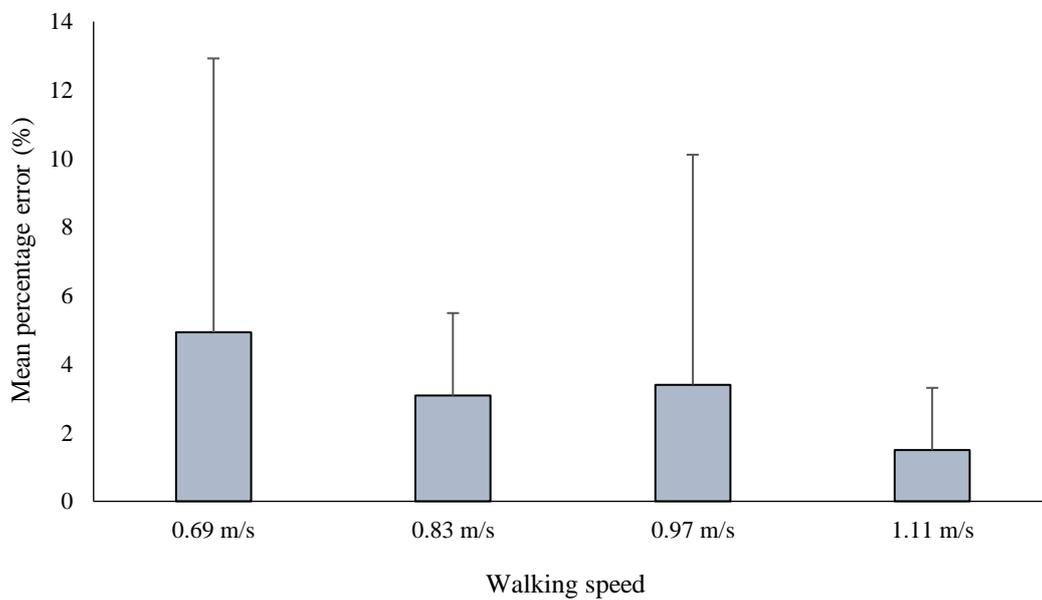


Figure 14. Mean percentage error of Fitbug pedometer at four pre-defined treadmill speeds in healthy participants. Error bar represents SD

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5.3.3.1 Treadmill walking speed (0.69 m/s)

Bland-Altman plot analysis illustrated the upper and lower LOA at 0.69 m/s were -39.29 to 33.20, with a bias of -3.04. Most of the points fall between the 95% LOA suggesting a normal distribution of difference (Figure 15). Deming regression analysis revealed no evidence of systematic [intercept (95% CI) = -10.38 (-84.89 to 64.14) steps] or proportional bias [slope (95% CI) = 1.04 (0.63 to 1.45) steps] between the pedometer and visual step counts at 0.69 m/s (Figure 16).

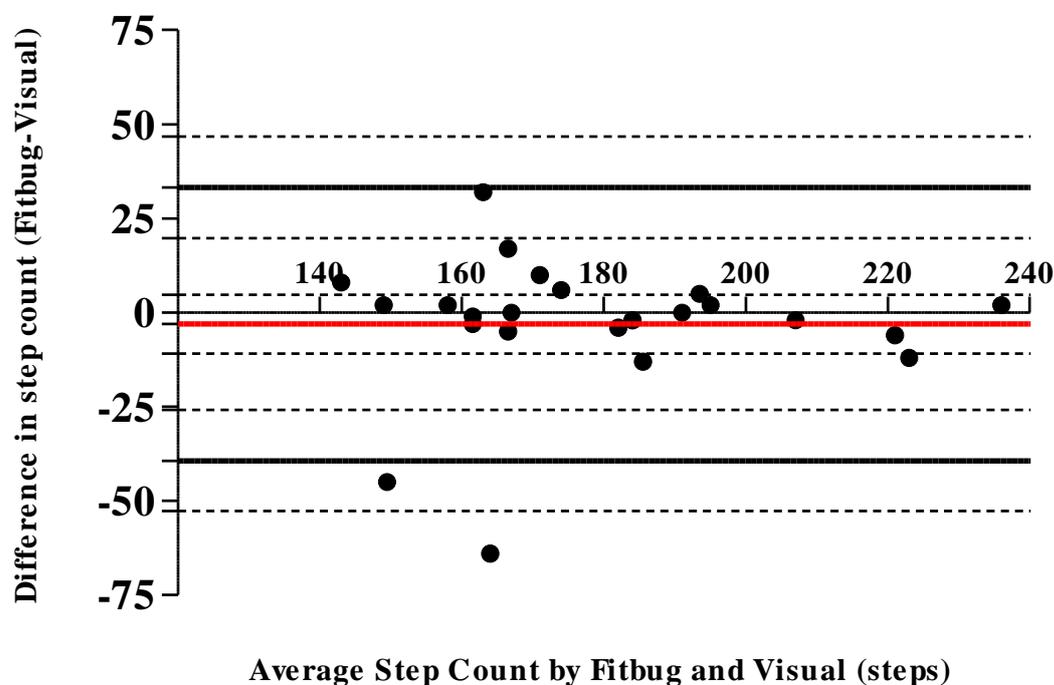


Figure 15. Bland Altman limits of agreement for healthy participants at 0.69 m/s (red line indicating the mean, black solid lines denoting the upper and lower limits of agreement & dashed lines indicating precision estimates 95% CI for the mean, upper and lower limits of agreement).

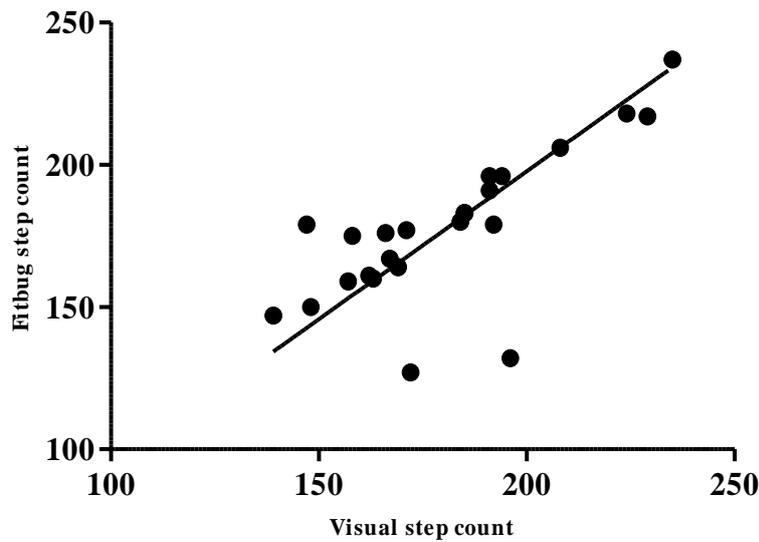


Figure 16. Deming regression analysis for healthy participants at 0.69 m/s (solid line represents the line of identity)

5.3.3.2 Treadmill walking speed (0.83 m/s)

At 0.83 m/s, Bland-Altman plot analysis illustrated the upper and lower LOA were -17.22 to 11.47, with a bias of -2.88. The majority of points fall between the 95% LOA suggesting a normal distribution of differences (Figure 17). Deming regression analysis revealed no systematic [2.96 (-26.87 to 32.80) steps] or proportional bias [0.97 (0.82 to 1.12) steps] between the pedometer and visual step counts, (Figure 18).

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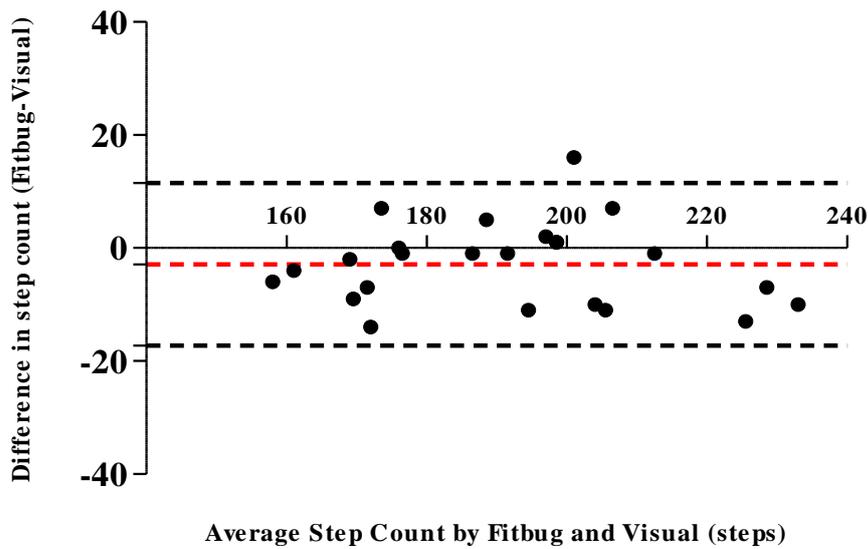


Figure 17. Bland Altman limits of agreement for healthy participants at 0.83 m/s (red line indicating the mean and dotted line denoting the upper and lower limits of agreement)

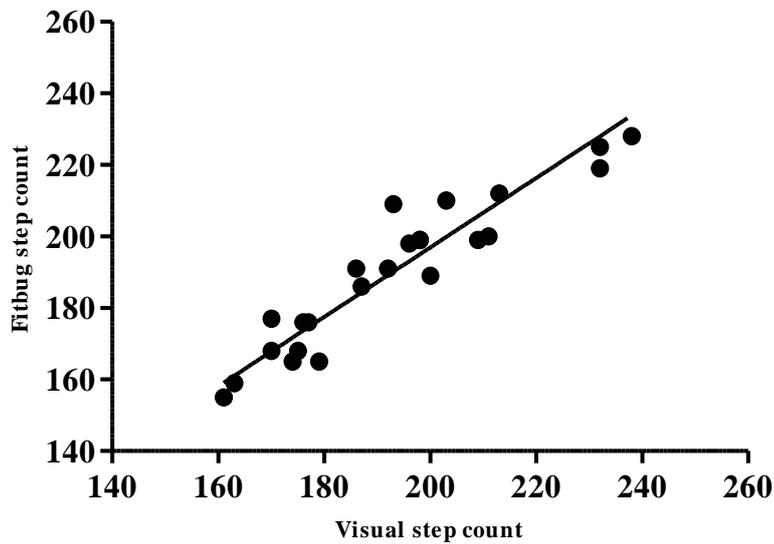


Figure 18. Deming regression analysis for healthy participants at 0.83 m/s (solid line represents the line of identity)

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5.3.3.3 Treadmill walking speed (0.97 m/s)

At 0.97 m/s, Bland-Altman plot analysis illustrated the upper and lower LOA were -11.53 to 15.70 and a bias of 2.08, with all but one data point falling between the 95% LOA suggesting a normal distribution of differences (Figure 19). Deming regression analysis revealed no systematic [-5.99 (-36.37 to 24.39) steps] or proportional bias [1.04 (0.89 to 1.19) steps] between the pedometer and visual step counts, (Figure 20).

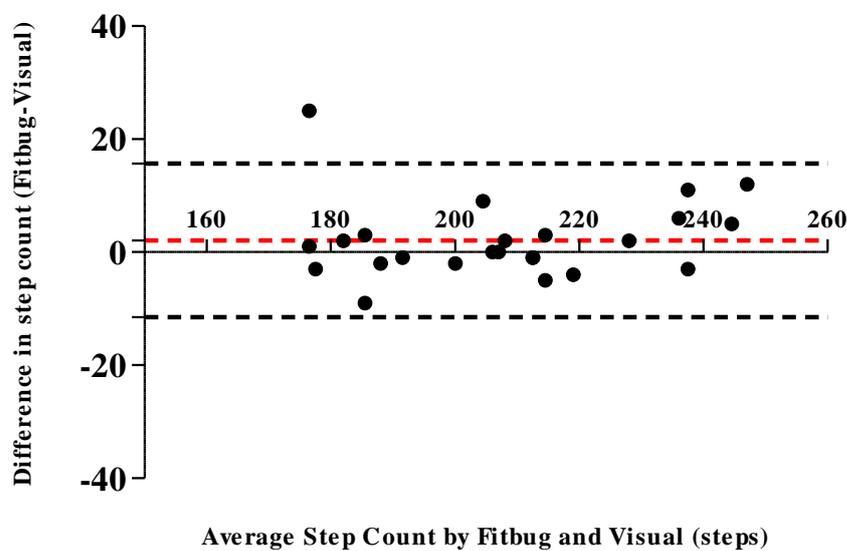


Figure 19. Bland Altman limits of agreement for healthy participants at 0.97 m/s (red line indicating the mean and dotted line denoting the upper and lower limits of agreement)

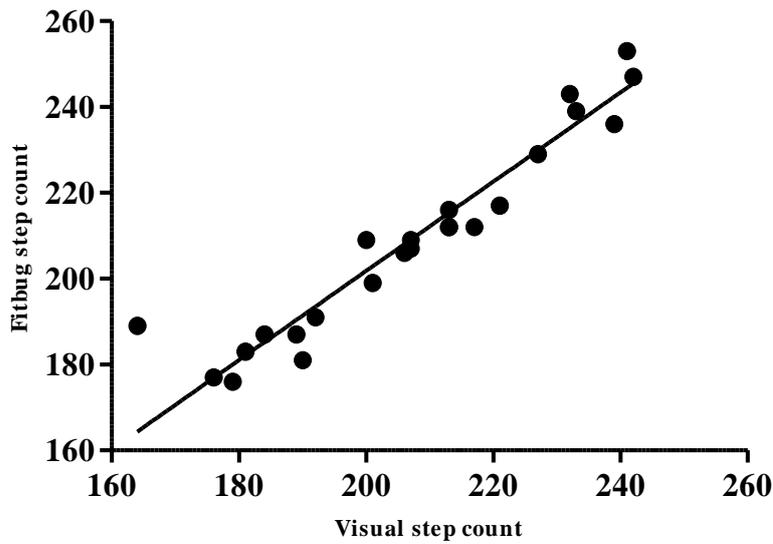


Figure 20. Deming regression analysis for healthy participants at 0.97 m/s (solid line represents the line of identity)

5.3.3.4 Treadmill walking speed (1.11 m/s)

The Bland-Altman plot analysis illustrated the upper and lower LOA were -10.02 to 10.85 and a bias of 0.42 at 1.11 m/s, with most of the data points falling between the 95% LOA suggesting a normal distribution of differences (Figure 21). Deming regression analysis revealed no systematic [-13.78 (-41.09 to 13.54) steps] or proportional bias [1.07 (0.94 to 1.19) steps] between the pedometer and visual step counts (Figure 22).

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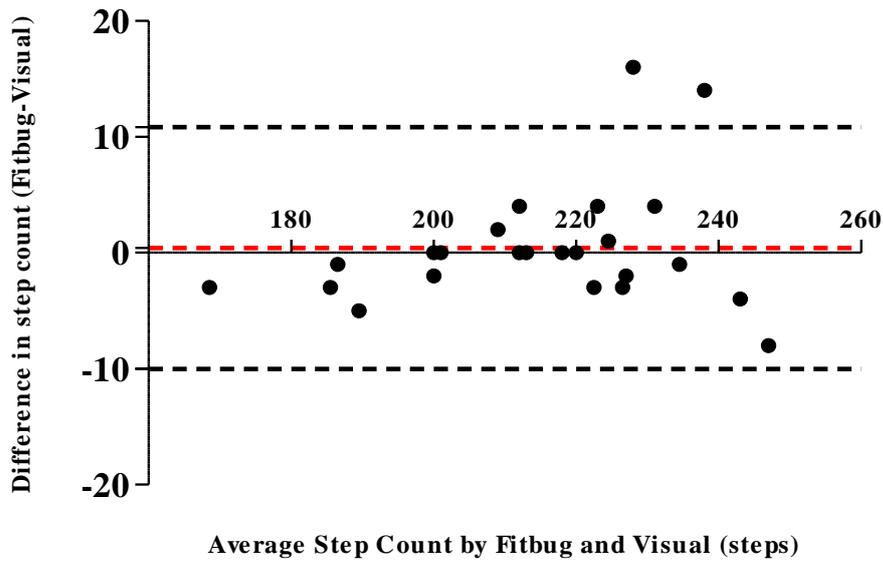


Figure 21. Bland Altman limits of agreement for healthy participants at 1.11 m/s (red line indicating the mean and dotted line denoting the upper and lower limits of agreement)

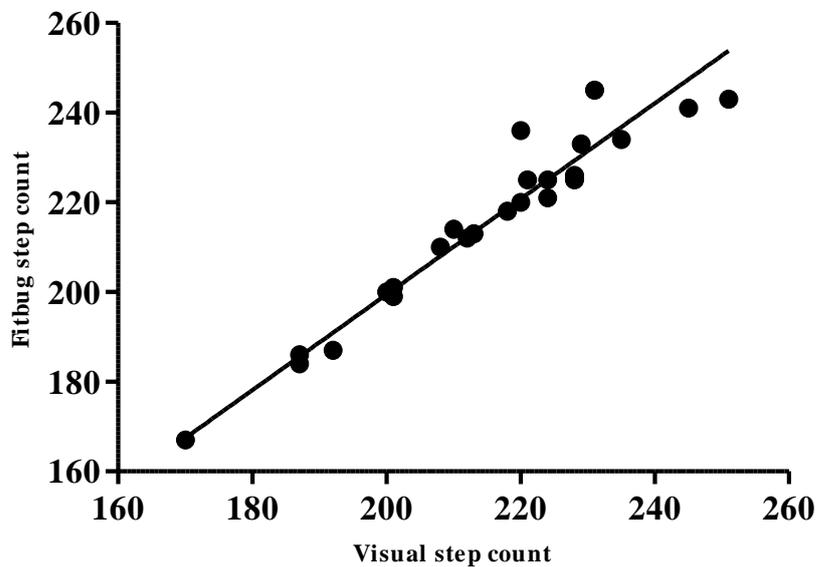


Figure 22. Deming regression analysis for healthy participants at 1.11 m/s (solid line represents the line of identity)

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5.3.4 Test-retest reliability in Healthy participants

The pedometer demonstrated moderate to excellent test-retest reliability at all treadmill walking speeds (ICC >0.81 and 95% CI >0.56). Absolute reliability was deemed good to excellent at all walking speeds, with CV% values of 9.2 (95% CI -7.4 to 2.0) %, 4.0 (3.3-5.1) %, 2.4 (2.0-3.1) % and 1.4 (1.1-1.8) % respectively (Table 10).

Table 10. Test-retest reliability of the Fitbug pedometer

Speed (m/s)	Test 1 Step counts Mean ± SD	Test 2 Step counts Mean ± SD	ICC (95% CI)	CV % (95% CI)
0.69	178±26	172±21	0.81(0.56 to 0.92)	9.2 (-7.4 to 2.0)
0.83	190±21	186±20	0.94(0.84 to 0.97)	4.0 (3.3 to 5.1)
0.97	209±31	205±20	0.97 (0.90 to 0.99)	2.4 (2.0 to 3.1)
1.11	215±20	213±19	0.97 (0.93 to 0.98)	1.4 (1.1 to 1.8)

Abbreviations: CV: Coefficient of variance, SD: Standard Deviation, ICC: Intra-class correlation coefficient. Intra-class correlation coefficient values (ICC_{2,1} values) denote the intra-device reliability of the Fitbug device.

5.4 Discussion

5.4.1 Summary of the main findings

This study examined the criterion validity and test re-test reliability of step counts from a low cost, commercially available pedometer (Fitbug) in a controlled environment prior to its inclusion in a PA behavioural modification intervention (Chapter 7) as a tool to self-monitor PA. No systematic or proportional bias were reported between step count measurement tools in either a laboratory or hospital setting, regardless of walking speed. The test re-test reliability of the Fitbug pedometer was good to excellent across all standardised walking speeds in both treadmill walking and during the 6MWT. The findings of this study support the use of the Fitbug pedometer for the measurement of step counts throughout this thesis in patients with COPD with slow average walking speeds. In addition, these findings have practical implications for both researchers and healthcare providers who wish to quantify PA in a large population and/or monitor PA over the longevity of an intervention feasibly and affordably.

5.4.2 Treadmill Validity and Reliability in Healthy Individuals

Much of the literature surrounding pedometer validity and reliability predominantly covers walking speeds ranging from 0.88 to 1.80 m/s, albeit at walking speeds commonly associated with healthy individuals (Crouter et al., 2003; Feito et al., 2012; Hasson et al., 2009; Kooiman et al., 2015; Takacs et al., 2014). A study by Hasson et al. (2009) validated two commercially available pedometers (Omran and Yamax) across a range of walking speeds in healthy participants (1.12-1.56 m/s), detailing high validity (percent random error = 0.7-1.7) at walking speeds of 1.56 m/s and above. However, when assessing the validity of the Yamax pedometer at the slowest walking speed (1.12 m/s), the level of validity declined considerably (percent error = 16%) (Hasson et al., 2009). In contrast, the performance of the Fitbug used in this study

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at a similar walking speed (1.11 m/s), reported much lower mean percent error than the Yamax (1.5%).

The association between slower walking speeds and reduced validity is well documented in research surrounding pedometers. In a study assessing ten commercially available pedometers across various treadmill walking speeds, authors cited that 6 of the 10 models gave poor validity at speeds varying from 0.90 to 1.11 m/s (Crouter et al., 2003).

It is thought that inconsistencies at primarily slow walking speeds are a result of less pronounced vertical accelerations at the hip (Crouter et al., 2003). These findings are commonly demonstrated in pedometers which use a spring-suspended lever arm mechanism. In such models, recordings are made through up and down movements of a lever arm in response to vertical acceleration at the hip. This momentum causes an electrical circuit, with electrical contacts translating into step counts (Crouter et al., 2005). With inferior vertical accelerations documented at slower walking speeds, the lever arm mechanism is unable to respond as accurately to movement, limiting the electrical contacts and therefore the translated number of step counts (Crouter et al., 2005). Alternatively, many modern pedometers, including the Fitbug, use a piezo-electric mechanism. This mechanism has been deemed more reliable at slower walking speeds due to a greater response to changes in vertical acceleration (Crouter et al., 2005). For example, piezo-electric pedometers have a horizontal cantilevered beam with a weight on the end, which causes compression on a piezo-electric crystal when acceleration commences, generating voltage. The generated voltage is proportionate to the acceleration of the individual, therefore the voltage oscillations formed are used to record step counts (Crouter et al., 2005).

The Fitbit One (Fitbit Inc., San Francisco, CA) pedometer, which incorporates a microelectromechanical triaxial accelerometer, converting acceleration into step counts, reported similar validity and reliability to the Fitbug in healthy participants (Takacs et al.,

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2014). High validity and reliability at various walking speeds, including those below 1.11 m/s were reported. Percentage relative error were found to be similar, with values below 1.3% and ICC >0.95 for all tested walking speeds (Takacs et al., 2014). The validity and reliability of the Fitbit one was not assessed at the slowest walking speeds relevant for COPD patients in the North East of England (0.67 m/s), but it supports the growing evidence that pedometers of that nature (Fitbit and Fitbug) are becoming a more valid tool for usage in clinical populations with predominately slower walking speeds. The ability of pedometers like the Fitbug to provide valid step counts at these slow walking speeds are essential to support interventions aimed at promoting PA (Bravata et al., 2007). This is particularly important when considering PA interventions in COPD patients who report extremely slow walking speeds, reported by those living in the North East of England (see next chapter). Often interventions assessing PA require large sample sizes, with high consumable costs due to the long-term monitoring of PA levels. Incorporating complex monitors (i.e. accelerometer) that are well-validated are desirable, however, they present high consumable costs and do not allow for easy PA monitoring/feedback (Van Remoortel et al., 2012b). As a result, having access to valid and reliable pedometers, that are inexpensive and commercially available, makes monitoring and promoting PA in a research setting more feasible.

5.4.3 6MWT Validity in COPD Patients

Similar findings have been reported when validating pedometers in patients with chronic respiratory diseases (Turner, Houchen, Williams, & Singh, 2012). Statistical analysis at various walking speeds while undertaking an endurance shuttle walk test found significant differences ($p < 0.05$) between the step counter and visual counts at slow (0.49 – 0.75 m/s) and medium (0.83 – 1.05 m/s) walking speeds, with valid step counts only reported in walking speeds greater than 1.14 m/s (Turner et al., 2012). This is contrary to the Fitbug which reported valid

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step counts at walking speeds below and above 0.85 m/s in patients with COPD while undertaking a 6MWT. It should be noted that agreement between pedometer and visual step counts in the Turner et al. (2012) study was determined using a one-way ANOVA, which is a test of differences rather than agreement (Phatak & Nimbalkar, 2017).

5.4.4 Strengths and Limitations

This study focused on the validity and test re-test reliability of the Fitbug pedometer in both healthy adults and COPD patients in a controlled environment, with several strengths. Firstly, novel data regarding the validity and reliability of a commercially available pedometer (Fitbug) in slow walking speeds, commonly documented in patients with COPD living in the North East of England, was documented. Secondly, the validity of the Fitbug among COPD patients within a clinical setting was determined, with the inclusion of data at both slower and faster walking speeds.

However, some limitations to the study should be noted. This study was unable to conduct the outcome measures in the same controlled conditions (exercise laboratory vs hospital) due to the complexity of ethical requirements and timeframes available.

Due to the assessment of the Fitbug pedometer taking place on a treadmill and during a 6MWT, the current study was unable to assess the validity and test re-test reliability of the Fitbug pedometer in a free-living environment, which comes with several limitations. Firstly, the controlled environments in the laboratory (treadmill) and hospital (6MWT) settings only allowed for one type of activity to be examined (walking) and failed to consider different activities of daily living (stair climbing, walking at an incline and changes in direction). These additional activities of daily living may have impacted the overall validity and reliability of the pedometer and should be investigated further in future research (Kooiman et al., 2015). Furthermore, differences in walking gait have been documented between treadmill walking and

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overground walking, which may have influenced the validity and reliability of step counts (Nagano, Begg, Sparrow, & Taylor, 2013).

However, it was felt best to use a treadmill walking protocol to standardise the walking speeds to replicate those commonly implemented by COPD patients. To address these limitations, future studies should aim to investigate the validity and reliability of commercially available pedometers in free-living external environments to ensure their practical use during everyday activities of daily living. In free-living external environments, observing step counts as a criterion measure is typically not feasible. Therefore, several methods have been administered to act as a criterion measure including (1) the use of previously validated activity monitors in the population of interest (Bassett, Toth, LaMunion, & Crouter, 2017), (2) remote video devices including a GoPro (Dedic, 2017) and (3) wireless inertial measurement units (OPAL) (Hwang, Reh, Effenberg, & Blume, 2018; Van Thanh et al., 2017).

The gold standard equivalent used for recording step counts was not standardised across testing locations. Throughout laboratory-based testing, a fixed video camera was used as a feasible gold standard tool to record step counts as the walking trials were administered on a fixed treadmill. This method was not possible in the hospital condition due to numerous complications. Firstly, the standardised corridor used for the 6MWT was narrow and didn't provide adequate space for a video camera to be used. Secondly, the nature of patients walking up and down a corridor made it difficult for a fixed video camera to accurately monitor steps at either end of the corridor.

Finally, increased levels of BMI and/or increased amounts of abdominal adipose tissue can have a negative influence on the accuracy of pedometers (Shepherd, Toloza, McClung, & Schmalzried, 1999). In the current study the majority of participants across both groups had a BMI ranging from 24-27, making it difficult to measure the influence of BMI on the validity of the Fitbug, which has been outlined in other step counters (Crouter et al., 2005).

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5.5 Conclusion

To conclude, agreement between the Fitbug pedometer and visual observations were good to strong at all treadmill walking speeds in healthy individuals and throughout the 6MWT in patient with COPD, with no systematic or proportional bias reported by Deming regression analysis. The test-retest reliability of the Fitbug pedometer was demonstrated as good at all walking speeds in healthy individuals. These findings support the use of the Fitbug pedometer in this thesis as a tool to provide feedback and form goals for improving PA levels in patients with COPD.

EXPERIMENTAL CHAPTERS OF THIS THESIS

- ◇ **CHAPTER SIX:** Evaluate PA, muscular strength and endurance and levels of anxiety and depression in patients with COPD living in the North East of England compared with healthy age matched individuals from the same region of the UK and identify possible correlates associated with PA levels in these patients.

- ◇ **CHAPTER SEVEN:** Investigate the feasibility, acceptability and efficacy of a novel intervention combining PA behavioural modification strategies, Pulmonary Rehabilitation and Cognitive Behavioural Therapy in patients with COPD.

CHAPTER 6

Chapter 6: Case Control and Cross Sectional

6.1 Introduction

It is recommended that people of all ages complete a minimum of 30 minutes moderate intensity daily PA to maintain an acceptable level of physical fitness (World Health Organization, 2020). Those failing to meet this standard of activity are considered insufficiently active, which may lead to increased levels of disability and deconditioning, which are strong predictors of mortality (Erikssen, 2001). Therefore, quantifying levels of daily PA in sedentary individuals is of great importance.

As detailed throughout this thesis, patients with COPD report significantly reduced levels of PA compared to age matched healthy controls, primarily due to high levels of breathlessness related to everyday activities of daily living (Hernandes et al., 2009; Pitta et al., 2005b; Singh & Morgan, 2001; Troosters et al., 2010; Vorrink et al., 2011; Walker et al., 2008; Waschki et al., 2012; Watz et al., 2009). A reduction in everyday activities forces patients into a downward spiral of symptom-induced inactivity, leading to deconditioning and muscle weakness, associated with the vicious cycle of inactivity detailed in Chapter 2 (Troosters et al., 2013). These factors are associated with increased risk of hospitalisation and mortality (Garcia-Aymerich et al., 2006; Garcia-Aymerich et al., 2009; Garcia-Rio et al., 2012; Vaes et al., 2014; Waschki et al., 2011).

Previous literature has objectively compared PA levels between patients with COPD and age-matched healthy controls in both Europe and the UK (Pitta et al., 2005b; Troosters et al., 2010; Watz et al., 2009), however this has not been conducted on a regional basis, within the North East of England. Statistics from Public Health England report that the North East of England has the highest proportion of people with smoking and drinking habits, which are associated with a high sedentary lifestyle (Windsor-Shellard, 2019). Specifically, the region as a whole has the lowest percentage of physically active adults in the UK, increasing the need to observe

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PA levels in this population. In addition, the prevalence of COPD and number of respiratory deaths in people aged over 65 is one of the highest of all UK regions (Snell et al., 2016). Therefore, it is plausible to believe, that patients with COPD living in the North East of England, may be increasingly deconditioned and portray a significantly inactive lifestyle in contrast to COPD patients of other regions in the UK and countries around the world. For many, this will present a greater risk of exacerbations, hospital admissions, morbidity and mortality (Garcia-Aymerich et al., 2006).

As detailed in Chapter 3, patients demonstrating lower levels of PA at baseline are less likely to benefit from an intervention of PA counselling alongside PR (Armstrong et al., 2019). As a result, assessing the baseline PA habits of a specific COPD group, prior to their inclusion in a PA intervention, may help the design and implementation of such an intervention. Based on this concept, and the understanding that COPD patients living in the North East of England were likely to be increasingly deconditioned and living inactive lifestyles, it was important to determine the degree of baseline PA habits in this patient group. Furthermore, it was important to assess the functional impairment of these patients to comprehend their level of disability compared to healthy age-matched individuals, also living in the North East of England.

Therefore, the objectives of this study were a) to evaluate PA levels, muscular function and anxiety and depression status in patients with COPD living in the North East of England in comparison to healthy age-matched individuals from the same region and b) to identify the possible correlates associated with physical inactivity in this group of COPD patients.

6.2 Methods

This case control and cross-sectional study was conducted to establish the daily PA habits of healthy individuals and patients with COPD living in the North East of England. For the case control section of this Chapter, 20 healthy individuals with no history of major medical illness

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and not undertaking regular exercise were recruited on a first come basis and matched according to age (± 3 years) with moderate severe COPD patients who were recruited to PR as part of Chapter 7 in this thesis. Full details on recruitment and inclusion/exclusion criteria for this chapter are detailed in Chapter 4. The 20 healthy individuals attended the exercise laboratory at Northumbria University on two separate occasions to perform lung function and demographic measurements, collect/return an accelerometer and perform measurements of muscular strength and endurance (detailed in Chapter 4). Meanwhile, the 20 COPD patients that were recruited from PR, performed the same measurements as healthy individuals during their baseline assessment for PR.

For the cross-sectional section of this Chapter, data was obtained from 60 COPD patients attending PR who consented to Chapter 7 of this thesis, with both secondary objectives and patient demographics evaluated to identify potential variables associated with physical inactivity.

6.2.1 Procedure (Visit 1)

6.2.1.1 Healthy individuals

Demographic data including age, sex, body mass and stature were obtained. Eligibility to the study was then confirmed based upon the inclusion and exclusion criteria detailed in Chapter 4 and written informed consent was obtained. Following this, an assessment of spirometry and arterial oxygen saturation measurements were conducted (detailed in Chapter 4). The HADS self-reported questionnaire was issued to determine anxiety and depression status. Following completion, participants were provided with an accelerometer (Actigraph GT3X; Actigraph LLC, Pensacola, FL, USA) and guided to wear the device for 7 consecutive days during waking hours (8:00-22:00) around the waist to measure daily PA levels (detailed in Chapter 4).

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6.2.1.2 COPD patients

COPD patients attended PR at either the RVI or Freeman hospitals, providing demographic data including age, gender, stature (cm), body mass (kg) and BMI. Measures of spirometry had previously been conducted as part of routine clinical care in chest clinic, in which data were collected from patient notes (detailed in Chapter 4). Eligibility to the study was then confirmed based upon the eligibility criteria and written informed consent was obtained (detailed in Chapter 4). The HADS self-reported questionnaire was issued, to determine anxiety and depression status. COPD patients were then provided with an accelerometer (Actigraph GT3X; Actigraph LLC, Pensacola, FL, USA) and guided to wear the device for 7 consecutive days during waking hours (8:00-22:00) around the waist, to measure daily PA levels. Assessment of both muscular strength and endurance were then performed, including a 30 second sit-to-stand test and assessment of handgrip and quadriceps strength (detailed in Chapter 4).

6.2.2 Procedure (Visit 2)

6.2.2.1 Healthy individuals

Following 7 consecutive days of wearing the accelerometer, participants attended (+/- 1 day) the exercise laboratory at Northumbria University to undertake muscular function measures including a 30 second sit-to-stand test and assessment of handgrip and quadriceps muscle strength (detailed in Chapter 4).

6.2.2.2 COPD patients

After wearing the accelerometer for 7 consecutive days, COPD patients returned the accelerometer to the hospital PR programme.

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6.2.3 Outcome Measures

6.2.3.1 Primary Outcome Measure

Accelerometer derived PA was determined using the Actigraph wGT3X triaxial accelerometer (Actigraph wGT3X, Actigraph LLC, Pensacola, FL, USA), with measures of steps/day, VMU and time spent in different domains of PA reported (detailed in Chapter 4).

6.2.3.2 Secondary Outcome Measures

- Muscular strength and endurance were evaluated by isometric maximal volitional limb muscle strength assessment (lower body strength), hand grip (upper body strength) and the 30 second sit to stand test (lower body muscle endurance) (detailed in Chapter 4).
- Levels of anxiety and depression were evaluated using the HADS questionnaire (detailed in Chapter 4).

6.2.4 Sample size justification

The minimum sample size for the case control study was based upon a study comparing steps/day recorded in COPD patients (n=19) with healthy age-matched volunteers (n=10), using the mean difference in steps/day (1995) and standard deviation (2088), calculated based upon 80% power and a two-sided 0.05 significance level (Latimer, 2019). A minimum total sample size of 20 participants required to detail significant differences in daily PA (steps/day) between COPD patients and healthy age matched controls was required.

6.2.5 Statistical Analysis

Data for both analyses were collected, coded and inputted into Microsoft Excel. SPSS version 26, (IBM Corp., Armonk, NY, USA) was used for all statistical analyses. Descriptive statistics

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are reported as mean \pm SD unless otherwise specified. Prior to analysis, the assumption of normality for all outcomes were assessed using the Shapiro Wilks test, with a p value >0.05 indicating normally distributed data.

6.2.5.1 Case control

Throughout this study, between-group data was reported as mean; 95% CI unless stated otherwise. To assess the between-group effect of outcome variables in COPD patients compared to healthy age-matched individuals, an independent t-tests or Mann-Whitney U test, if data was non-normally distributed, was used. To assess the linear trend in PA across GOLD stages, a repeated measures ANOVA, with appropriate post hoc analysis, was used.

6.2.5.2 Cross sectional

Following the Shapiro Wilks test, PA variables including steps per day, VMU and MVPA were found to be non-normally distributed. As a result, Spearman's correlation coefficient was implemented to assess for correlations between PA variables, secondary variables and demographic data. Following this, a multiple linear regression model, using a backward stepwise method, was constructed to assess the variability of all variables that were significantly associated with PA.

6.3 Results

Of the 42 healthy individuals who expressed interest, 32 returned the eligibility form and were assessed against the inclusion criteria. Following confirmation of the inclusion criteria, 20 healthy participants matched the age (± 3 years) of the 20 COPD patients and were recruited to the study. The most common reasons for exclusion were not matching the age criteria ($n=9$). Other reasons included smokers ($n=2$) and musculoskeletal implications ($n=1$). Participant flow through this study is presented in Figure 23.

6.3.1 Baseline characteristics

Baseline characteristics of healthy individuals and COPD patients are included in Table 11. Of the overall sample, 26 (65%) were male and 14 were female (35%), with all participants/patients of white ethnicity. Healthy individuals ($n=20$) had a mean age of 66 ± 7 , with a range of ages from 52-75 years. Just under half of the healthy individuals were in part- or full-time employment while the remaining individuals were retired. Clinical characteristics of the healthy individuals included a mean BMI of 27.8 ± 5 kg/m², resting heart rate of 70 ± 12 beats/min and resting oxygen saturation of $98\pm 1\%$. Lung function characteristics included a FEV₁ of $111\pm 13\%$ predicted. COPD patients ($n=20$) had a mean age of 68 ± 5 , with a similarly wide age range of 52-76 years. Most patients were retired (87%) with the rest in part-time employment. Clinical characteristics of the COPD patients included a mean BMI of 25.3 ± 6 kg/m², resting heart rate of 81 ± 11 beats/min and resting oxygen saturation of $93\pm 1\%$. Pulmonary characteristics included a FEV₁ of $41\pm 15\%$ predicted.

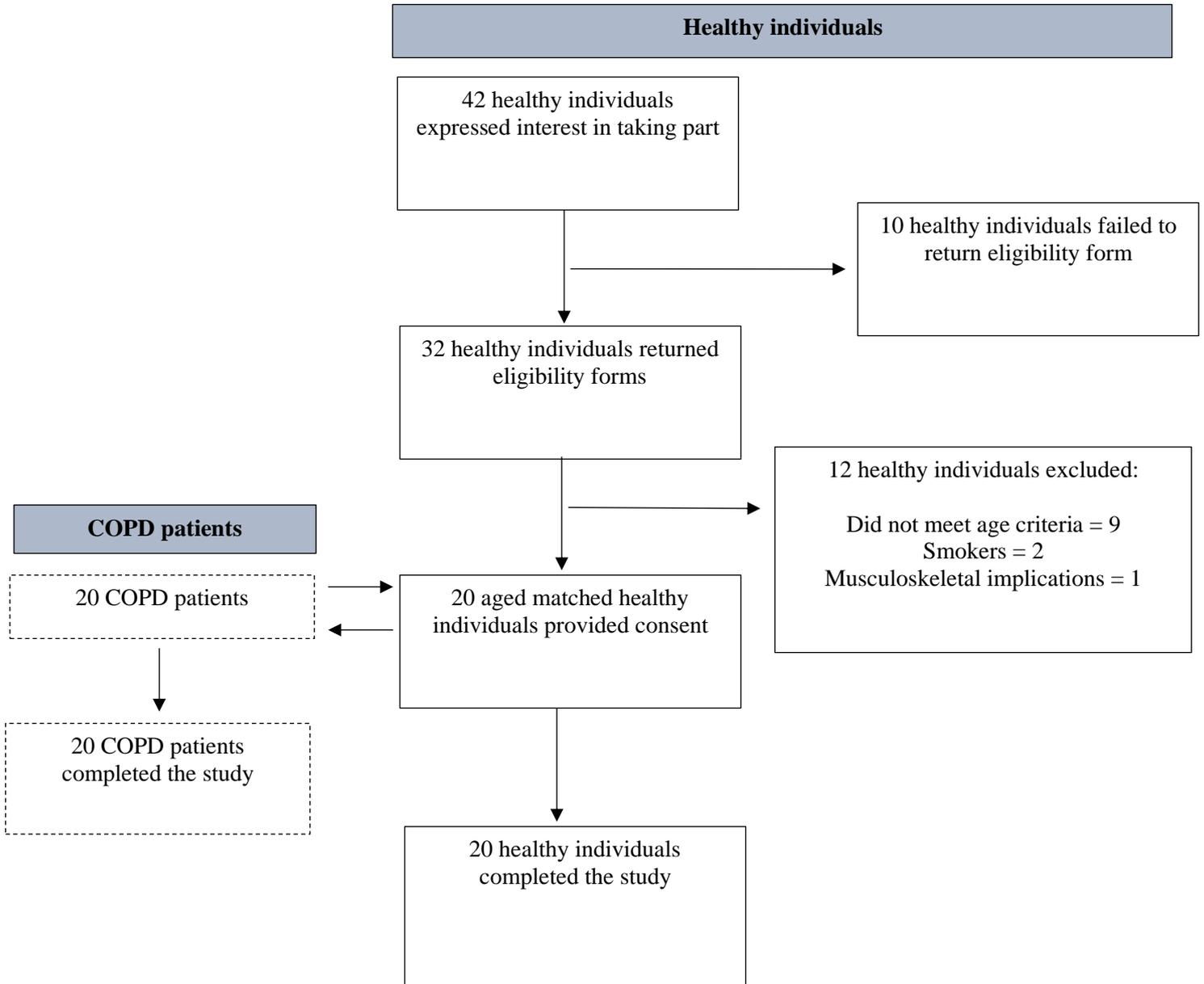


Figure 23. Flow of participants and patients through the case control study

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Table 11. Baseline Characteristics

Baseline Characteristics	COPD n = 20	Healthy n =20	p-value
Age, years	68±5	66±7	0.185
Sex, male/female	13/7	13/7	n/a
Ethnicity (WB)	20	20	n/a
Height, cm	167±11	171±8	0.216
Body mass, kg	71±15	80±15	0.053
BMI, kg/m ²	25.3±6	27.8±5	0.221
HR beats/min	81±11	70±12	0.105
SPO ₂ (%)	93±1	98±1	0.243
FEV ₁ , Litres	1.10±0.4	3.17±0.8	< 0.001
FEV ₁ , % PRED	41±15	111±13	< 0.001
FVC, Litres	2.20±0.7	3.82±1.0	< 0.001
FEV ₁ /FVC, %	51±13	83±0.07	< 0.001
MRC	3±1	n/a	n/a
Gold Stage I	0	n/a	n/a
Gold Stage II	6	n/a	n/a
Gold Stage III	8	n/a	n/a
Gold Stage IV	6	n/a	n/a
6MWD, m	272±96	n/a	n/a

Abbreviations: WB: White British, cm: Centimetres, kg: Kilograms, BMI: Body Mass Index, m²: Metres squared, HR: Heart Rate, SPO₂: oxygen saturation, FEV₁: Forced Expiratory Volume in 1 second, FVC: Forced Vital Capacity. MRC: Medical Research Council Dyspnea scale, 6MWD: Six Minute Walk Distance, m: Metres, n/a: data not available.

Mean ± S.D are indicated for all columns unless stated.

6.3.2 Outcome measures

6.3.2.1 Physical activity

All PA outcome measures between COPD patients and healthy controls are provided in Table 12. Compared to healthy individuals, COPD patients reported significantly lower step/day (by -4833 steps/day; 95% CI -6862 to -2802 steps/day, $p = 0.000$) and movement intensity (by -361 VMU; 95% CI -490 to -233 VMU, $p = 0.001$). In addition, time spent in activities of

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MVPA were significantly lower in COPD patients than healthy individuals (by -34 mins; 95% CI -45 to -22 mins, $p = 0.001$). When comparing PA levels across GOLD stages, Figure 24 illustrated a gradual reduction in steps/day, movement intensity and MVPA with increased disease severity. Specifically, step/day was reduced by $-60\pm 62\%$, $-63\pm 68\%$ and $-76\pm 63\%$ across GOLD stages II to IV, respectively. Both the movement intensity and time spent in MVPA in COPD patients were also reduced by $-48\pm 42\%$, $-57\pm 53\%$, and $-69\pm 60\%$ VMU and -75 ± 61 , -83 ± 65 , and $-94\pm 87\%$ min in GOLD stages II, III and IV, respectively (Figure 24). These differences all reached statistical significance as of GOLD stage II ($p < 0.05$).

Table 12. PA outcome measures in COPD patients and healthy age-matched individuals

PA outcome measures	COPD n = 20	Healthy n = 20	<i>p-value</i>
	Mean \pm SD		
Step/day	2493 \pm 1497	7326 \pm 945	< 0.001
Movement Intensity (VMU)	264 \pm 127	625 \pm 57	< 0.001
Sedentary PA (< 1.5 METs) mins	521 \pm 84	486 \pm 18	0.203
Light PA (1.5-3.0 METs) mins	133 \pm 49	155 \pm 11	0.162
MVPA (> 3.0 METs) mins	6 \pm 8	40 \pm 6	< 0.001

Abbreviations: METS: Metabolic equivalents, PA: Physical Activity, mins: Minutes.
Mean \pm S.D are indicated for all columns unless stated.

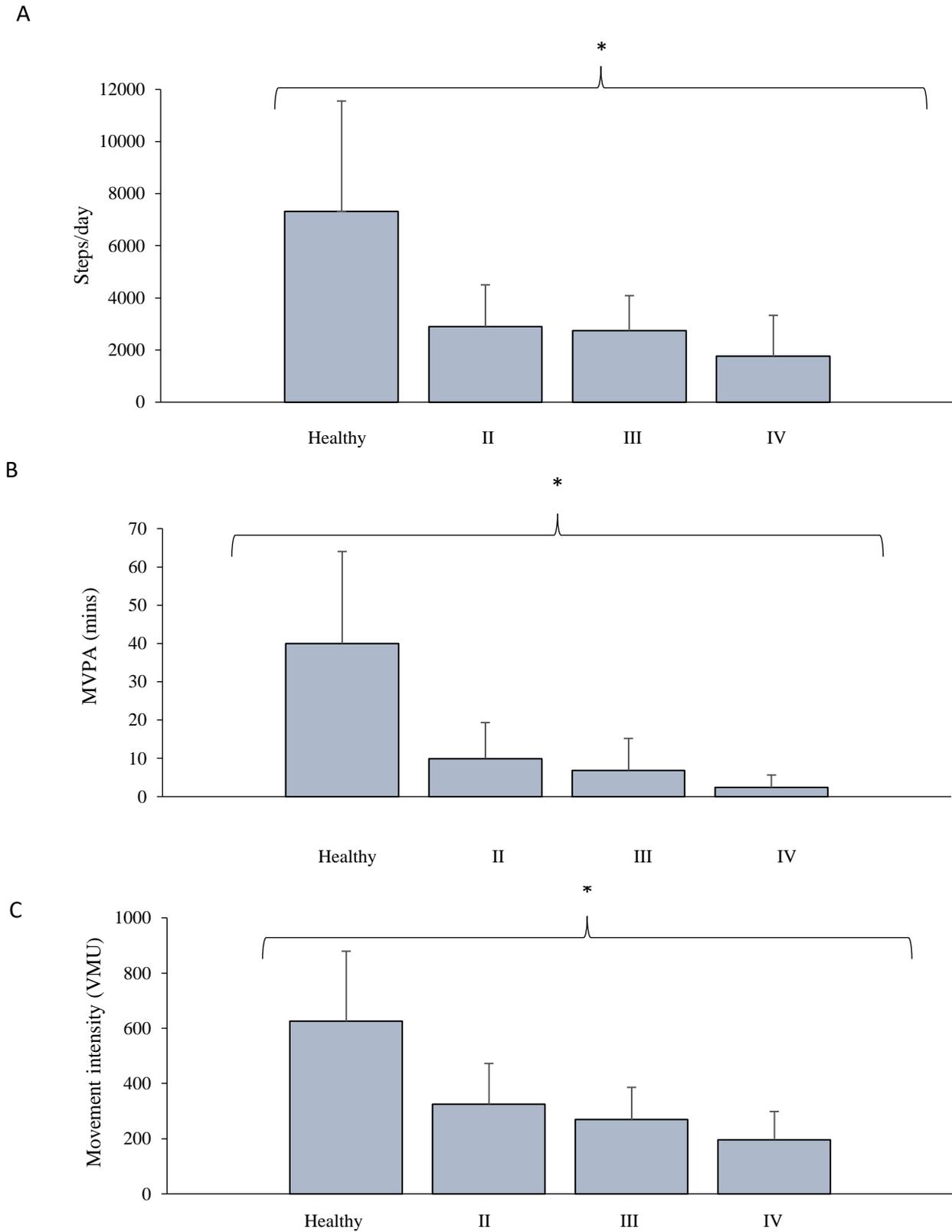


Figure 24. Change in (A) steps/day (B) MVPA (C) Movement intensity in both healthy individuals and Gold stage II-IV COPD respectively. (Error bars represent SD, * Represents statistical significance [<0.05])

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6.3.2.2 *Muscular strength and endurance*

All muscular strength and endurance outcome measures between COPD patients and healthy controls are provided in Table 13. COPD patients reported significantly reduced lower body muscle strength (by -20.2; 95% CI -27.1 to -14.8 kg, $p = 0.001$), strength (by -12.9; 95% CI -18.9 to -6.8 kg, $p = 0.001$) and sit to stand repetitions (by -8; 95% CI -11 to -6 reps, $p = 0.0001$) compared to healthy age-matched individuals.

6.3.2.3 *Anxiety and Depression*

Anxiety and depression scores determined using the HADS questionnaire between COPD patients and healthy controls are provided in Table 13. COPD patients experienced significantly higher levels of both anxiety and depression in comparison to healthy individuals (by 8; 6 to 11 points, $p = 0.000$ and by 8; 6 to 10 points, $p = 0.001$) respectively. Across GOLD stages of COPD, both HADS anxiety and depression were significantly lower as of GOLD stage II compared with healthy individuals, with anxiety scores being higher by 7 ± 5 , 9 ± 6 and 9 ± 3 points, respectively and depression scores being higher by 6 ± 4 , 9 ± 6 and 9 ± 5 points in GOLD stages II-IV, respectively.

Table 13. Other outcome measures in COPD patients and healthy age-matched individuals

Other outcome measures	COPD n = 20		Healthy n = 20	p-value
	Mean ± SD			
QMVC (kg)	20.7±7.3		40.9±11.4	0.001
HG (kg)	19.8±8.2		32.7±10.6	0.001
Sit to Stand (reps)	10±3		18±5	0.001
HADS Anxiety	10±5		2±1	0.001
HADS Depression	9±5		1±2	0.001

Abbreviations: QMVC: Quadriceps Muscle Voluntary Contraction, HG: Hand Grip.
Mean ± S.D are indicated for all columns unless stated.

6.3.3 Correlates of physical activity in COPD patients

Table 14 provides a detailed overview of the single correlations observed between PA outcome measures, namely steps/day, VMU and MVPA, with various secondary outcomes and baseline demographics of 60 COPD patients. Steps/day were significantly associated with pulmonary function variables (FEV₁, FEV₁ % Pred, FVC and FEV₁/FVC %), 6MWD, QMVC, domains of the CCQ questionnaire, HADS depression, MRC and Gold stage of COPD.

VMU was significantly associated with pulmonary function variables (FEV₁, FEV₁ % Pred, FVC and FEV₁/FVC %), 6MWD, CCQ total, symptom and functional domains, HADS depression, MRC and Gold stage of COPD.

Finally, the time COPD patients spent in MVPA was significantly associated with both FEV₁ and FEV₁/FVC %, 6MWD, QMVC, CCQ symptoms, MRC and Gold stage of COPD.

Further analysis of our data through a final multivariable linear regression model provided in Table 15 showed that, in patients with COPD living in the North East of England, FEV₁ % predicted and the functional domain of the CCQ accounted for most of the variability in the

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stepwise multiple regression model for steps per day (adjusted $R^2 = 30\%$). In terms of VMU, MRC dyspnea scale and FEV₁ % predicted accounted for most of the variability in the stepwise multiple regression model (adjusted $R^2 = 24\%$). Finally, FEV₁ % predicted and QMVC accounted for the most variability in the stepwise multiple regression model for MVPA (adjusted $R^2 = 22\%$).

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Table 14. Spearman’s correlation of PA (steps/day) with outcomes in COPD patients

	Steps/day	VMU	MVPA
BMI	-0.091	-0.146	-0.070
FEV ₁ , Litres	0.448**	0.433**	0.369**
FEV ₁ % Pred	0.289*	0.378**	0.214
FVC, Litres	0.391**	0.260*	0.238
FEV ₁ /FVC, %	0.263*	0.323*	0.301*
6WMD, metres	0.429**	0.367**	0.395**
30s STS	0.160	-0.030	0.156
Leg Strength (QMVC), kg	0.352**	0.219	0.288*
HG strength, kg	0.144	0.053	0.118
CAT	-0.55	-0.38	-0.31
CCQ total	0.384**	-0.293*	-0.230
CCQ Symptoms	-0.432**	-0.309*	-0.262*
CCQ Functional	-0.403**	-0.321*	-0.232
CCQ Mental	-0.281*	-0.171	-0.150
HADS anxiety	-0.182	-0.194	-0.113
HADS depression	-0.252*	-0.268*	-0.086
MRC	-0.435**	-0.425**	-0.445**
Gold Stage, II, III, IV	-0.314*	-0.413**	-0.267*

Abbreviations: BMI: Body Mass Index, FEV₁: Forced Expiratory Volume in 1 second, FVC: Forced Vital Capacity, 6MWD: Six Minute Walk Distance, s: Seconds, kg: Kilograms, CAT: COPD Assessment Test, CCQ: Clinical COPD questionnaire, HADS: Hospital Anxiety and Depression Scale, MRC: Medical Research Council dyspnea scale.

*. Significance <0.05, **. Significance <0.01

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Table 15. Final multivariable linear regression models for PA outcome measures

PA		Unstandardised coefficients		Standardised coefficients		
		<i>B</i>	Std. Error	Beta	t	Sig
Steps/day	(Constant)	2816.071	795.077		3.542	0.001*
	FEV ₁ % predicted	1446.415	465.805	.350	3.105	0.003*
	CCQ F	-444.346	143.625	-.349	-3.094	0.003*
VMU	(Constant)	391.893	94.335		4.154	0.001*
	MRC	-63.486	23.657	-.317	-2.684	0.009*
	FEV ₁ % predicted	97.361	36.480	.315	2.669	0.010*
MVPA	(Constant)	-4.375	2.447		-1.787	0.079
	FEV ₁ % predicted	4.982	1.949	.310	2.556	0.013*
	QMVC	0.221	0.093	.290	2.385	0.020*

Abbreviations: FEV₁: Forced Expiratory Volume in 1 second, CCQ: Clinical COPD questionnaire, MRC: Medical Research Council dyspnea scale, QMVC: Quadriceps muscle voluntary contraction.

*. Correlation is significant at the 0.05 level (2-tailed)

6.4 Discussion

6.4.1 Summary of main findings

The findings of this study identified that COPD patients living in the North East of England had significantly lower levels of daily PA, impaired upper and lower body muscular strength and lower body muscular endurance and elevated anxiety and depression compared to healthy age-matched individuals living in the North East of England. To our knowledge, this is the first study to assess PA levels in COPD patients living in the North East of England region, providing novel data that can be used to compare the activity levels of COPD patients across various regions of the UK and Europe. Furthermore, this study has documented a gradual reduction in PA outcomes across GOLD-stages, delivering additional evidence that more severe COPD patients are at greater risk of physical inactivity and the associated risks that follow (Garcia-Aymerich et al., 2006). Given the diminished levels of PA documented in COPD patients living in the North East of England and the associated risk factors, as well as the North East of England presenting one of the highest prevalence's of respiratory deaths nationally (Snell et al., 2016), the requirement for PA behavioural modification interventions to support these patients at regional level has never been greater.

6.4.2 Physical activity outcomes

The overall results of this study demonstrate that COPD patients living in the North East of England have significantly lower PA levels than healthy age-matched individuals living in the same region of the UK. These findings support several single and multi-centre studies that have objectively measured PA in COPD patients (Coronado et al., 2003; Hernandez et al., 2009; Mercken et al., 2005; Pitta et al., 2005b; Schonhofer et al., 1997; Singh & Morgan, 2001; Troosters et al., 2010; Walker et al., 2008; Waschki et al., 2012; Watz et al., 2009).

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In terms of steps/day, an outcome which is conventionally assessed using pedometers and accelerometers, two multi-centre studies (Troosters et al., 2010; Waschki et al., 2012), reported a reduced number of steps/day equating to -40% and -54% respectively in COPD patients compared to healthy controls (Troosters et al., 2010; Waschki et al., 2012). In contrast, the current study reports a greater reduction in steps/day of -65% between COPD patients and healthy individuals, suggesting that COPD patients living in the North East of England were at greater risk of decline in steps/day compared to their healthy counterparts. These differences could be explained by the severity of COPD patients across the various studies. For instance, the 70 COPD patients recruited from outpatient clinics in the Troosters et al. (2010) study reported a greater baseline FEV₁ % Pred (54±23%) than documented in the current study (41±15%), which may have postulated the lower steps/day. Interestingly, when looking at the study of Waschki et al. (2012), FEV₁ was matched, however baseline steps/day were considerably lower in the current study. This contrast may have been a result of several factors, including superior exercise capacity and lower MRC dyspnea scores in the Waschki et al. (2012) study. As discussed earlier in this thesis, the association between greater levels of PA and more preserved functional exercise tolerance, consistent with the idea of “functional reserve”, has been reported previously (Osadnik et al., 2018). Therefore, COPD patients living in the North East of England may be less capable of maintaining greater levels of PA due to an inhibitory ceiling limitation caused by the low functional reserve (Osadnik et al., 2018). Meanwhile, a number of studies including that of Waschki et al. (2012) have confirmed a significant association between higher MRC dyspnea scores and lower PA levels (Watz et al., 2009).

Regarding the time spent in MVPA, significant reductions were documented in COPD patients compared to healthy age matched controls. Both Troosters et al. (2010) and Watz et al. (2009) reported reductions in MVPA in patients with COPD when compared to healthy age-matched

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individuals. However, time spent in MVPA was considerably lower in the current study than both other studies (Troosters et al., 2010; Watz et al., 2009). Notably, it is emphasised by the WHO that those over the age of 65 years should target a minimum of 150 minutes of moderate intensity aerobic activity or 75 minutes of vigorous intensity per week in order to protect cardiovascular health in adults (World Health Organization, 2020). Based on these recommendations, it is clearly shown that COPD patients living in the North East of England do not meet the WHO guidelines.

With an obvious deterioration of daily PA levels in COPD patients living in the North East of England, it was important to understand how these PA levels compare with patients living in other residential location in mainland Europe and the UK. Specifically, data from this study was compared to data from the multicentre study of Boutou et al. (2019). Interestingly, a significant reduction in steps/day (-42%) was reported when data from the North East of England was compared to five other European cities (Athens, Edinburgh, Leuven, London and Groningen) (Boutou et al., 2019). On closer analysis with cities in the UK, patients living in the North East of England continued to experience significant reductions in daily PA levels compared to those living in both London (-41%) and Edinburgh (-25%) (Boutou et al., 2019). Potential factors that have been shown to influence PA levels across geographical locations include; climate (rainfall, daylight & temperature), socio-cultural, socio-economic and micro/macro environments of the area of living (Boutou et al., 2019). When looking specifically at patients living in the North East of England, one could assume that many of these potential factors that are documented to reduce levels of PA may have had an impact on this patient population.

6.4.3 Gold stages of COPD and PA

Another major finding of this study was the significant gradual reduction in PA levels with increasing COPD severity. Although a weak correlation between PA and lung function has previously been demonstrated (Watz et al., 2014), data from the current study clearly demonstrated a significant association between FEV₁% Pred and PA variables, meaning the PA levels of COPD patients living in the North East of England are reduced with greater severity of COPD. These findings are similar to three other studies that implemented a similar methodology for assessing daily PA levels (Troosters et al., 2010; Watz et al., 2008; Watz et al., 2009). Specifically, an accumulation of steps/day across the three previous studies decreased by 69%, 71%, 65% and 76% from GOLD stage I to GOLD stage IV, respectively compared to healthy controls (Troosters et al., 2010; Watz et al., 2008; Watz et al., 2009). Interestingly, compared to the other studies (Troosters et al., 2010; Watz et al., 2008; Watz et al., 2009), healthy individuals from the current study reported the lowest number of steps/days, which alongside the greatest reduction in steps/day from healthy to GOLD stage IV, continues to highlight the diminished level of PA in individuals living in the North East of England, regardless of health status. These findings may present an opportunity to tailor future PA interventions based on the severity of patients and the associated levels of PA. For instance, less severe COPD patients with a sustained level of PA at baseline may find exercise training, as part of PR, effective in order to maintain and support a gradual gain in daily PA levels. Whereas those more severe COPD patients with diminished baseline PA levels, may require a multifaceted approach incorporating aspects of exercise, behavioural support and motivation (Spruit et al., 2015).

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6.4.4 Muscular Function

This study identified that COPD patients living in the North East of England reported significant impairment in upper and lower body muscular strength and lower body muscular endurance compared to healthy age matched individuals, suggesting that overall muscle function in patients with COPD living in the North East of England is majorly diminished.

Early work from Serres, Gautier, Varray, and Prefaut (1998) aimed to determine whether COPD patients had impaired skeletal muscle performance (i.e. maximal strength and endurance) compared to healthy controls. Their analysis of peripheral muscle performance reported no significant differences in maximal muscle strength between groups, while muscular endurance was significantly decreased compared to healthy controls (Serres et al., 1998). They suggested that reduced muscular endurance was a result of abnormal muscle metabolism, with such changes consistent with the metabolic changes commonly observed in skeletal muscle of COPD patients.

Since these findings, research regarding muscular function in COPD has evolved. In a review article from Donaldson, Maddocks, Martolini, Polkey, and Man (2012), they documented that compared with age and gender matched healthy controls, isometric quadriceps strength was reduced by around 20%-30% in patients with COPD (Bernard et al., 1998; Man et al., 2005). In terms of quadriceps endurance, they found that studies reported an increased susceptibility to fatigue, with a rapid decline in quadriceps performance during both continuous (Allaire et al., 2004; Man et al., 2003) and repeated bouts of exercise (Coronell et al., 2004; Mador, Deniz, Aggarwal, & Kufel, 2003). Such reductions in muscle strength were largely explained by a comparable reduction in quadriceps cross-sectional area and mass, assessed by magnetic resonance imaging and ultrasound or computed tomography (Marquis et al., 2002; Mathur, Takai, MacIntyre, & Reid, 2008; Seymour et al., 2009). Meanwhile the reductions in

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quadriceps endurance were more likely related to the loss of fatigue-resistant type I fibres and subsequent reduction in oxidative capacity (Gosker et al., 2007).

6.3.5 Anxiety and Depression

Anxiety and depression measured via the HADS questionnaire was impaired in patients with COPD compared to healthy controls. Remarkably, to our knowledge this is the first study to assess levels of anxiety and depression in COPD patients compared to healthy individuals. Contrary to this lack of research, elevated levels of anxiety and depression have been reported in 40% and 25% of COPD patients respectively (Panagioti, Scott, Blakemore, & Coventry, 2014). Furthermore, anxiety and depression may have a considerable impact on PA levels, with reductions in steps/day greater than the clinically important difference in patients with COPD who reported elevated levels of anxiety and depression via the HADS questionnaire (Boutou et al., 2019).

6.3.6 Correlates of physical activity parameters in patients with COPD

As well as understanding the severity of physical inactivity in COPD patients in the North East of England, it was necessary to understand the factors associated with physical inactivity, in order to consider these aspects when designing and implementing a PA behavioural modification intervention. Results from this study demonstrated several statistically significant correlates of steps/day, VMU and MVPA, including several demographic variables, pulmonary function variables, 6MWD, QMVC, quality of life domains (CCQ), depression and dyspnea. Further analysis confirmed that FEV₁ (% predicted) alongside MRC, CCQ F and QMVC provided the largest variability in steps/day, VMU and MVPA, respectively. However, these coefficients only accounted for around 22-30% of the variability and further evaluation of the potential association between variables of PA and patient demographics are necessary.

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Several previous studies have explored such relationships in COPD patients, particularly the response of FEV₁ values (Belza et al., 2001; Pitta et al., 2005b; Schonhofer et al., 1997; Singh & Morgan, 2001; Steele et al., 2000; Troosters et al., 2010; Waschki et al., 2012). Both the findings of Troosters et al. (2010) and Waschki et al. (2012) reported a positive association between lung function and steps/day in COPD patients. On the other hand, Pitta et al. (2008a) documented that FEV₁ provided no correlation with steps/day or any domains of PA for that matter. Intriguingly, they did report that measures of Inspiratory Capacity and Maximum Voluntary Ventilation were significantly correlated with all PA variables. They suggested that this association may be a result of Maximum Voluntary Ventilation providing a reflection of the ventilatory reserve available to respond to increased physiological demands of PA (Pitta et al., 2008a). Furthermore, Inspiratory Capacity measurements estimate levels of dynamic hyperinflation, which has been well documented to influence levels of PA in COPD patients (Garcia-Rio et al., 2009).

In terms of exercise capacity, the majority of studies report a common association between the results of a 6MWT and PA (Altenburg et al., 2013; Belza et al., 2001; Eliason, Zakrisson, Piehl-Aulin, & Hurtig-Wennlöf, 2011; Garcia-Aymerich et al., 2009; Pitta et al., 2005b; Waschki et al., 2012; Watz et al., 2009), with it generally hypothesised that variations in exercise capacity and PA levels are similar (Altenburg et al., 2013).

Limited associations between peripheral muscle weakness and PA were documented in this study, with only QMVC and the PA outcomes; steps/day and MVPA reporting an association. Pitta et al. (2005b) reported a moderate correlation between measures of handgrip and quadriceps muscle strength with levels of PA using a bivariate model. However, an association between handgrip muscle weakness and physical inactivity was not confirmed using a multivariate model analysis in this study. Early findings from Gosselink, Troosters, and Decramer (1996) provided evidence that isometric quadricep strength was a significant

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predictor of exercise limitation, which could provide evidence of a similar trend in relation to daily PA levels. Therefore, it seems plausible that levels of PA are influenced by quadriceps muscle strength.

Knowledge regarding PA, health related quality of life and psychological variables remains unclear. In this study, it was shown that reduced CCQ scores relating to symptoms, functional and mental state as well as reduced depression symptoms were associated with greater steps/day and VMU, with only CCQ symptoms associated with MVPA. Specifically, it was shown that the functional domain of the CCQ, which provides a subjective analysis of patient's limitation towards different activities of daily living due to lung disease (Sundh, Janson, Lisspers, Montgomery, & Ställberg, 2012), accounted for the second highest variability in steps/day through a multiple regression model. It could be assumed that such an association may link to the fact PA is a complex health behaviour that involves both physiological and psychological traits of an individual patient (Bauman et al., 2012). Similar findings were reported by Altenburg et al. (2013) who studied variables affecting PA levels in 155 COPD patients. Both the CCQ functional score and depression were inversely associated with greater PA. However, a multiple regression analysis in this study failed to report a large amount of variability with the CCQ functional score.

With respect to levels of depression, the findings of the current study and that of Altenburg et al. (2013) do not compare with two earlier studies (Moy, Matthess, Stolzmann, Reilly, & Garshick, 2009; Watz et al., 2009). This disparity may be the result of a different questionnaire used to assess depression (Beck depression scale) (Moy et al., 2009; Watz et al., 2009) or a smaller sample size (Moy et al., 2009).

6.4.7 Strengths and limitations

A major strength of this study was the novelty of several findings. Firstly, to our knowledge, data from this study was the first to have assessed the PA levels of COPD patients on a regional basis in the UK compared to healthy age-matched individuals. Secondly, it was able to compare levels of anxiety and depression in COPD patients compared to healthy age-matched controls. With the ever-increasing knowledge surrounding mental health and its association with physiological variables, it was felt that this was an important area of research in chronic diseases. Finally, this chapter has provided updated research surrounding correlates of daily PA levels, which are essential in order to progress PA behavioural modification interventions in this population in the future.

The study did have some limitations that are worth noting. Firstly, the study consisted of a single centre study that was performed in patients who were interested in research and taking part in an RCT (chapter 7). These factors may have limited the applicability across difference centres and clinical settings. Secondly, the analysis of daily PA levels was not conducted across all seasons due to the timescale of data collection. Previous literature has documented that limited PA assessment in winter months may positively influence findings (Boutou et al., 2019), however we feel that this did not affect the overall findings of the current study. Thirdly, due to constraints with the location of data collection for healthy participants, we were unable to conduct the 6MWT, meaning we were unable to compare exercise capacity across groups. However, as we were able to collect data on lower and upper muscle strength and endurance, it was felt that a sufficient analysis of exercise capacity was included in this study. Fourthly, both type I error (rejecting a null hypothesis) and type II error (not rejecting a null hypothesis) should be considered. Specifically, type I error involves rejecting a null hypothesis when it is true and may have been exemplified in table 14 spearman's correlation due to many variables in one analysis that may skew the overall findings. Finally, the implementation of a cross-

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sectional design to determine the correlates of PA levels was another limitation of the study, as correlation does not necessarily imply causation, therefore further research is required to determine a causal relationship.

6.5 Conclusion

In conclusion, the present case control and cross-sectional study reported for the first time that levels of PA in patients with COPD living in the North East of England are significantly lower than healthy age-matched individuals living in the same region. Furthermore, PA variables including steps/day, VMU and MVPA were found to significantly decrease with increasing COPD severity. This study has been able to strengthen the evidence base regarding variables that significantly influence levels of PA in patients with COPD, providing valuable evidence that can support the implementation of future PA behavioural modification interventions in COPD.

A major concern arising from this study is the substantial deterioration in levels of daily PA documented in patients living in the North East of England compared to COPD patients living in other regions of the UK and Europe. Considering the increased risk of hospital admissions and mortality as a result of increased physical inactivity, these findings provide vital evidence that PA behavioural modification related interventions are urgently needed in order to suppress the decline in daily PA levels and promote a more physically active lifestyle for COPD patients living in the North East of England.

With the findings of Chapter 3 highlighting that PA counselling interventions are more effective in COPD patients who exhibit greater baseline PA levels, it is apparent that COPD patients living in the North East of England may require additional support to improve the outcomes of PA counselling interventions.

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Therefore, the next chapter of this thesis will use these novel findings to assess the feasibility and efficacy of combining PA behavioural modification strategies, PR and psychological behavioural modification through CBT, in patients with COPD living in the North East of England, to investigate whether additional support to improve the outcomes of PA counselling are both feasible and effective at improving diminished levels of daily PA.

CHAPTER

7

Chapter 7: Randomised Controlled Trial

7.1 Introduction

As detailed in Chapter 6, patients with COPD living in the North East of England reported significantly lower PA levels (steps/day) compared to both healthy age-matched individuals living in the same region and patients with COPD living in other regions of the UK and across Europe (Boutou et al., 2019). These findings are important due to the association between low levels of PA and increased risk of hospitalisation and mortality (Garcia-Aymerich et al., 2006; Garcia-Aymerich et al., 2009; Garcia-Rio et al., 2012; Vaes et al., 2014; Waschki et al., 2011). Therefore, behavioural modification interventions to achieve a sustained improvement in PA are urgently needed to suppress the decline in PA in this geographical group of patients.

PA counselling has been employed to address the complex behaviour of PA, with the majority of previous studies demonstrating improvements in PA (steps/day) both as a standalone intervention and alongside PR in patients with COPD (Armstrong et al., 2019). This is accomplished by stimulating patients to increase their PA levels by incorporating lifestyle activities into daily life in conjunction with patient monitoring and feedback of their daily steps alongside frequently adjusted goal setting (Mantoani et al., 2016). However, as previously reported, those patients with low baseline levels of PA (≤ 4000 steps/day), failed to achieve a clinically important change in PA following PA counselling interventions alongside PR (Armstrong et al., 2019). As a result, COPD patients living the North East of England would likely fail to benefit from interventions of this nature. Consequently, investigating the potential of comprehensive behavioural modification approaches to increase PA alongside PR in this COPD population is necessary.

In addition, the behavioural modification approach involves the incorporation of a psychological behavioural modification tool, namely CBT, as an intervention to support COPD patients with profound psychological difficulties such as anxiety and depression (Heslop &

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Foley, 2009; Heslop-Marshall et al., 2018). Importantly, many of these patients are less able to manage symptoms of anxiety and depression (Thew et al., 2017), and are therefore less likely to improve levels of PA (Yohannes & Alexopoulos, 2014). CBT focuses on understanding how experiences are interpreted and provides an understanding of the interaction between thoughts, mood, behaviour and physical sensation, which are intrinsically linked (Heslop & Foley, 2009). Many of the techniques used in CBT help to break patient inactivity, which can lead to improved mood and better physical conditioning (Dueñas-Espín et al., 2016; Yohannes & Alexopoulos, 2014). Across the NuTH, CBT is administered to those patients with elevated levels of anxiety and depression as part of standard care PR, making it feasible to incorporate CBT as part of PR alongside a PA behavioural modification intervention. This combined approach may support an improved mood, better physical conditioning and improved PA levels in those patients with elevated levels of anxiety and depression who are typically less able to manage symptoms and improve levels of PA (Thew et al., 2017; Yohannes & Alexopoulos, 2014).

To date, studies investigating PA counselling interventions in patients with COPD have focused primarily on the frequency, intensity, duration and type of PA, which are quantified by means of activity monitors (Van Remoortel et al., 2012a). This method of assessment, however, fails to fully capture patients' experiences of PA (Gimeno-Santos et al., 2015). Qualitative research has indicated that while patients engage in daily physical activities, they experience symptoms which adversely impact on their lifestyle (Dobbels et al., 2014). In order to gauge a better understanding of these symptoms and experiences of PA during a PA behavioural modification intervention alongside PR, the C-PPAC instrument was incorporated in this thesis, combining subjective questions regarding the amount and difficulty of PA alongside objective measures of steps/day and movement intensity (VMU) (Gimeno-Santos et al., 2015).

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Therefore, this chapter investigated whether a PA behavioural modification intervention alongside PR in patients with COPD reporting low baseline PA levels was effective in term of improving PA levels and patients' experiences of PA, exercise capacity, quality of life, symptoms, and wellbeing. As this novel behavioural modification intervention alongside standard care PR in COPD patients with profoundly low PA levels had yet to be investigated, it was important to establish patient acceptability and compliance to the components of this behavioural modification intervention and assess whether recruitment and retention was affected by adding this behavioural modification intervention to PR compared to PR alone.

It was hypothesised that the PA behavioural modification intervention incorporating motivational interviewing, face-to-face twice weekly goal setting, step count monitoring and feedback, combined with PR, would be superior to PR alone in improving all aspects of PA.

7.2 Methods

7.2.1 Study design

This chapter consists of a prospective, single centre, two parallel-group, RCT. Following baseline assessment (visit 1-pre-PR) patients were randomly allocated 1:1 to either standard care 8-week PR (PR alone) or standard care 8-week PR alongside a PA behavioural modification intervention (PR+PA) (Figure 25). Patients were stratified by 6MWT data ($6MWT \leq 300$ m or $6MWT > 300$ m) and the average HADS score for anxiety and depression (< 8 points or ≥ 8 points) using a block size of 4 at the onset of the PR programme. Following randomisation, those patients documenting elevated levels of HADS anxiety and/or depression score (≥ 8) received CBT alongside either PR alone or PR+PA intervention. All trial outcomes were conducted at baseline and following 8-weeks of PR (post-PR).

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7.2.2 Trial setting and recruitment

As detailed in Chapter 4, patients with COPD were recruited from NuTH Chest Clinic and PR waiting lists across both the RVI and Freeman hospital sites. Patients were initially approached by a healthcare professional associated with either the Chest Clinic or PR programme (i.e., consultant respiratory physicians, specialist respiratory nurses, respiratory physiotherapists) who documented the study requirements and provided a participant information sheet to any patient who expressed an initial interest in the trial. With agreement, patients provided contact details to the healthcare professional which were subsequently passed to a member of the research team. Following a 24-hour period allocated to allow interested patients time to read the participant information sheet and consider their options regarding the trial, a researcher contacted the patients over telephone and delivered a screening assessment, as outlined below.

7.2.3 Screening telephone assessment

The initial screening assessment was completed over telephone, with the nature and objectives of the study explained to the patient in more detail and an opportunity to ask any questions to the research team was provided. Patients were asked to confirm eligibility to the study based on the inclusion/exclusion criteria outlined below. On confirmation of eligibility, patients were offered an invitation to attend a baseline assessment visit at either the RVI or the Freeman hospital sites depending on patient preference.

Patient inclusion and exclusion criteria are detailed below.

Inclusion criteria:

1. COPD confirmed by obstructive spirometry.
2. Clinically stable male or female COPD patients aged 40 years or older.
3. Optimised medical therapy

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4. Able to provide informed consent

Exclusion criteria:

1. Orthopaedic, neurological or other concomitant diseases that significantly impair normal biomechanical movement patterns, as judged by the investigator.
2. Moderate or severe acute exacerbation of COPD within 4 weeks.
3. Unstable ischaemic heart disease, including myocardial infarction within 6 weeks.
4. Moderate or severe aortic stenosis or hypertrophic obstructive cardiomyopathy.
5. Uncontrolled hypertension and another condition likely to limit life expectancy to less than one year (principally metastatic malignancy).

7.2.4 Baseline assessment visit 1 (pre-PR)

Patients attended the physiotherapy department at either the RVI or Freeman hospital sites. On arrival, patients provided confirmation that they met the inclusion/exclusion criteria and written informed consent was obtained, conforming to the MRC guidelines (Skivington et al., 2018).

Demographic data including age, sex, body mass and stature were obtained. Lung function measurements were recorded from patient notes, and were unavailable, spirometry was performed (detailed in Chapter 4). Data were collected from patient notes on pharmacological therapy and medication. Baseline outcome measures (detailed below) were completed and upon completion, an Actigraph accelerometer was provided to patients (detailed in Chapter 4).

7.2.5 Baseline assessment visit 2 (PR session 1)

Following a 7-day period of wearing the Actigraph accelerometer, patients returned to the physiotherapy department to attend their 1st session of PR. Prior to the start of PR, accelerometer data was analysed, and confirmation of valid accelerometer data was ensured.

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Following this, patients were allocated an appointment for CBT based on a HADS anxiety and/or depression score of ≥ 8 .

7.2.6 Randomisation and allocation

Following confirmation of valid accelerometer data, patients were randomly assigned 1:1 to either PR+PA or PR alone (Figure 25). An online randomisation programme (www.randomization.com) was used by a researcher, who took no part in the recruitment process of the study, to generate the randomisation sequence. Stratification was based on 6MWT data ($6MWT \leq 300$ m or $6MWT > 300$ m), (Camillo et al., 2016) and the average HADS score for anxiety and depression (< 8 points or ≥ 8 points) (Nowak et al., 2014) to ensure a balanced sample size between the two study groups. Balanced group allocation blocks were conducted by a researcher at Northumbria University who was independent of the research team.

7.2.7 Final pulmonary rehabilitation session

The same procedure as baseline visit 1 (pre-PR) with patients issued an Actigraph accelerometer to be worn for 7 days (detailed in chapter 4). Patients in the PR+PA intervention returned their pedometer and remaining step diaries and were asked to complete a project tailored satisfaction questionnaire anonymously at home.

7.2.8 Post assessment visit (1-week post-PR)

On arrival at the post assessment visit (at least 7 days following final PR session), patients provided their Actigraph accelerometer and anonymously handed their satisfaction questionnaire into the PR team. The same procedures as baseline visit 1 (pre-PR) were implemented with all outcome measures completed.

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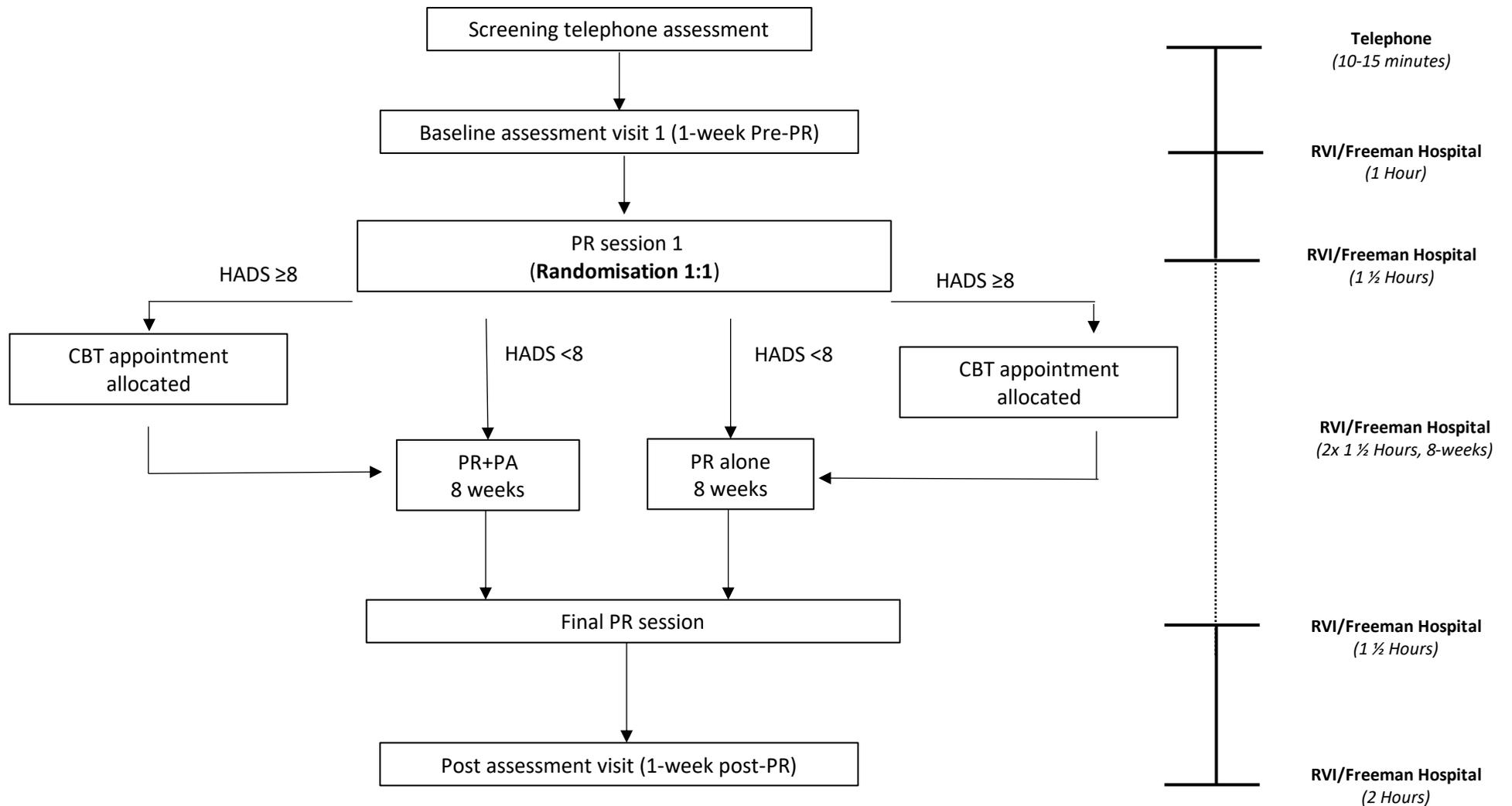


Figure 25. Overall study diagram.

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7.2.9 *Physical activity behavioural modification intervention added to pulmonary rehabilitation (PR+PA)*

Patients assigned to the behavioural modification intervention (PR+PA) received 8-week standard care PR (detailed below) alongside an additional PA behavioural modification intervention comprising motivational interviews, monitoring and feedback using a pedometer and goal setting.

Prior to the start of the PR+PA intervention, patients received a one-to-one semi-structured motivational interview with a member of the research team discussing motivation issues, favourite activities, facilitators and barriers to PA and strategies to become more physically active (Miller & Rollnick, 2002). Motivational interviewing is defined as “a collaborative, person-centred form of guiding to elicit and strengthen motivation for change” and involved creating an atmosphere in which the patient became the main advocate and primary agent for change (Miller & Rollnick, 2002). The motivational interviews delivered in this study were based on the general principles taken from Miller and Rollnick (2002) including, (1) expressing empathy (2) developing discrepancy (3) avoiding argumentation (4) rolling with resistance and (5) supporting self-efficacy. Specifically, the researcher focused on engaging with the patient’s thoughts and feeling regarding their levels of PA, focusing on a clear direction and goal towards improving PA, evoking a patient’s own internal motivations for change, based on the goals identified in the focusing process, and planning, that encompasses both developing a commitment to change and formulating a specific action plan to build upon. To support the implementation of these processes, the basic skills of Open questions, Affirmations, Reflections, and Summarisations, (OARS) were used throughout (Miller & Rollnick, 2002). On completion of the motivational interview, each patient created 3 concrete actions that were used throughout the PR+PA intervention to stimulate patient’s self-motivation and self-efficacy towards achieving greater levels of PA.

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The overall design of this PA behavioural modification intervention was based on the findings of Chapter 3, which reported that irrespective of the way the intervention was designed or implemented (i.e. frequency of goal setting, duration, type of feedback & measure of PA), improvements in PA were of a similar magnitude. Specifically, the PA behavioural modification intervention delivered in this study incorporated the provision of a pedometer (Fitbug, Camden, London), an individualised daily step count target, and a daily step count diary provided weekly during the 8-week PR programme. The pedometer used in this study has shown good validity and test-retest reliability in a controlled environment at walking speeds adopted by COPD patients ranging from 0.69-1.11 m/s, as detailed in Chapter 5.

The first week's step count target was based on baseline Actigraph accelerometer step count data, with a 10% increase in step counts calculated (e.g. 100 additional steps from a baseline step count of 1000 steps). During subsequent weeks, the 10% increase in step counts was based on pedometer (Fitbug) step count data, retrieved from the daily step count diary. Patients were encouraged to discuss the daily step count target with the researcher if they felt it was unrealistic as an individualised approach was promoted for every target. A weekly step-count increase of 10% in the current study was chosen based on the study from Nolan et al. (2017), that did not result in any meaningful improvements in PA alongside PR with a 5% weekly step-count increase. Once confirmed, the daily step count target was documented on the daily step count diary and support was provided at every PR session (twice weekly) to achieve the prescribed daily target. Patients were asked to note their daily step count using the daily step count diary at the end of each day, making note of whether the daily target was achieved. Furthermore, patients were asked to document their daily wellbeing on the daily step count diary via a simple 3 face tool (1-smiley face, 2- satisfied face and 3- sad face).

Prior to each PR session (twice weekly), patients provided the step diary to the researcher, who was not involved in the PR programme delivery. Face-to-face advice and support to achieve

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current and future goals were given to patients during each PR session and a new daily step-count target was provided at every other PR session (once weekly). In addition, the researcher assessed the adherence to components of the intervention through means detailed earlier in this chapter. If the patient missed a recording on their diary step count diary, this was retrieved from the pedometer memory function. However, for the analysis of adherence, it was reported as a missing data point. If the patient did not attend PR in person, the weekly target was prescribed by telephone.

During each face-to-face PA review session, the patient and researcher discussed the importance of achieving the weekly step-count target and advice on how to increase PA levels was given. Each session was patient led with a focus on discussing the barriers and opportunities facing each patient and considerations were made towards the 3 concrete actions set during the motivational interview. An emphasis was placed on several behaviour modification techniques, including goal setting, action planning and guidance on self-monitoring and management. Such behavioural components have been shown to benefit COPD patients' readiness, motivation and confidence to engage in PA and were associated with significant improvements in PA behaviour (Bourbeau et al., 2021). The aims of a greater face-to-face component were to use the techniques detailed above to empower and motivate patients to engage in more daily PA, to support greater improvements in overall PA.

7.2.10 Standard care pulmonary rehabilitation

All patients enrolled to the study attended the same centre-based PR programme at either the RVI or Freeman hospital sites. Both hospital sites ran a symmetrical programme delivered in accordance to the BTS guidelines for PR (Bolton et al., 2013). Specifically, patients attended a group programme twice weekly for 8 weeks (16 sessions) for approximately 60 minutes of exercise and 20 minutes of education or relaxation between November 2018 and February

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2021. Due to the COVID-19 pandemic, 6 patients (n=3 in the PR alone control and n=3 in the PR+PA intervention) completed one exercise session under socially distanced supervision and one unsupervised session at home. Respiratory physiotherapists supervised the exercise programme which involved an individually tailored programme of aerobic continuous and interval exercises (cycling and walking) and strengthening exercises (machines and free weights). Initial endurance cycling using a cycle ergometer was set at a workload to achieve level 4 on the Modified Borg Dyspnea scale (1-10 scale). The ATS/ERS guidelines for PR (Spruit et al., 2013) were used to prescribe lower body resistance exercises. Examples of resistance exercises include seated leg press, leg extensions, sit to stand and step ups with appropriate free weights and leg weights. Upper body resistance training exercises included bicep curls, punches and shoulder press using free weights. The duration and intensity of lower and upper body exercises were monitored after every exercise using the Modified Borg Dyspnea scale (1-10 scale). For patients to be exercising at both an effective as well as feasible intensity, they were expected to aim for a perceived exertion on the Modified Borg Dyspnea scale of 4 (moderately to moderately severe), with the intensity and/or duration increased when Borg scale levels were below 4 (Spruit et al., 2013). Patients from both groups received a home exercise programme with example exercises and a recording section, enabling physiotherapists to monitor and support additional home exercises during the PR programme.

The education components were delivered by a multidisciplinary team, including physiotherapists, dieticians, psychologists, respiratory nurses, respiratory consultants, social workers, speech and language therapists and occupational therapists. The aim of these sessions were to develop patients understanding and management of their disease, as well as topics including smoking cessation, PA and exercise, medication use, diet, relaxation, coping strategies, as well as rescue medication and community support (Bolton et al., 2013; Spruit et al., 2013). Regardless of group allocation in the study, generic advice on improving PA was

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provided with an emphasis on barriers and facilitators to improving levels of PA. Furthermore, each patient received a British Lung Foundation exercise handbook which provided added support regarding the educational sessions as well as resources to record exercise and PA conducted outside of the weekly PR sessions.

7.2.11 Cognitive Behavioural Therapy (CBT)

CBT was administered by respiratory nurses as part of standard care PR at the RVI and Freeman hospital sites for patients who presented a HADS score ≥ 8 . CBT sessions were conducted either in the Chest Clinic at the RVI or at home, lasting around 30 minutes. The protocol used to deliver CBT in this study was in accordance with a previously published RCT from Heslop-Marshall et al. (2018). The number of CBT sessions suggested and timescale for such sessions were co-developed with the patients depending on their individual response to treatment and managing symptoms based on their subjective feedback, HADS questionnaire results and patient preference (Heslop-Marshall et al., 2018). CBT focused on understanding how experiences were interpreted, made up of four elements: behaviour, cognition/thoughts, feelings/emotions, and physical sensations (Greenberger & Padesky, 1995). A number of techniques were used to aid symptoms of anxiety and depression including education on anxiety and depression and COPD, distraction techniques, breathing control, relaxation and rating achievement/pleasure of PA (Heslop-Marshall et al., 2018).

7.2.12 Targets for recruitment, randomisation and completion rates

To assess patient recruitment, patient randomisation and completion rates this study aimed at achieving the following criteria: (1) Recruitment of at least 30% of eligible patients (2) Randomisation of at least 80% of patients following informed consent (3) At least 80% of randomised patients should complete the intervention period and post assessment visit. The

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criteria were based on consultations with health care professionals involved in the delivery of PR and on previous literature (Leon et al., 2011; Ward et al., 2018).

7.2.13 Assessment of patient acceptability to the physical activity behavioural modification intervention

The acceptability of the PR+PA intervention was assessed through a qualitative project-tailored questionnaire previously administered by (Loeckx et al., 2018a). During the final PR visit, patients were provided with the questionnaire and asked to complete at home. The anonymised, self-administered, project tailored, questionnaire involved questions regarding patient experiences with the PR+PA intervention and asked the usefulness of its components. In the final part of the questionnaire, patients were asked to comment on which components of the intervention they would change in the future and provide any final comments regarding their experiences of the intervention. Patients returned the questionnaire to the physiotherapy department (post-assessment visit). A member of the research team collated and anonymised answers into an excel file, which was subsequently used for analysis.

7.2.14 Assessment of adherence to physical activity behavioural modification components

Adherence was assessed through the degree which components of the intervention were used by patients (Donkin et al., 2011). Specifically, it was assessed by (1) The number of weekly goal setting targets met, based on a percentage of the 8 weekly step targets provided throughout the intervention, (2) Weekly completion of the daily step count diaries based on researcher's observation of patient diaries twice weekly, (3) Pedometer wear time, based on a minimum of 70 steps for a valid day of wearing, in line with a previous study (Loeckx et al., 2018a), (4) Accelerometer wear time based on a minimum of 8 hours recording time for a valid day of

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wearing (Demeyer et al., 2014). Furthermore, patients subjectively reported their usage of the step counter and step count diary using the project-tailored questionnaire.

7.2.15 Primary outcome measure

7.2.15.1 Patients physical activity experiences

The Clinical PROactive C-PPAC instrument, which was previously validated for use in patients with COPD (Dobbels et al., 2014), required both questionnaire and accelerometer-derived PA data (Actigraph wGT3X, Actigraph LLC, Pensacola, FL, USA) and was implemented one week prior to the onset of the PR programme and one week following completion of the PR programme. The C-PPAC questionnaire included 12-items with a 7-day recall and was completed using paper and pen. Patients were also instructed to wear the Actigraph accelerometer, that has previously been validated to be part of the C-PPAC tool (Gimeno-Santos et al., 2015). C-PPAC scores were calculated by combining questionnaire items with two objective variables from the activity monitor (steps/day and VMU). Three scores were generated (amount of PA, difficulty of PA and total PA experience) ranging from 0 to 100, where higher numbers indicated a better score (Gimeno-Santos et al., 2015).

7.2.16 Secondary outcome measures

7.2.16.1 Physical activity outcomes

Levels of daily PA were collected at baseline and following completion of PR, using the Actigraph accelerometer (Actigraph wGT3X, Actigraph LLC, Pensacola, FL, USA), with PA outcome measures including steps/day, VMU, sedentary time, light time, MVPA time. The Actigraph accelerometer was positioned above the anterior spine of the iliac crest in line with

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the anterior axillary line of the dominant hip. This placement location has been reported to result in the highest accuracy (Swartz et al., 2000). All patients were instructed on how to use the Actigraph accelerometer prior to initiation. This included information on (1) correct positioning of the device; (2) the period worn for (e.g., device worn the moment you woke up until the moment you went to bed “wakefulness hours”), with instructions to keep on wearing the device even during sedentary time and illness; (3) when to take off the device (e.g., during water activities, bathing and showering); (4) date of when to stop assessment. A detailed explanation of accelerometry data collection, processing, validity and reliability are provided in Chapter 4.

7.2.16.2 Exercise capacity

The 6MWT was administered to assess exercise capacity at baseline and following completion of PR. The test was completed over a marked 30-metre corridor in accordance to the ATS/ERS technical standards (Holland et al., 2014). Measurements of SpO₂ and heart rate using an oximeter and sensation of dyspnea and leg discomfort using the Modified Borg scale were taken prior to the test, after 3 minutes, on completion of the test and 2 minutes following the completion of the test. Further details on the 6MWT are provided in Chapter 4.

7.2.16.3 Upper and lower body muscle strength and endurance

Upper and lower body muscle strength and lower body muscle endurance were assessed at baseline and following completion of PR. Upper body muscle strength was assessed by handgrip strength using a calibrated hand-dynamometer (Camry EH101, Camry Electronic CO. Ltd., Zhongshan, China). Lower body muscle strength (QMVC) was assessed by isometric maximal volitional limb muscle strength assessment at baseline and following PR using a calibrated myometer (MIE Medical Research Ltd., Leeds, UK). Lower body muscle endurance

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was assessed using the 30-second sit to stand test at baseline and following completion of PR. A detailed explanation of the set-up, implementation, analysis, validity and reliability of all muscle strength and endurance measures are detailed in Chapter 4.

7.2.16.4 Health related quality of life

Health related quality of life was assessed using two questionnaires, namely the CCQ and CAT questionnaires at baseline and following completion of PR. A detailed explanation of both the CCQ and CAT questionnaires and their validity and reliability in COPD are provided in Chapter 4.

7.2.16.5 Anxiety and depression

Both anxiety and depression were assessed using the HADS questionnaire at baseline and following completion of PR. A detailed explanation of the HADS questionnaire and its validity and reliability in COPD are provided in Chapter 4.

7.2.16.6 Breathlessness

The degree of breathlessness was assessed using the MRC Dyspnea scale at baseline and following completion of PR. A detailed explanation of the MRC Dyspnea scale and its validity and reliability in COPD are provided in Chapter 4.

7.2.17 Subgroup analysis for patients with ≥ 8 HADS

The subgroup analysis gauged a better understanding of the overall effectiveness of the PR+PA versus PR alone in patients with HADS ≥ 8 who were provided with CBT alongside their allocated group (either PR+PA+CBT or PR+CBT).

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7.2.18 Statistical analysis and sample size calculation

All statistical analyses were performed using the SPSS version 25 (IBM Corporation, UK). Descriptive statistics were reported as mean \pm SD unless otherwise specified. Prior to analysis, the assumption of normality for all outcomes were assessed using the Shapiro Wilks test, with a p value >0.05 indicating normally distributed data. Continuous variables were expressed as means \pm SD or means (95% CI) (normal distribution) or as medians (25th-75th percentiles [P25-P75]; skewed distribution), unless otherwise stated. Categorical variables were expressed as percentages, unless otherwise stated. The level of significance was set at 0.05 for all statistical tests.

Data from the project-tailored questionnaire were scored as categorical variables and reported as frequencies and percentages (i.e., number of patients indicating each answer), except for the usefulness ratings of the project-tailored questionnaire, which were expressed as median (P25-P75).

Within and between group differences pre- to post PR for both groups for all outcome measures were reported as mean, (95% CI). Independent sample t tests were implemented to compare baseline group characteristics. A two-way repeated measures ANOVA was implemented for all outcome variables to identify differences between the two interventions followed by appropriate post hoc analysis when ANOVA revealed significant difference. Statistical significance was set at $p < 0.05$ for all analyses. The intention-to-treat principle was used to analyse the primary outcome measure (C-PPAC) and the per-protocol principle was used to analyse all secondary outcome measures.

Verification of the sample size was based on the study by Louvaris et al. (2016) comparing PR to control. Based on the mean difference in the C-PPAC total score (7.4 units) between PR and control and observed SD (8.5 units), an alpha significance level of 0.05 (2-sided) and 80% power, a minimum sample of 24 patients per group was considered to be sufficient to detect

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significant differences in the total C-PPAC score between PR+PA and PR. Based on previous studies on similar PR programmes in the UK (Nolan et al., 2017), considering an attrition rate of 20% the total sample size was increased to 58 patients.

7.2.19 Blinding

Due to the nature of the intervention, members of the research team and enrolled patients were aware of their group allocation. However, to reduce the risk of bias physiotherapists running the PR sessions and the respiratory nurses running the CBT sessions were blinded to patient allocation. Patients were asked to conceal their intervention arm to the physiotherapists and CBT nurses, which was adhered to by all patients.

7.3 Results

7.3.1 Targets for recruitment, randomisation, and completion rates

Of the 350 patients referred to the NuTH PR unit during the study period, 155 (56%) were diagnosed with COPD and therefore screened for inclusion in this RCT. The 195 patients excluded were diagnosed with other respiratory diseases: ILD (n = 45), Asthma (n = 84), Bronchiectasis (n = 50), other respiratory condition (n = 16). The 155 eligible patients comprised of 84 females (54%) and 71 males (46%). Figure 26 provides the gender and age distribution of the screened patients.

Patient flow through the trial is presented in Figure 27. Of the 155 COPD patients who were screened for inclusion, 35 (23%) patients declined to participate when approached by a healthcare professional, 13 (8%) patients did not meet the specific study eligibility criteria and 37 (24%) patients did not wish to attend the PR sessions following their PR screening visit. Therefore 70 (45%) patients agreed to participate in this RCT and signed the informed consent.

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Of these, 10 patients were not randomised due to 5 patients not able to provide 4 valid days of PA assessment, 4 patients failing to attend the first PR session and 1 patient not wishing to continue the study. Therefore, following the informed consent of 70 patients, 60 (86%) patients were randomised to either the PR+PA intervention (n = 31) or PR alone control (n = 29). Of the 60 patients randomised, 33 (55%) patients reported elevated levels of anxiety and/or depression (≥ 8 HADS) and were allocated a session of CBT alongside their allocated PR+PA (n=17) or PA alone (n=16) group.

Forty-eight (80%) patients attended the follow-up appointment post PR (n = 24 PR+PA and n = 24 PR alone). 7 (24%) patients in the PR+PA group and 5 (17%) patients in the PR alone group were lost to the end of PR. Reasons for withdrawal are shown in Figure 28. Of the 48 patients who attended the follow up appointment post PR, 23 (48%) had received a session of CBT alongside their allocated PR+PA (n=11) or PR alone (n=12) group.

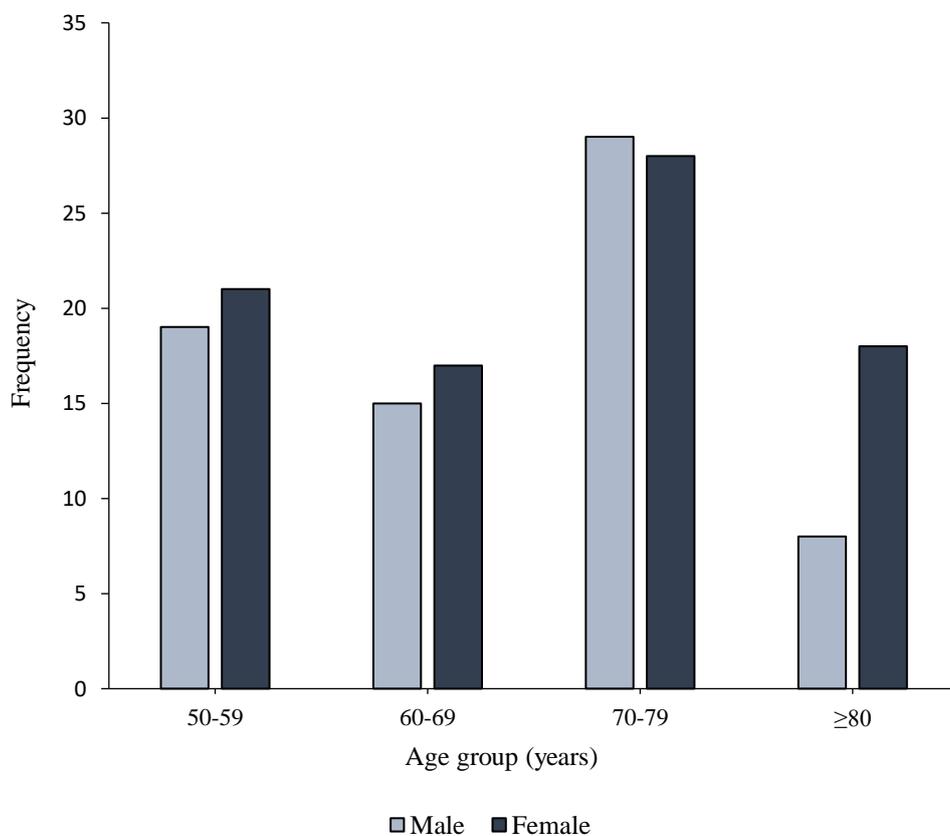


Figure 26. Age and gender distribution for screened patients

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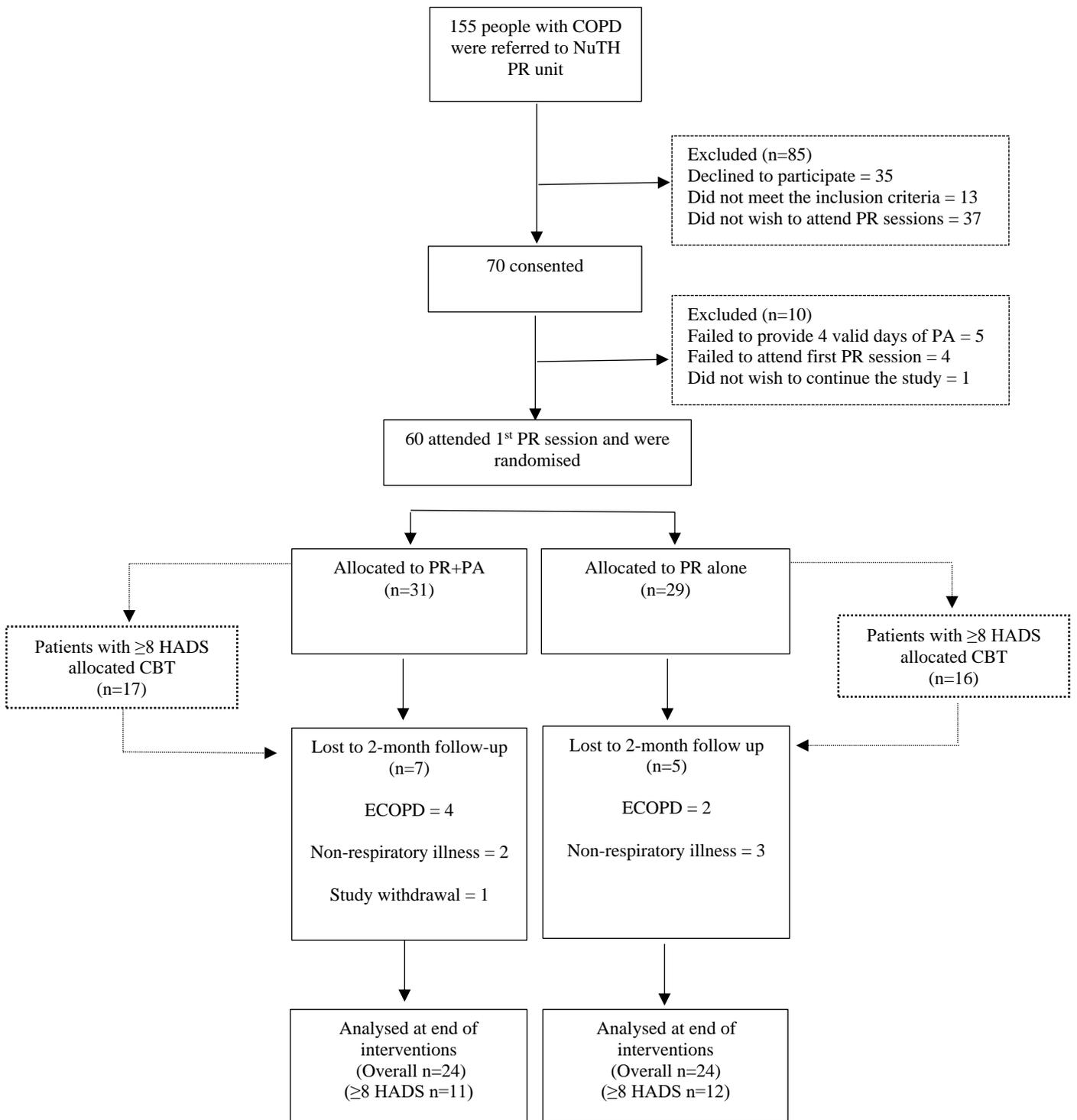
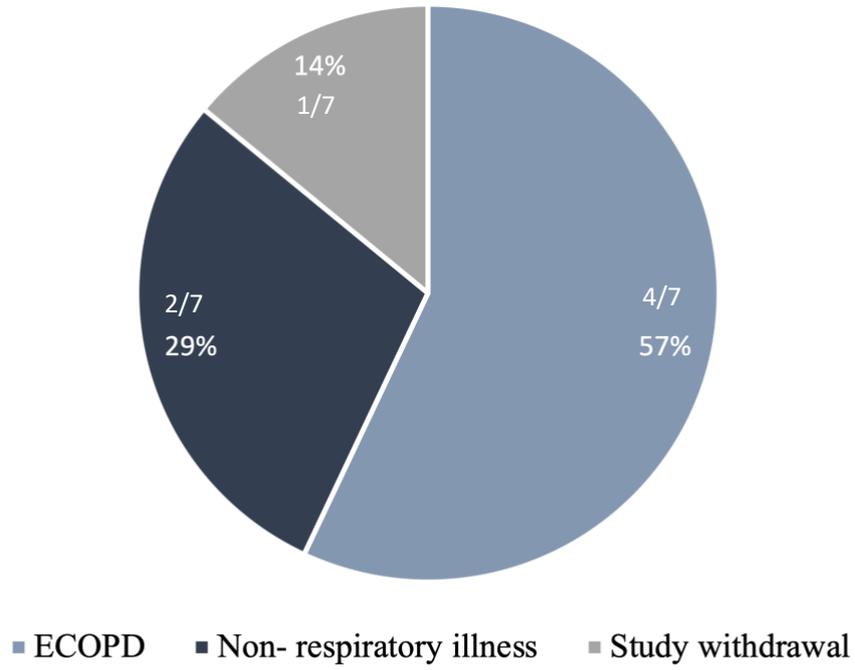


Figure 27. Consolidation Standards of Reporting Trials diagram

A



B

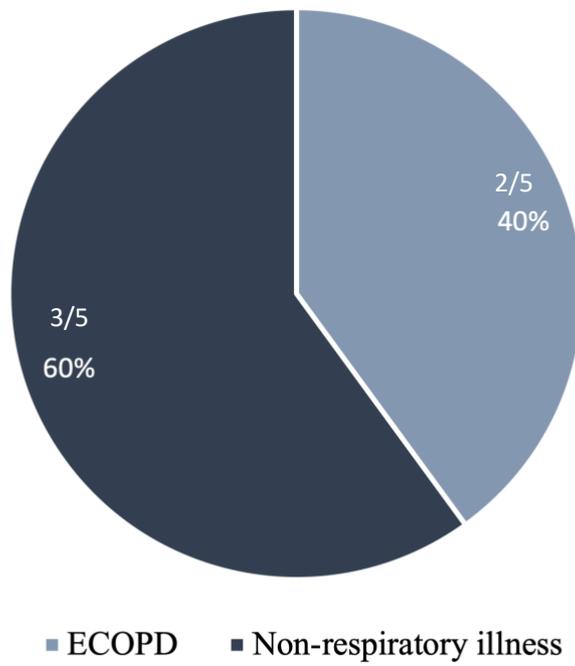


Figure 28. Reasons for withdrawal during the study in the (A) PR+PA (B) PR alone arms

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7.3.2 Baseline patient characteristics

Baseline demographic information and disease characteristics of patients consented to the study are summarised in Table 16. Of the 60 randomised patients, 22 (37%) were male and 38 (63%) were female, the majority of patients were of white ethnicity (98%) with a mean age of 71±9 years/old and a mean BMI of 26.4±6.2 kg/m². Most patients were retired (92%), with the remaining patients still in full/part time employment (8%). The majority of patients lived with family/partner (70%) and were grandparents (72%). Overall, 75% of patients were former smokers and the remaining patients were still smoking (25%).

No differences in clinical characteristics were observed between the groups at baseline ($p > 0.05$). Patients reported a mean MRC dyspnea grade of 3 and pulmonary function measures of FEV₁ % pred (49±18%) and FEV₁/FVC % (52±14%) which demonstrated moderate-severe severity of COPD in the 60 patients. The majority of patients were taking long (70%) and/or short-acting bronchodilators (80%) at the onset of the trial and 23% of patients required ambulatory oxygen at home. In addition, 18% of patients required long-term oxygen therapy throughout the study.

Patients had low baseline PA levels in terms of steps/day (3171±1858) and MVPA (5.8±7.2 mins) reported from an accelerometer as well as low baseline exercise capacity via the 6MWT (282±92 m). Self-reported health-related quality of life reported via the CAT questionnaire was poor in patients (27±6).

7.3.3 Follow-up characteristics

For the 48 patients who completed the trial, 15 (31%) were male and 33 (69%) were female, with a mean age of 73±8 years/old and a mean BMI of 27±5. The baseline PA of those who completed the trial was not different in terms of steps/day (3293±2000 steps/day) and MVPA

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(6.4 ± 8.3 mins) compared to the total group at baseline. Both exercise capacity and QoL were similar to the total group at baseline (289 ± 85 m & 27 ± 6 points, respectively).

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Table 16. Baseline patient characteristics for the whole group and group allocation

Variable	Whole Group (n=60)	PR + PA (n=31)	PR alone (n=29)	<i>P</i> value
Age, years	71±9	70±9	71±9	0.106
Male gender (%)	22 (37)	9 (29)	13 (45)	0.245
Female gender (%)	38 (63)	22 (71)	16 (55)	0.143
BMI, kg/m ²	26.4±6.2	27.7±6.7	25.1±4.7	0.081
Employment status (%)				
<i>Retired</i>	55 (92)	28 (90)	27 (93)	0.697
<i>Employed</i>	5 (8)	3 (10)	2 (7)	0.697
Smoking status (%)				
<i>Current</i>	15 (25)	11 (35)	4 (14)	0.053
<i>Former</i>	45 (75)	20 (65)	25 (86)	0.456
MRC grade	3±1	3±1	3±1	0.283
SPO ₂ %	94±3	95±3	94±3	0.470
<u>Lung function</u>				
FEV ₁	1.15±0.44	1.20±0.43	1.11±0.44	0.435
FEV ₁ % Pred	49±18	50±17	48±19	0.534
FEV ₁ /FVC %	52±14	52±13	52±12	0.844
<u>Medication, n (%)</u>				
Long-acting bronchodilators	42 (70)	21 (68)	21 (72)	0.693
Short-acting bronchodilators	48 (80)	20 (65)	28 (97)	0.002*
Inhaled corticosteroids	41 (68)	18 (58)	23 (79)	0.077
Oral steroids (maintenance)	6 (10)	4 (13)	2 (7)	0.438
Long-term oxygen therapy	11 (18)	5 (16)	6 (21)	0.648
Non-invasive ventilation	2 (3)	1 (3)	1 (3)	0.962
<u>Walking aids, n (%)</u>				
None	51 (85)	26 (84)	25 (86)	0.876
Walking stick	8 (13)	4 (13)	4 (14)	0.657
Walking frame	1 (2)	1 (2)	0 (0)	0.876
<u>Physical activity</u>				
Accelerometer steps/day	3171±1858	3326±1547	3006±2156	0.509
MVPA, min	5.8±7.2	5.7±5.3	5.9±8.8	0.922
<u>Exercise capacity</u>				
6MWT, m	282±92	297±97	267±83	0.196
<u>Health-related quality of life</u>				
CAT	27±6	27±6	27±6	0.892
<u>Social</u>				
Living with family/partner (%)	42 (70)	22 (71)	20 (69)	0.866
Grandparents	43 (72)	21 (68)	22 (76)	0.485

Abbreviations: BMI: Body Mass Index, kg/m²: kilograms/metres squared, SPO₂: oxygen saturation, FEV₁: Forced Expiratory Volume in 1 second, FVC: Forced Vital Capacity. MRC: Medical Research Council Dyspnea scale, 6MWT: Six Minute Walk Test, MVPA: Moderate Vigorous Physical Activity, CAT: COPD Assessment Test.

Mean ± S.D are indicated for all columns unless stated.

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7.3.4 Patient Acceptability to the PA behavioural modification intervention

Overall, the PA behavioural modification intervention was well received by the patients as 75% (18/24) indicated that they “Liked it a lot” when asked how much they enjoyed taking part in the study. Furthermore, most patients (58%, 14/24) claimed that the PA behavioural modification intervention “helped them a lot”, to coach themselves to increase PA outside of PR. Most of the patients (79%, 19/24) experienced the proposed weekly increases in step goals as “reasonable”, whereas 21% (5/24) of patients experienced these increases as “a little too high” or “a little too low”. The usability of the step counter/pedometer was deemed “very easy” in 96% (23/24) of patients, with one patient documenting the step counter/pedometer as “easy” to use.

Patients rated the usefulness of components of the PA behavioural modification intervention with scores based on a 0-10 satisfaction scale (0 terrible to 10 perfect); with the step counter/pedometer (median [P25-P75]; 9 [8-10]), daily step goals (8.5 [8-9]), feedback from researchers (9 [8-10]), CBT sessions (those with ≥ 8 HADS only) (8 [7-9]) and the step diary (10 [9-10]) all deemed useful parts of the intervention (Figure 29).

Patients were asked to document how often they performed the following actions: “look at your step counter/pedometer” and “look and use your daily step diary”. Most patients (71%, 17/24) interacted with their step counter/pedometer “several times a day”, while the remaining patients used their step counter/pedometer “once daily” (21%, 5/24) or “sometimes, but not every day” (8%, 2/24) (Figure 30). In terms of using the daily step diary, 42% (10/24) used the step diary “several times per day”, 29% (7/24) “once per day”, 25% (6/24) “sometimes, but not every day” and one patient “once or twice per week” (Figure 30).

When patients were asked to name which parts of the intervention, they would be willing to use further in the future, 58% (14/24) of patients chose all aspects of the intervention (step counter/daily step diary/PR sessions). The remaining 42% (10/24) of patients said they would

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use the step counter/pedometer and daily step count diary again. Patients with ≥ 8 HADS who received the CBT session were asked whether they would recommend CBT to future patients in a similar position, 72% (8/11) said they would recommend.

Finally, patient's wellbeing while completing the PA behavioural modification intervention was deemed good at baseline and was found to improve as patient's pedometer step counts increased over the 8-week programme (Figure 31).

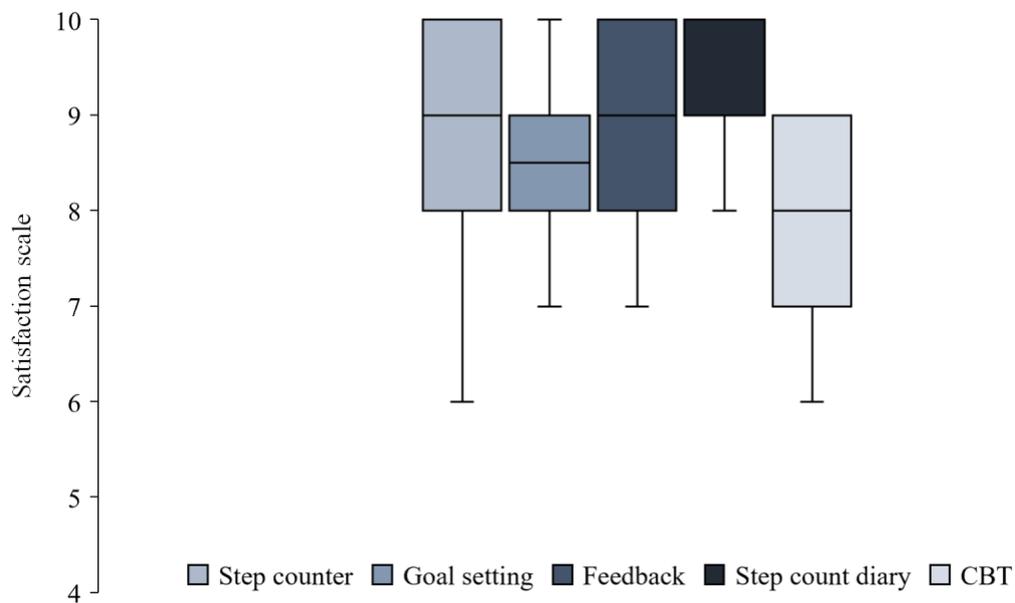


Figure 29. Usefulness of components of the PA intervention. Minimum, median, interquartile range (Q1-Q3) and maximum values are indicated. Error bars represent SD

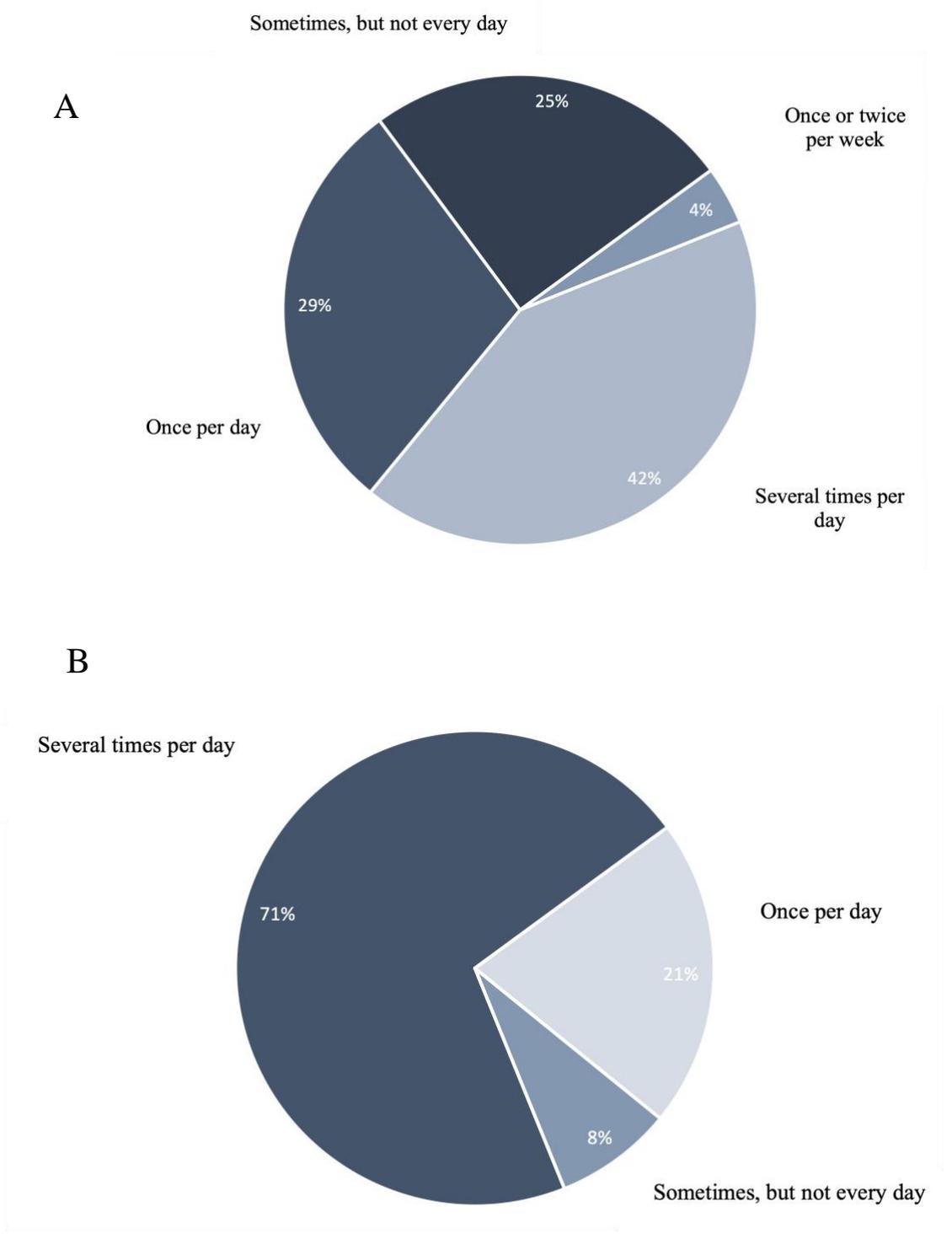


Figure 30. How often patients (A) looked and used their daily step diary (B) looked at their pedometer. Percentages are presented

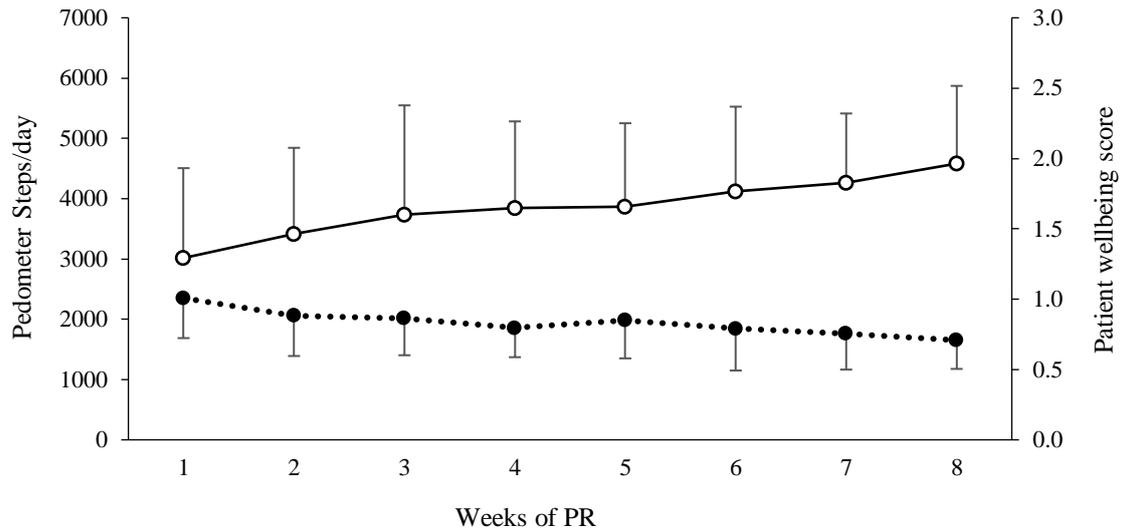


Figure 31. Fitbug pedometer mean steps/day (solid line) alongside self-reported patient wellbeing scores (dotted line) taken from step diaries (1 being excellent, 3 being poor) in the group undertaking the PA behavioural modification intervention. Error bars represent SD

7.3.5 Adherence to PA behavioural modification components

The average number of days a pedometer was worn across the 8-week programme was 54 days (96%), representing a median (IQR) number of 6.6 (6.2-7) days worn per week (Figure 32). The Actigraph accelerometer was worn for a median (IQR) number of 10.4 (8.4-12.7) hours per day at baseline and post PR. Adherence to the step count diary to self-report daily step counts was high ($93\pm 17\%$), with a median (IQR) number of 55 (49-56) recorded days over the 8 weeks (Figure 33). The number of weekly step goal targets met throughout the 8 weeks were good, with an average $67\pm 12\%$ of step goals achieved (Figure 34). Furthermore, patients in the PR+PA intervention did not increase their target step goal by 10% on a mean \pm SD of 3 ± 1 occasions during the 8 week PR programme.

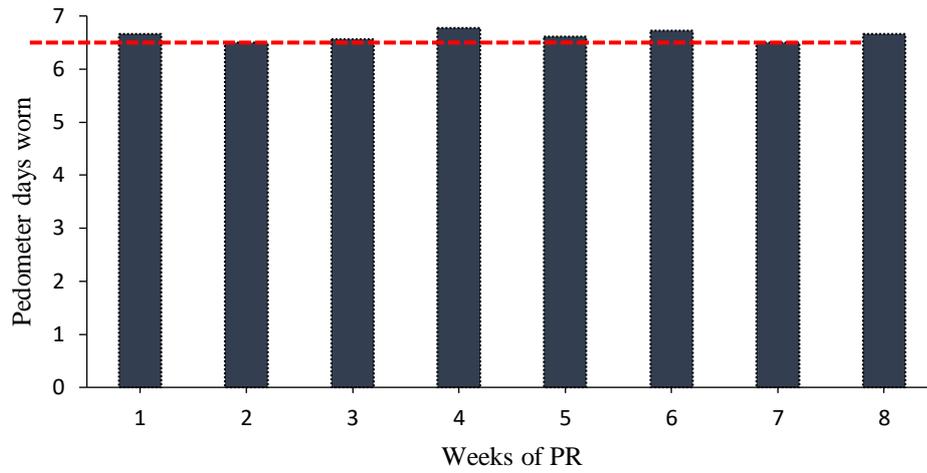


Figure 32. Adherence to the pedometer across the 8-week PR+PA intervention. Dashed red line represents average

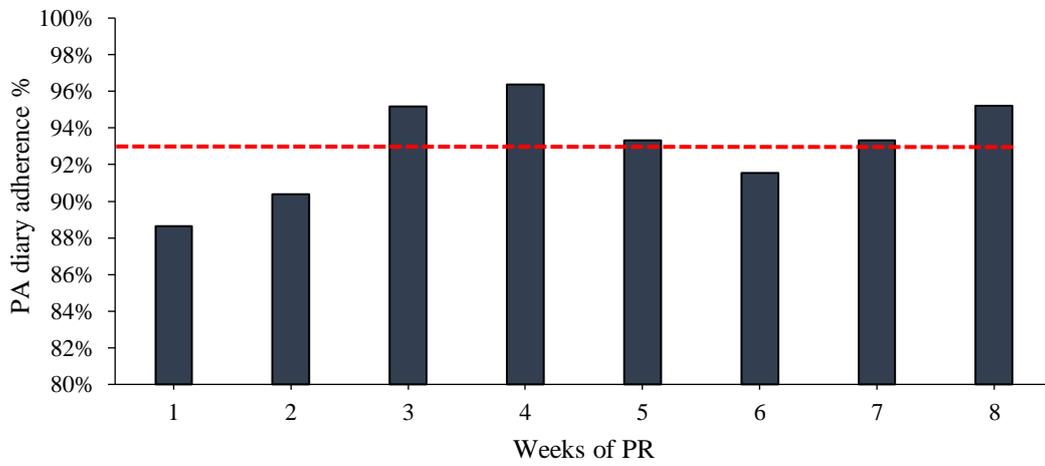


Figure 33. Adherence to the step count diary across the 8-week PR+PA intervention. Dashed red line represents average

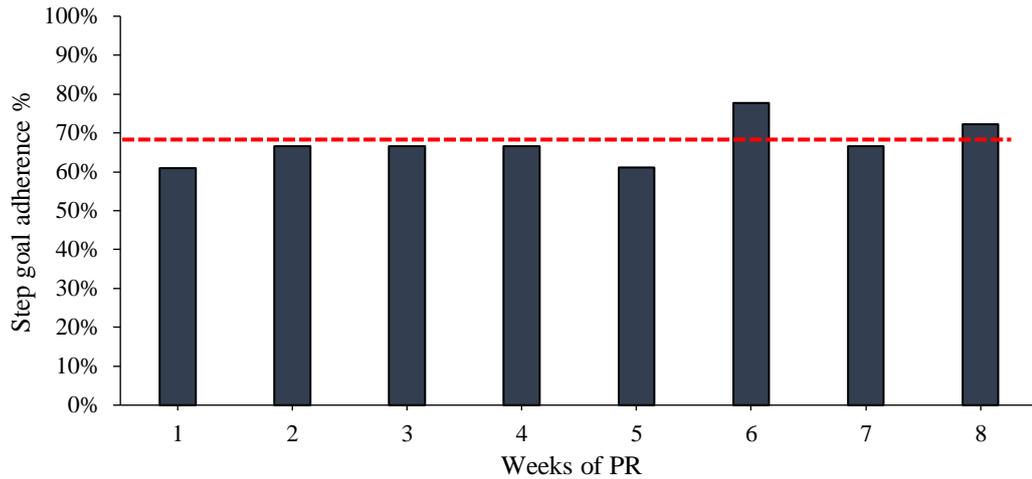


Figure 34. Adherence of achieving weekly step goal targets across the 8-week PR+PA intervention. Dashed red line represents average.

7.3.6 Primary outcome measure

7.3.6.1 Patients experiences of physical activity

The effect of the PR+PA intervention compared to the PR alone control on all dimensions of the C-PPAC instrument for each individual patient is shown in Figure 37. Following PR, the *total score* of the C-PPAC instrument improved by a significant and clinically important margin in those who undertook the PR+PA intervention (by 9 points; 95% CI 6 to 11 points, $p = 0.001$, Table 17) compared with those who undertook the PR alone control (by 2 point; 95% CI -1 to 4 points, $p = 0.193$, Table 17). A between group difference of 7 points (95% CI 4 to 11 points, $p = 0.001$, Table 17) was both statistically significant and clinically important. In regard to the *difficulty score* of the C-PPAC instrument, significant and clinically important improvements were reported in those who undertook the PR+PA intervention (by 7 points; 95% CI 3 to 10 points, $p = 0.001$, Table 17) compared with those who undertook the PR alone control (by -2 point; 95% CI -4 to 4 points, $p = 0.743$, Table 17). A between group difference of 9 points (95% CI 3 to 15 points, $p = 0.002$, Table 17), was both statistically significant and clinically important. Finally, significant and clinically important improvements in the *amount*

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score of the C-PPAC tool were reported in those who undertook the PR+PA intervention (by 11 points; 95% CI 7 to 15 points, $p = 0.001$, Table 17) compared to those who undertook the PR alone control (by 3 points; 95 CI -2 to 6 points, $p = 0.378$, Table 17). A between group difference of 8 points (95% CI 2 to 11 points, $p = 0.004$, Table 17) was both statistically significant and clinically important.

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Table 17. Change in primary outcome measures using ITT in the PR+PA (n = 31) and PR alone (n = 29) interventions

	Group	Baseline	Post PR	Within Group Mean Difference	P value	Between Group Difference	P value
C-PPAC Total score	PR+PA	61±16	70±16	9 (6 to 11) *	0.001	7 (4 to 11) *	0.001
	PR alone	59±14	61±15	2 (-1 to 4)	0.193		
C-PPAC Difficulty score	PR+PA	62±15	69±15	7 (3 to 10)*	0.001	9 (3 to 15)*	0.002
	PR alone	62±16	60±15	-2 (-4 to 4)	0.734		
C-PPAC Amount score	PR+PA	59±20	70±20	11 (7 to 15)*	0.001	8 (2 to 11)*	0.004
	PR alone	56±19	59±21	3 (-2 to 6)	0.378		

Abbreviations: C-PPAC = Clinical visit-PROactive physical activity in COPD, Min = Minutes, PA = Physical activity, PR = pulmonary rehabilitation, MVPA = moderate to vigorous physical activity, ITT = Intention-To-Treat. Values are means. Within and between group differences are reported with 95% confidence intervals (CI). *Clinically important improvement

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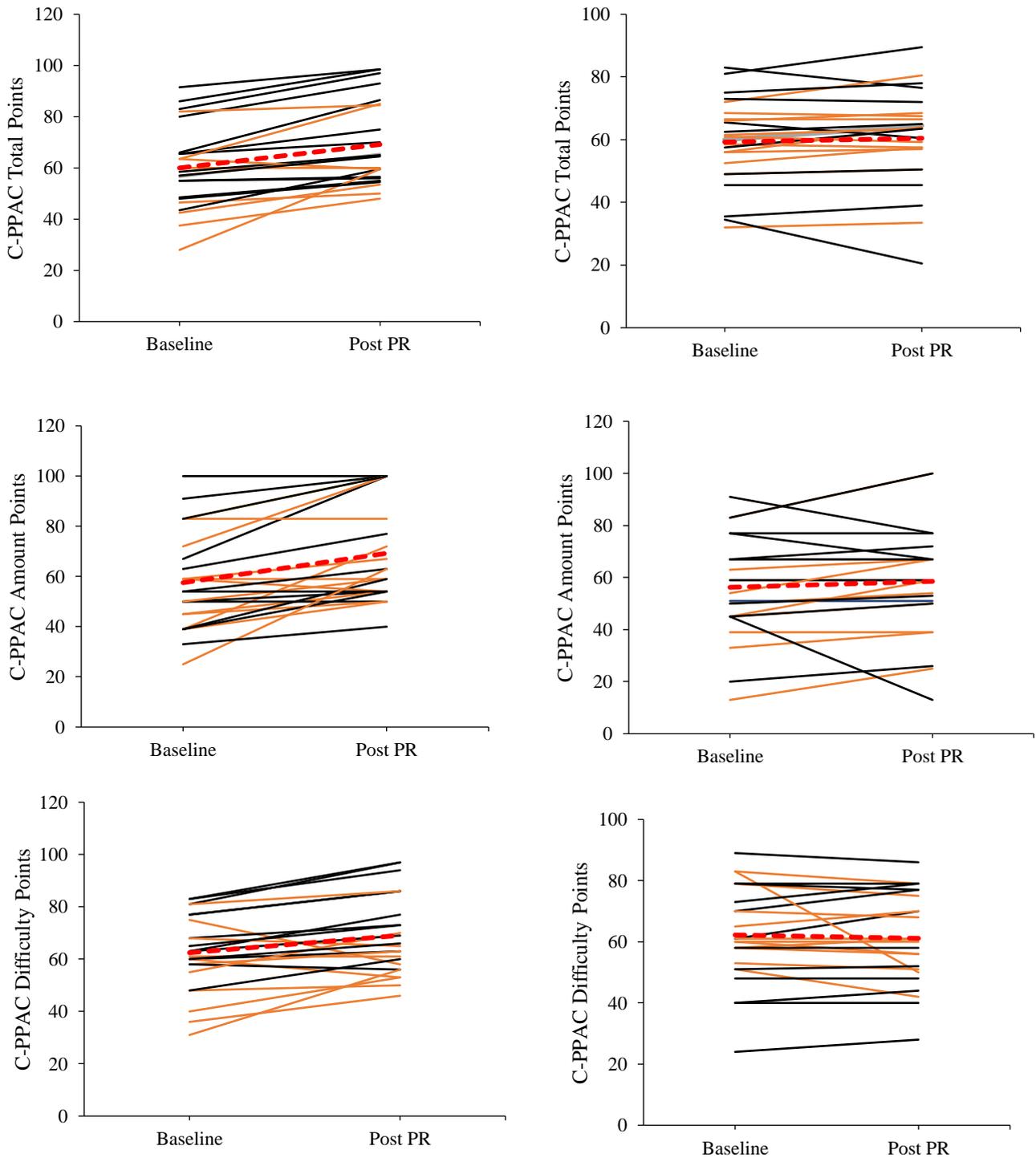


Figure 37. Individual responses to the C-PPAC instrument for: total score PR+PA (Top left), total score PR alone (Top right), amount score PR+PA (Middle left), amount score PR alone (Middle right), difficulty score PR+PA (Bottom left), difficulty score PR alone (Bottom right). (Red dashed line indicates average response in steps/day [Actigraph]), orange line indicates individual patients who received CBT.

7.3.7 Secondary outcome measures

7.3.7.1 Physical activity outcomes

The effect of PR+PA compared to PR alone on PA outcome measures are shown in Table 17 and individual responses to steps/day are shown in Figure 35. Following PR, significant and clinically important improvements in accelerometer steps/day were demonstrated in those who undertook the PR+PA intervention (by 976 steps/day; 95% CI 651 to 1300 steps/day, $p = 0.001$, Table 17), but not in those who undertook the PR alone control (by -40 steps/day; 95% CI -365 to 284 steps/day, $p = 0.805$, Table 17). A between group difference of 1016 steps/day (95% CI 556 to 1474 steps/day, $p = 0.001$, Table 17) was both statistically significant and clinically important. Following PR, significant improvements in accelerometer movement intensity (VMU) were demonstrated in those who undertook the PR+PA intervention (by 73 VMU; 95% CI 37 to 109 VMU, $p = 0.001$, Table 17), but not in those who undertook the PA alone control (by -20 VMU; 95% CI -57 to 17 VMU, $p = 0.281$, Table 17). A between group difference of 93 VMU (95% CI 41 to 145 VMU, $p = 0.001$, Table 17) was statistically significant.

Following PR, a significant decrease in time spent in sedentary PA was demonstrated in those who undertook the PR+PA intervention (by -37 mins; 95% CI 12 to 62, $p = 0.005$, Table 17), but not in those who undertook the PR alone control (by -22 mins; 95% CI -48 to 3 mins, $p = 0.088$, Table 17). A between group difference in time spent in sedentary PA of -15 (95% CI -51 to 21, $p = 0.406$, Table 17) was demonstrated. A significant improvement in time spent in light PA was demonstrated in those who undertook the PR+PA intervention (by 20 mins; 95% CI 6 to 35 mins, $p = 0.006$, Table 17), but not in those who undertook the PR alone control (by -2 mins; 95% CI -17 to 12 mins, $p = 0.741$, Table 17). A between group difference in time spent in light PA of 22 mins (95% CI 2 to 43 mins, $p = 0.030$, Table 17) was statistically significant. Finally, a significant improvement in time spent in MVPA was demonstrated in

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those who undertook the PR+PA intervention (by 3 mins; 95% CI 0 to 6 mins, $p = 0.041$, Table 17) but not in those who undertook the PR alone control (by 0 mins; 95% CI -3 to 3 mins, $p = 0.791$, Table 17). A between group difference of 3 mins (95% CI -1 to 7 mins, $p = 0.185$, Table 17) was demonstrated in time spent in MVPA.

Patients randomised to the PR+PA intervention were provided with a pedometer to monitor steps/day throughout the trial. Significant and clinically important improvements in pedometer derived steps/day following completion of PR were reported (by 1566; 95% CI 684 to 2357 steps/day, $p = 0.001$, Figure 36).

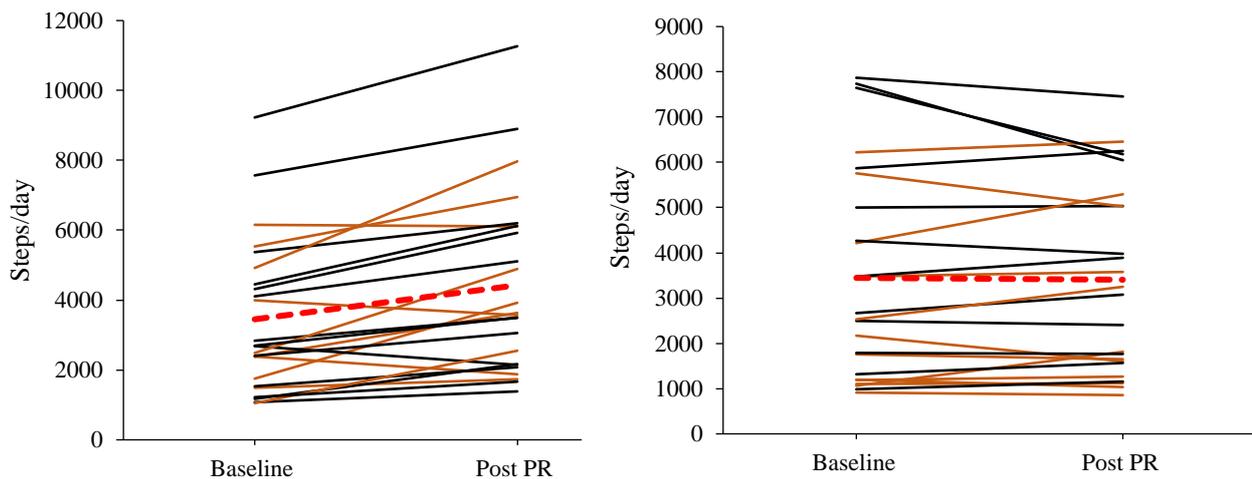


Figure 35. Individual steps/day responses (Actigraph) to the PR+PA intervention (Left panel) and PR alone (Right panel). Dashed red line indicates average response in steps/day (Actigraph), orange line indicates individual patients who received CBT.

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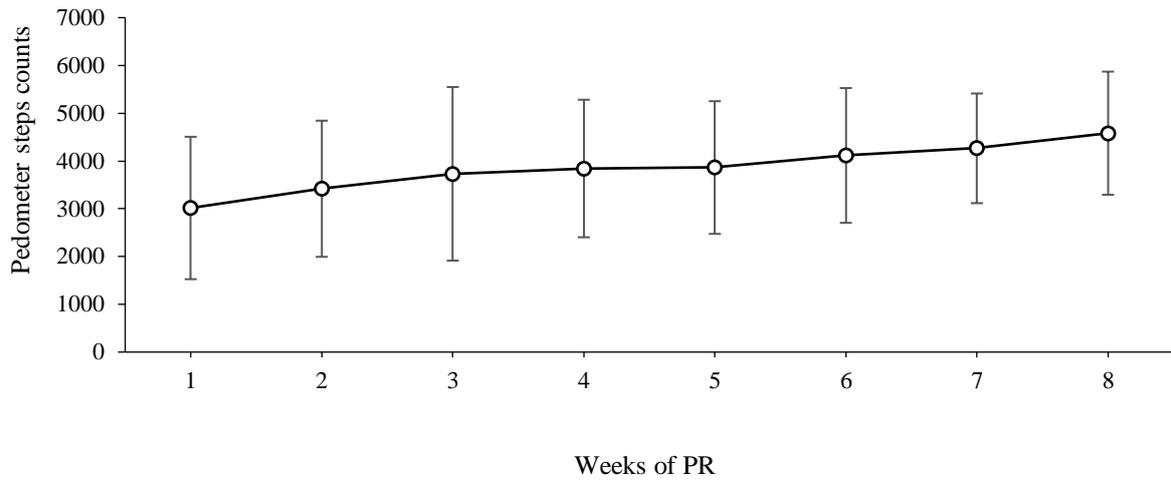


Figure 36. Average improvement in pedometer (Fitbug) steps/day for patients undertaking the PR+PA intervention

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Table 17. Change in secondary outcome measures for PA outcomes in the PR+PA (n = 24) and PR alone (n = 24) interventions

	Group	Baseline	Post PR	Within Group Mean Difference	P value	Between Group Difference	P value
Steps/day	PR+PA	3450±2168	4426±2577	976 (651 to 1300)*	0.001	1016 (556 to 1474)*	0.001
	PR alone	3446±2342	3406±2095	-40 (-365 to 284)	0.805		
Movement intensity (VMU)	PR+PA	337±154	410±231	73 (37 to 109)	0.001	93 (41 to 145)	0.001
	PR alone	307±170	287±133	-20 (-57 to 17)	0.281		
Sedentary time (min)	PR+PA	495±84	458±111	-37 (12 to 62)	0.005	-15 (-51 to 21)	0.406
	PR alone	541±90	519±103	-22 (-48 to 3)	0.088		
Light time (min)	PR+PA	167±56	187±73	20 (6 to 35)	0.006	22 (2 to 43)*	0.030
	PR alone	135±57	133±48	-2 (-17 to 12)	0.741		
MVPA (min)	PR+PA	7±8	10±14	3 (0 to 6)	0.041	3 (-1 to 7)	0.185
	PR alone	7±10	7±8	0 (-3 to 3)	0.791		

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7.3.7.2 Exercise capacity

Following PR, significant and clinically important improvements (>30m) in exercise capacity measured by the 6MWT were demonstrated in those who undertook the PR+PA intervention (by 54 m; 95% CI 36 to 72 m, $p=0.001$, Table 18) and PR alone control (by 38 m; 95% CI 20 to 57 m, $p=0.001$, Table 18). A between group difference of 16 m (95% CI -10 to 41 m, $P=0.236$, Table 18) was demonstrated.

7.3.7.3 Upper and lower body muscular strength and endurance

Following PR, significant improvements in lower body muscle strength (QMVC) were demonstrated in those who undertook the PR+PA intervention (by 5.0 kg; 95% CI 3.4 to 6.8 kg, $p=0.001$, Table 18) and PR alone control (by 2.5 kg; 95% CI 0.8 to 4.2 kg, $p=0.005$, Table 18). A between group difference of 2.5 kg (95% CI 0.2 to 4.9 kg, $p=0.033$, Table 18) was statistically significant.

Significant improvements were demonstrated in upper body muscle strength in those who undertook the PR+PA intervention (by 3.3 kg; 95% CI 2.1 to 4.5 kg, $p=0.001$, Table 18) but not in the those who undertook the PR alone control (by 1.2 kg; 95% CI 0.2 to 2.5, $p=0.083$, Table 18). A between group difference of 2.1 kg (95% CI 0.3 to 3.9 kg, $p=0.022$, Table 18) was statistically significant. Significant and clinically important improvements (≥ 2 reps) in lower body muscle endurance were reported in those who undertook the PR+PA intervention (by 3 reps; 95% CI 2 to 4 reps, $p=0.001$, Table 18) and those who undertook PR alone control (by 2 reps; 95% CI 1 to 3reps, $p=0.001$, Table 18) A between group difference of 1 rep (95% CI -1 to 2 reps, $p=0.446$, Table 18) was demonstrated.

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7.3.7.4 Health-related quality of life

Following PR, significant and clinically important improvements (> -2 units) in health-related quality of life measured by the CAT questionnaire were demonstrated in those who undertook the PR+PA intervention (by -4 ; 95% CI -5 to -3 points, $p = 0.001$, Table 18) and those who undertook the PR alone control (by -2 ; 95% CI -3 to -1 points, $p = 0.002$, Table 18). A between group difference of -2 points (95% CI -4 to 0 points, $p = 0.025$, Table 18) was both statistically significant and clinically important. No differences in health-related quality of life were demonstrated by the CCQ questionnaire using the following domains in the PR+PA intervention or PR alone control, following PR; total score (by -0.3 ; 95% CI -0.6 to 0.1 , $p = 0.068$ vs -0.1 ; 95% CI -0.4 to 0.2 , $p = 0.599$, Table 18), symptoms score (by -0.3 ; 95% CI -0.7 to 0.1 , $p = 0.169$ vs -0.1 ; 95% CI -0.5 to 0.4 , $p = 0.805$, Table 18), functional score (by -0.3 ; 95% CI -0.7 to 0.1 , $p = 0.134$ vs -0.2 ; 95% CI -0.6 to 0.2 , $p = 0.326$, Table 18) and mental score (by -0.1 ; 95% CI -0.5 to 0.8 , $p = 0.677$ vs 0 ; 95% CI -0.7 to 0.6 , $p = 0.859$, Table 18). No between group difference were demonstrated for any CCQ domains ($p > 0.05$, Table 18).

7.3.7.5 Anxiety and depression

Following PR, no reductions in HADS Anxiety were demonstrated in those who undertook the PR+PA intervention (by -1 ; 95% CI -2 to 0 units, $p = 0.065$, Table 18) or those who undertook the PR alone control (by 0 ; 95% CI -2 to 1 units, $p = 0.461$, Table 18). A between group difference of -1 units (95% CI -2 to 1 units, $p = 0.421$, Table 18) was demonstrated.

Following PR, significant reductions in HADS depression were demonstrated in those who undertook the PR+PA intervention (by -1 ; 95% CI -2 to 0 units, $p = 0.004$, Table 18) and those who undertook the PR alone control (by -1 ; 95% CI -2 to -1 units, $p = 0.036$, Table 18). A between group difference of 0 units (95% CI -2 to 1 units, $p = 0.527$, Table 18) was demonstrated.

7.3.7.6 Breathlessness

Following PR, no mean differences in MRC breathlessness were demonstrated in either the PR+PA intervention or PR alone control (Table 18).

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Table 18. Change in exercise capacity, muscular strength/endurance, health-related quality of life and anxiety and depression outcome measures in the PR+PA (n = 24) and PR alone (n = 24) interventions

	Group	Baseline	Post PR	Within Group Mean Difference	P value	Between Group Difference	P value
6MWT (m)	PR+PA	285±92	339±90	54 (36 to 72)*	0.001	16 (-10 to 41)	0.236
	PR alone	276±92	314±99	38 (20 to 57)*	0.001		
HG (kg)	PR+PA	22.7±8.9	26.0±9.2	3.3 (2.1 to 4.5)	0.001	2.1 (0.3 to 3.9)	0.022
	PR alone	18.3±6.1	19.5±7.3	1.2 (0.2 to 2.5)	0.083		
QMVC (kg)	PR+PA	24.6±8.7	29.6±9.7	5.0 (3.4 to 6.8)	0.001	2.5 (0.2 to 4.9)	0.033
	PR alone	21.0±10.2	23.5±10.7	2.5 (0.8 to 4.2)	0.005		
Sit to Stand (reps)	PR+PA	10±3	13±4	3 (2 to 4)*	0.001	1 (-1 to 2)	0.446
	PR alone	11±4	13±5	2 (1 to 3)*	0.001		
CCQ (T)	PR+PA	2.5±1.1	2.2±1.1	-0.3 (-0.6 to 0.1)	0.068	-0.2 (-0.7 to 0.2)	0.349
	PR alone	2.5±1.3	2.4±1.3	-0.1 (-0.4 to 0.2)	0.599		
CCQ (S)	PR+PA	2.5±1.2	2.2±1.1	-0.3 (-0.7 to 0.1)	0.169	-0.2 (-0.9 to 0.4)	0.435
	PR alone	2.7±1.2	2.6±1.4	-0.1 (-0.5 to 0.4)	0.805		
CCQ (F)	PR+PA	2.4±1.2	2.1±1.3	-0.3 (-0.7 to 0.1)	0.134	-0.1 (-0.7 to 0.5)	0.722
	PR alone	2.4±1.4	2.2±1.4	-0.2 (-0.6 to 0.2)	0.326		
CCQ (M)	PR+PA	1.8±1.5	1.7±1.6	-0.1 (-0.5 to 0.8)	0.677	-0.1 (-1.0 to 0.8)	0.869
	PR alone	1.9±1.5	1.9±1.5	-0 (-0.7 to 0.6)	0.859		
CAT	PR+PA	26±6	22±6	-4 (-5 to -3)*	0.001	-2 (-4 to -0)*	0.025
	PR alone	27±6	25±7	-2 (-3 to -1)*	0.002		
HADS (A)	PR+PA	7±6	6±4	-1 (-2 to 0)	0.065	-1 (-2 to 1)	0.421
	PR alone	7±4	7±4	0 (-2 to 1)	0.461		
HADS (D)	PR+PA	6±6	5±4	-1 (-2 to 0)	0.004	0 (-2 to 1)	0.527
	PR alone	7±4	6±3	-1 (-2 to -1)	0.036		
MRC	PR+PA	3±1	3±1	0 (-1 to 1)	0.345	0 (-1 to 1)	0.345
	PR alone	3±1	3±1	0 (-1 to 1)	0.345		

Abbreviations: 6MWT = Six Minute Walk Test, HG = Hand grip strength, QMVC = Quadriceps Muscle Voluntary Capacity, CCQ = Clinical COPD Questionnaire, T = Total, S = Symptoms, F = Functional, M = Mental, CAT = COPD Assessment Test, HADS = Hospital Anxiety and Depression Scale, A = Anxiety, D = Depression, m = Metres, PA = Physical activity, PR = Pulmonary Rehabilitation. Values are mean±SD. Within and between group differences are reported with 95% confidence intervals (CI).

*Clinically important improvement

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7.3.8 Subgroup analysis of patients with ≥ 8 HADS score at baseline

Baseline characteristics of those included in the subgroup analysis (≥ 8 HADS) and those who weren't (< 8 HADS) for patients who completed PR (n=48) are documented in table 19.

Table 19. Baseline characteristics of PR completers with ≥ 8 HADS and < 8 HADS in both PR+PA and PR alone groups

Variable	Patients ≥ 8 HADS (n= 23)	Patients < 8 HADS (n=25)	P value
Age	67 \pm 9	74 \pm 7	0.005
BMI	26.8 \pm 6.8	27.6 \pm 3.9	0.713
FEV1 % Pred	40 \pm 17	59 \pm 20	0.001
FEV1/FVC %	46 \pm 14	57 \pm 13	0.006
6MWD	269 \pm 82	308 \pm 75	0.101
Steps/day	2913 \pm 1821	4018 \pm 2549	0.090
MVPA	5.3 \pm 6.0	7.4 \pm 13.4	0.425
CAT	31 \pm 5	27 \pm 6	0.001
Anxiety	11 \pm 3	4 \pm 3	0.001
Depression	11 \pm 4	4 \pm 2	0.001

Abbreviations: BMI = Body Mass Index, FEV₁ = Forced Expiratory Volume in the 1st second, L = Litres, FVC = Forced Vital Capacity, 6MWD = Six Minute Walk Distance, m = metres, MVPA = Moderate Vigorous Physical Activity, CAT = COPD Assessment Test, HADS = Hospital Anxiety and Depression Scale, Values are mean \pm SD.

7.3.8.1 Physical activity outcomes

The effect of PR+CBT+PA compared to PR+CBT on PA outcome measures are shown in Table 20 and individual responses to steps/day are shown in Figure 38. Following PR, significant and clinically important improvements in steps/day data were demonstrated in those who undertook PR+CBT+PA (by 1065 steps/day; 95% CI 498 to 1631 steps/day, $p = 0.001$, Table 20), but not in those who undertook PR+CBT (by 113 steps/day; 95% CI -429 to 655 steps/day, $p = 0.669$, Table 20). A between group difference of 952 steps/day (95% CI 167 to 1736 points, $p = 0.020$, Table 20) was both statistically significant and clinically important.

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Following PR, positive, non-significant improvements in movement intensity were demonstrated in those who undertook PR+CBT+PA (by 67 VMU; 95% CI -2 to 134 VMU, $p = 0.056$, Table 20), while a decrease in those who undertook PR+CBT was demonstrated (by -36 VMU; 95% CI -101 to 29 VMU, $p = 0.267$, Table 20). A between group difference of 103 VMU (95% CI 8 to 196 VMU, $p = 0.035$, Table 20) was statistically significant.

In terms of the time spent in different domains of PA, following PR, a significant reduction in time spent in sedentary PA was demonstrated in those who undertook PR+CBT+PA (by -48 mins; 95% CI -91 to -5 mins, $p = 0.030$, Table 20), but not in those who undertook PR+CBT (by -15 mins; 95% CI -56 to 26 mins, $p = 0.442$, Table 20). A between group difference of -33 mins (95% CI -92 to 27 mins, $p = 0.269$, Table 20) was demonstrated. No significant improvements in light PA time were demonstrated in those who undertook PR+CBT+PA (by 19 mins; 95% CI -7 to 44 mins, $p = 0.148$, Table 20) or PR+CBT (by -1 min; 95% CI -26 to 23 mins, $p = 0.908$, Table 20). A between group difference of 20 mins (95% CI -16 to 55 mins, $p = 0.256$, Table 20) was demonstrated. Finally, following PR, no improvements in time spent in MVPA were demonstrated in those who undertook PR+CBT+PA (by 0 mins; 95% CI -3 to 4 mins, $p = 0.760$, Table 20), or PR+CBT (by 1 min; 95% CI -2 to 4, $p = 0.566$, Table 20). A between group difference of -1 mins (95% CI -5 to 4 mins, $p = 0.850$, Table 20) was demonstrated.

Patients randomised to the PR+CBT+PA group were provided with a pedometer to monitor steps/day throughout the trial. Significant and clinically important improvements in pedometer derived steps/day following completion of PR were reported (by 1354; 95% CI 344 to 2364 steps/day, $p = 0.014$).

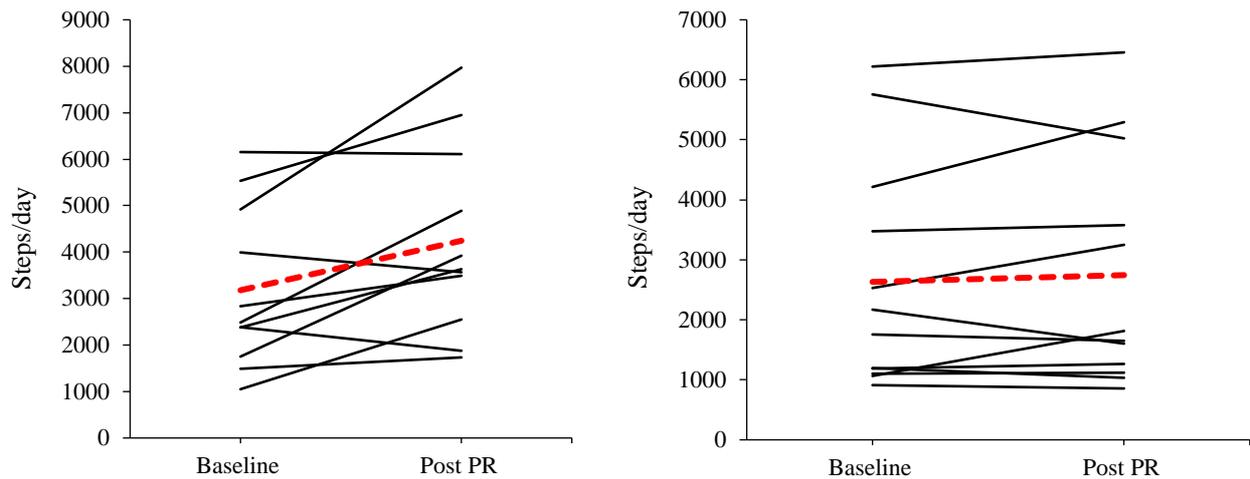


Figure 38. Individual responses to the PR+CBT+PA (Left Panel) and PR+CBT (Right Panel) based on change in steps/day in patients reporting elevated anxiety and depression. (Red dashed line indicates average response in steps/day [Actigraph]).

7.3.8.2 Patient experiences of physical activity

The effect of PR+CBT+PA compared to PR+CBT on all dimensions of the C-PPAC instrument are shown in Table 20. Following PR, the *total score* of the C-PPAC instrument improved by a significant and clinically important margin in those who undertook PR+CBT+PA (by 8 points; 95% CI 3 to 14 points, $p = 0.004$, Table 20) compared with those who undertook PR+CBT (by 1 point; 95% CI -4 to 6 points, $p = 0.698$, Table 20). A between group difference of 7 points (95% CI 1 to 15 points, $p = 0.047$, Table 20) was both statistically significant and clinically important. In regard to the *difficulty score* of the C-PPAC instrument, significant and clinically important improvements were reported in those who undertook PR+CBT+PA (by 8 points; 95% CI 1 to 16 points, $p = 0.034$, Table 20) and clinically important improvements in those who undertook PR+CBT (by 6 point; 95% CI -1 to 14 points, $p = 0.097$, Table 20). A between group difference of 2 points (95% CI -9 to 13 points, $p = 0.664$, Table 20), was demonstrated. Finally, significant and clinically important improvements in the amount score of the C-PPAC tool were reported in those who undertook PR+CBT+PA (by 8 points; 95% CI

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2 to 14 points, $p = 0.010$, table 20) compared to those who undertook PR+CBT (by -4 points; 95% CI -10 to 1 points, $p = 0.131$, Table 20). A between group difference of 12 points (95% CI 4 to 21 points, $p = 0.005$, Table 20) was both statistically significant and clinically important.

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Table 20. Change in PA outcome measures in the PR+CBT+PA (n = 11) and PR+CBT (n = 12) interventions.

	Group	Baseline	Post PR	Within Group Mean Difference	P values	Between Group Difference	P values
C-PPAC Total score	PR+CBT+PA	54±14	62±12	8 (3 to 14)	0.004*	7 (1 to 15)	0.047*
	PR+CBT	58±11	59±12	1 (-4 to 6)	0.698		
C-PPAC Difficulty score	PR+CBT+PA	56±15	64±16	8 (1 to 16)	0.034*	2 (-9 to 13)	0.664
	PR+CBT	52±18	58±19	6 (-1 to 14)	0.097		
C-PPAC Amount score	PR+CBT+PA	52±17	60±11	8 (2 to 14)	0.010*	12 (4 to 21)	0.005*
	PR+CBT	65±11	61±11	-4 (-10 to 1)	0.131		
Steps/day	PR+CBT+PA	3180±1714	4245±2034	1065 (498 to 1631)	0.001*	952 (167 to 1736)	0.020*
	PR+CBT	2632±1877	2745±1933	113 (-429 to 655)	0.669		
Movement intensity (VMU)	PR+CBT+PA	325±109	392±225	67 (-2 to 134)	0.056	103 (8 to 196)	0.035*
	PR+CBT	281±189	245±134	-36 (-101 to 29)	0.267		
Sedentary time (min)	PR+CBT+PA	511±83	463±102	-48 (-91 to -5)	0.030*	-33 (-92 to 27)	0.269
	PR+CBT	544±73	529±89	-15 (-56 to 26)	0.442		
Light time (min)	PR+CBT+PA	153±43	172±73	19 (-7 to 44)	0.148	20 (-16 to 55)	0.256
	PR+CBT	129±57	128±46	-1 (-26 to 23)	0.908		
MVPA (min)	PR+CBT+PA	7±6	7±5	0 (-3 to 4)	0.760	-1 (-5 to 4)	0.850
	PR+CBT	5±7	6±7	1 (-2 to 4)	0.556		

Abbreviations: C-PPAC = Clinical visit-PROactive physical activity in COPD, Mins = Minutes, PA = Physical activity, PR = Pulmonary Rehabilitation. Values are mean±SD.

Within and between group differences are reported with 95% confidence intervals (CI). *Clinically important improvement

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7.3.8.3 Exercise capacity

Following PR, significant and clinically important improvements (>30m) in exercise capacity measured by the 6MWT were demonstrated in those who undertook PR+CBT+PA (by 59m; 95% CI 37 to 82 m, $p = 0.001$, Table 21) and PR+CBT (by 30m; 95% CI 8 to 52m, $p = 0.010$, Table). A between group difference of 29m (95% CI -2 to 61m, $p = 0.067$, Table 21) was demonstrated.

7.3.8.4 Upper and lower body muscular strength and endurance

Significant improvements in lower body muscle strength (QMVC) were demonstrated following PR in those who undertook PR+CBT+PA (by 4.6 kg; 95% CI 2.2 to 7.1 kg, $p = 0.001$, Table 21) and PR+CBT (by 3.9 kg; 95% CI 0.4 to 7.3 kg, $p = 0.026$, Table 21). A between group difference of 0.7 kg (95% CI -3.3 to 4.9 kg, $p = 0.676$, Table 21) was demonstrated. Significant improvements were also demonstrated in upper body muscle strength (HG) in those who undertook PR+CBT+PA (by 4.7 kg; 95% CI 2.9 to 6.5 kg, $p = 0.001$, Table 21) but not in the those who undertook PR+CBT (by 0.5 kg; 95% CI -2.5 to 1.4, $p = 0.587$, Table 21). A between group difference of 4.2 kg (95% CI 1.6 to 6.9 kg, $p = 0.003$, Table 21) was statistically significant. Finally, in terms of lower body muscle endurance (STS), significant and clinically important improvements (≥ 2 reps) following PR were reported in those who undertook PR+CBT+PA (by 2 reps; 95% CI 2 to 4 reps, $p = 0.001$, Table 21) but not in those who undertook PR+CBT (by 1 rep; 95% CI 0 to 3 reps, $p = 0.121$, Table 21). A between group difference of 1 rep (95% CI 0 to 3 reps, $p = 0.125$, Table 21) was demonstrated.

7.3.8.5 Health related quality of life

Significant and clinically important reductions (>-2 units) in health-related quality of life measured by the CAT questionnaire were demonstrated following PR in those who undertook

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PR+CBT+PA (by -5 points; 95% CI -7 to -3 points, $p = 0.001$, Table 21) and those who undertook PR+CBT (by -2 points; 95% CI -4 to 0 points, $p = 0.028$, Table 21). A between group difference of -3 points (95% CI -6 to 1 points, $p = 0.075$, Table 21) was demonstrated. Significant reductions in health-related quality of life measured by the CCQ questionnaire were demonstrated in the following domains following PR in those who undertook PR+CBT+PA; total score (by -0.6 points; 95% CI -1.1 to -0.1 points, $p = 0.015$, Table 21), symptom score (by -0.4 points; 95% CI -0.8 to -0.1, $p = 0.032$, Table 21) and functional score (by -0.7 points; 95% CI -1.3 to 0.0, $p = 0.050$, Table 21). In addition, a non significant reduction in mental score was demonstrated (by -0.9 points; 95% CI -1.8 to 0.1, $p = 0.051$, Table 21). No reductions in those who undertook PR+CBT were demonstrated in the total score (by -0.1; 95% CI -0.5 to 0.5, $p = 0.965$, Table 21), symptom score (by -0.2; 95% CI -0.6 to 0.3, $p = 0.445$, Table 21), functional score (by -0.3; 95% CI -1.0 to 0.4, $p = 0.375$, Table 21) and mental score (by 0.1 points; 95% CI -1.0 to 0.9, $p = 0.874$, Table 21). No between group difference were reported for any CCQ domains ($p > 0.05$).

7.3.8.6 Anxiety and depression

A significant and clinically important reduction (<1.5 units) in HADS anxiety following PR was demonstrated in those who undertook PR+CBT+PA (by -3 units; 95% CI -5 to -1 units, $p = 0.024$, Table 21) but not in those who undertook PR+CBT (by -1 unit; 95% CI -4 to 1 units, $p = 0.214$, Table 21). A between group difference of 2 units (95% CI -4 to 2 units, $p = 0.397$, Table 21) was demonstrated.

A significant and clinically important reduction in HADS depression following PR was demonstrated in those who undertook PR+CBT+PA (by -2 units; 95% CI -4 to -1 units, $p = 0.002$, Table 21) and those who undertook PR+CBT (by -3; 95% CI -3 to -1 units, $p = 0.002$,

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Table 21). A between group difference of -1 unit (95% CI -2 to 2 units, $p = 0.898$, Table 21) was demonstrated.

7.3.8.7 *Breathlessness*

No mean differences in MRC breathlessness were reported following PR in those who undertook PR+PA+CBT or PR+CBT (Table 21).

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Table 21. Change in exercise capacity, muscular strength/endurance, health-related quality of life and anxiety and depression outcome measures in the PR+CBT+PA (n = 11) and PR+CBT (n = 12) interventions.

	Group	Baseline	Post PR	Within Group Mean Difference	P value	Between Group Mean Difference	P value
6MWT (m)	PR+CBT+PA	265±95	324±88	59 (37 to 82)	0.001*	29 (-2 to 61)	0.067
	PR+CBT	245±84	275±85	30 (8 to 52)	0.010*		
HG (kg)	PR+CBT+PA	18.7±6.4	23.4±8.2	4.7 (2.9 to 6.5)	0.001*	4.2 (1.6 to 6.9)	0.003*
	PR+CBT	19.6±5.2	20.1±7.3	0.5 (-2.5 to 1.4)	0.587		
QMVC (kg)	PR+CBT+PA	22.7±6.2	27.3±8.1	4.6 (2.2 to 7.1)	0.001*	0.7 (-3.3 to 4.9)	0.676
	PR+CBT	20.6±9.0	24.5±10.0	3.9 (0.4 to 7.3)	0.026*		
Sit to Stand (reps)	PR+CBT+PA	10±3	12±5	2 (2 to 4)	0.001*	1 (0 to 3)	0.125
	PR+CBT	10±2	11±3	1 (0 to 3)	0.121		
CCQ (T)	PR+CBT+PA	2.9±1.2	2.3±1.3	-0.6 (-1.1 to -0.1)	0.015*	-0.5 (-1.2 to 0.1)	0.074
	PR+CBT	3.3±1.2	3.3±1.2	-0.1 (-0.5 to 0.5)	0.965		
CCQ (S)	PR+CBT+PA	2.7±1.1	2.3±1.2	-0.4 (-0.8 to -0.1)	0.032*	-0.2 (-0.9 to 0.3)	0.308
	PR+CBT	3.5±1.0	3.4±1.4	-0.2 (-0.6 to 0.3)	0.455		
CCQ (F)	PR+CBT+PA	2.8±1.9	2.1±1.4	-0.7 (-1.3 to 0.0)	0.050*	-0.4 (-1.3 to 0.6)	0.442
	PR+CBT	3.3±1.2	3.0±1.3	-0.3 (-1.0 to 0.4)	0.375		
CCQ (M)	PR+CBT+PA	2.5±1.9	1.6±1.6	-0.9 (-1.8 to 0.1)	0.051	1.0 (-2.3 to 0.4)	0.137
	PR+CBT	2.8±1.6	2.8±1.6	0.1 (-1.0 to 0.9)	0.874		
CAT	PR+CBT+PA	29±4	24±4	-5 (-7 to -3)	0.001*	-3 (-6 to 1)	0.075
	PR+CBT	31±5	29±6	-2 (-4 to 0)	0.028*		
HADS (A)	PR+CBT+PA	12±5	9±4	-3 (-5 to -1)	0.024*	2 (-4 to 2)	0.397
	PR+CBT	10±3	9±4	-1 (-4 to 1)	0.214		
HADS (D)	PR+CBT+PA	10±6	8±4	-2 (-4 to -1)	0.002*	-1 (-2 to 2)	0.898
	PR+CBT	11±2	8±3	-3 (-3 to -1)	0.002*		
MRC	PR+CBT+PA	3±1	3±1	0 (-1 to 1)	0.345	0 (-1 to 1)	0.345
	PR+CBT	3±1	3±1	0 (-1 to 1)	0.345		

Abbreviations: 6MWT = Six Minute Walk Test, HG = Hand grip, QMVC = Quadriceps Muscle Voluntary Capacity, CCQ = Clinical COPD Questionnaire, T = Total, S = Symptoms, F = Functional, M = Mental, CAT = COPD Assessment Test, HADS = Hospital Anxiety and Depression Scale, A = Anxiety, D = Depression, m = Metres, PA = Physical activity, PR = Pulmonary Rehabilitation. Values are mean±SD. Within and between group differences are reported with 95% confidence intervals (CI). *Clinically important improvement.

7.4 Discussion

7.4.1 Summary of main findings

To the author's knowledge this is the first study to investigate the efficacy of a PA behavioural modification intervention alongside PR (and CBT in those with profound anxiety and depression) in patients with COPD exhibiting low baseline PA and exercise capacity levels.

Compared to the PR alone group, the PR+PA intervention, incorporating motivational interviewing, face-to-face twice weekly goal setting, step count monitoring and feedback, alongside exercise training and psychological support in those with ≥ 8 HADS, demonstrated significant and clinically important improvements in PA levels (steps/day, movement intensity and time spent in light PA) and PA experiences using the C-PPAC instrument.

These findings are supported by evidence of adequate intervention completion rates, high patient acceptability and adherence to the components of the PA behavioural modification intervention, including the pedometer and step count diary to self-monitor and report daily step counts. Collectively these findings suggest that a PA behavioural modification intervention alongside PR provide insightful support to patients with low baseline levels of PA to translate PR-induced improvements in exercise capacity into improvements in overall PA outcomes.

One of the most interesting findings of this chapter was demonstrated in the subgroup analysis of COPD patients with $HADS \geq 8$ who received CBT alongside either PR+PA or PR alone. In these patients, who typically reported lower baseline PA levels compared to those with $HADS < 8$, significant and clinically important improvements in both steps/day and patients' experiences of PA were reported following PR+PA+CBT compared to PR+CBT. Accordingly, it becomes apparent that in patients with profound anxiety and depression, PA behavioural modification strategies need to compliment CBT approaches in order to translate PR-induced improvements in exercise capacity into enhanced PA levels and PA experiences.

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7.4.2 *Physical activity outcomes*

7.4.2.1 *Steps/day*

The findings of this study demonstrate significant and clinically important improvements in steps/day following completion of the PR+PA intervention compared to the PR alone control in patients with COPD exhibiting low baseline PA levels. These improvements in steps/day were supported by significant and clinically important improvements in all domains of the C-PPAC instrument, indicating overall improvements in patients' experiences of PA, and significant improvements in movement intensity and time spent in light PA.

Previous studies have reported the impact of a PR+PA intervention compared to PR alone on steps/day in patients with COPD exhibiting low baseline PA, with limited improvements demonstrated (de Blok et al., 2006; Holland et al., 2017; Nolan et al., 2017). Specifically, as detailed in the systematic review and meta-analysis (Chapter 3), the combined change in steps/day from baseline to post PR of the three studies (de Blok et al., 2006; Holland et al., 2017; Nolan et al., 2017) with patients reporting baseline steps/day ≤ 4000 , failed to report a clinically important improvement in steps/day (Armstrong et al., 2019). Prior to these findings, previous studies have highlighted that the majority of patients with poor exercise capacity, measured through the 6MWT, and/or low PA levels at baseline were unlikely to improve PA following an intervention to promote PA (Demeyer et al., 2017; Loeckx et al., 2018a; Osadnik et al., 2018). A plausible reason for these findings involves the concept of "functional reserve", indicating that patients with a higher tolerance to exercise and PA may have greater opportunities to become more physically active within their tolerance limits (i.e. high functional reserve). On the other hand, those with low tolerance to exercise and PA may be less capable of increasing PA due to an inhibitory ceiling limitation (i.e. low functional reserve) (Langer & Demeyer, 2016; Leidy, 1994; Osadnik et al., 2018).

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Of the three studies investigating PR+PA in patients with COPD exhibiting low baseline PA, only de Blok et al. (2006) were able to demonstrate a clinically important improvement in steps/day following completion of PR+PA. Interestingly, the PA counselling intervention implemented by de Blok et al. (2006) incorporated four face-to-face counselling sessions, while the current study implemented significantly more (16 sessions). However, these findings were reported across a very small sample size ($n=8$), making it difficult to analyse the overall effectiveness of this programme (de Blok et al., 2006). Furthermore, the primary outcome was based around pedometer step counts, which can often overestimate steps/day; whereas the triaxial accelerometer used to measure PA at baseline and post-PR in this study is considered a more accurate measure of PA (Rabinovich et al., 2013).

The other two studies from Holland et al. (2017) and Nolan et al. (2017) failed to report significant or clinically important improvements in steps/day following PR+PA compared to a PR alone group. In the study from Holland et al. (2017), a telephone based PA counselling intervention was added to home-based PR sessions. Their failure to achieve meaningful gains in PA was attributed to a lack of integration of health-enhancing behaviours into daily life, concluding that new methods of behaviour change are necessary in order to investigate tools to promote more effective health-enhancing behaviours (Holland et al., 2017).

Interestingly, the study from Nolan et al. (2017) and the current study bears many similarities, with both incorporating the same twice-weekly, supervised, 8-week outpatient PR program in line with the BTS guidelines, based in the UK (Bolton et al., 2013). Furthermore, both studies delivered PA counselling in a similar manner, with pedometer feedback and daily step-count targets provided across the 8-weeks. However, there are several feasible reasons that may support the superior findings reported in the current study.

Firstly, patients across this study were encouraged to reach a step target based on 10% of the previous week, which was both feasible and achievable in this group of patients. Alternatively,

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Nolan et al. (2017) based their weekly step targets on 5% of the previous week, which was not achieved as regularly as the current studies targets. Moreover, the individualised approach used when delivering PA targets across this study may have stimulated the greater achievement of step goal targets, therefore improving the overall PA response.

Secondly, patients in the present study had the opportunity to consult face-to-face with the researcher at every PR session (twice weekly), compared to every other PR session (once weekly) in the Nolan et al. (2017) study. This added face-to-face support, which was deemed acceptable by patients, provided the researcher with more opportunities to consult the patient on behaviour change techniques, including goal setting, action planning and guidance on self-monitoring and management. Such behavioural components have been shown to benefit COPD patients' readiness, motivation and confidence to engage in PA and were associated with significant improvements in PA behaviour (Bourbeau et al., 2021). As a result, the greater face-to-face support may have empowered and motivated patients to engage in more daily PA, supporting the greater improvement in PA demonstrated in this study.

Finally, inconsistencies surrounding the method of PA analysis exist between the two studies. Nolan et al. (2017) used the recommendations of Watz et al. (2009) requiring 5 valid days of PA data, including 3 weekdays and 2 weekend days from a total of 7 days. In contrast, in the current study, the recommendations from Demeyer et al. (2014) were followed, with 4 valid weekdays from a total of 7 days required. As detailed in Chapter 4, COPD patients typically report lower levels of PA during the weekend than during weekdays, which often influences the variability of data (Demeyer et al., 2014). Therefore, this may have been a key source of discrepancy between interventions across both studies.

In terms of improvements in pedometer steps/day in those patients who completed the PR+PA intervention, improvements were significant and clinically important in line with recent data from an editorial letter by Polgar et al. (2021). Specifically, they demonstrated that an

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improvement in pedometer PA following PR of 427 steps/day was deemed clinically important (Polgar et al., 2021). Based on the findings from Polgar et al. (2021) , it's clear that the combined approach of a PA behavioural modification intervention alongside PR presented substantially greater improvements in pedometer steps/day than a regular PR programme.

7.4.2.2 Movement intensity

The current study is the first to assess the influence of a PR+PA intervention compared to PR alone on movement intensity. Two published studies have assessed movement intensity during a PA tele coaching intervention (Demeyer et al., 2017), and interval training exercise programme (Louvaris et al., 2016) in patients with COPD. Demeyer et al. (2017) reported significant improvements in movement intensity after a 12-week semiautomated tele coaching programme compared to usual care. Unfortunately, it isn't possible to interpret these findings with those of the current study as movement intensity was assessed using different units across the separate studies (m/s vs VMU). Meanwhile, Louvaris et al. (2016) reported significant improvements in movement intensity after 12-weeks of high-intensity interval exercise training compared to usual care. The same VMU was used between Louvaris et al. (2016) and the current study, with similar improvements equating to 20% and 22% respectively. Interestingly, baseline VMU values were much greater for COPD patients in the Louvaris et al. (2016) study, further demonstrating the level of deconditioning in COPD patients living in the North East of England.

7.4.2.3 C-PPAC instrument

The significant and clinically important improvements in steps/day and movement intensity detailed above are supported with significant and clinically important improvements in all domains of the C-PPAC instrument, indicating overall improvements in patients' experiences

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of PA, following completion of the PR+PA intervention compared to PR alone. Although this comes as little surprise as the objective components of the C-PPAC instrument include steps/day and movement intensity, it presents additional knowledge on the subjective difficulties patients face while conducting PA and amount of PA they subjectively believe they complete on a weekly basis (Gimeno-Santos et al., 2015).

To the authors knowledge, this is the first study to evaluate patients' experiences of PA via the C-PPAC instrument following a PR+PA intervention compared to PR alone group. However, previous literature has documented the response of the C-PPAC instrument in two PA counselling standalone interventions and one interval exercise training intervention (Arbillaga-Etxarri et al., 2018; Demeyer et al., 2017; Louvaris et al., 2016).

Demeyer et al. (2017) found a significant between group difference in both the total and amount dimensions of the C-PPAC instrument following 12 weeks of semi-automated PA tele-coaching delivered via a smartphone app compared to usual care. It should be noted that the usual care group reported a large decrease in C-PPAC scores following a 12-week period, with only small improvements in C-PPAC scores reported following the tele-coaching intervention, thereby suggesting that the tele-coaching intervention only had marginal effects on the C-PPAC tool. Furthermore, Demeyer et al. (2017) were unable to demonstrate an improvement in the difficulty dimension of the C-PPAC instrument. The difficulty dimension has demonstrated a moderate-strong correlation with health status, chronic dyspnea and exercise capacity (Gimeno-Santos et al., 2015), which is not captured by the amount dimension of the C-PPAC. Demeyer et al. (2017) did not include any specific exercise training and as a result was unsuccessful in demonstrating improvements in exercise capacity, which may support the lack of improvement in the difficulty domain following 12-weeks of tele-coaching. In the current study, the significant and clinically important improvements in both exercise capacity

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and PA were most likely the reason for improvements in the difficulty domain of the C-PPAC tool following the PR+PA intervention.

Arbillaga-Etxarri et al. (2018) implemented a 12-month urban training programme that incorporated behavioural and community-based exercise in patients with COPD. The C-PPAC instrument was able to detect a significant improvement from baseline to 12 months in both the amount and difficulty C-PPAC scores, however improvements were not significant between the intervention and the usual care groups (Arbillaga-Etxarri et al., 2018). Considering the magnitude of change in the C-PPAC total scores between intervention and control groups in Arbillaga-Etxarri et al. (2018) (4.5 units) and Demeyer et al. (2017) (4.5 units) compared to that of the current study (7 units), it is clear that PA modification/counselling interventions added to PR are superior to those interventions alone in improving the total score of the C-PPAC instrument.

Meanwhile, Louvaris et al. (2016) investigated the impact of an interval exercise training intervention as part of PR, with significant and clinically important improvements in the total score of the C-PPAC instrument following the intervention (5.6 units). Interestingly, following completion of PR alone in the current study, improvements in the total score of the C-PPAC instrument were minimal (1 unit). Louvaris et al. (2016) provided a different type of PR, with their programme consisting of 3 sessions per week for a total of 10 weeks, whilst the current study consisted of 2 sessions per week for 8 weeks. Secondly, Louvaris et al. (2016) prescribed high-intensity interval exercise, whereas the current study implemented moderate intensity exercise. Furthermore, COPD patients in Louvaris et al. (2016) presented greater baseline levels of PA and 6MWD than the current study, which has previously been documented to influence the effectiveness of interventions to improve PA (Armstrong et al., 2019).

Based on the significant and clinically important improvements in PA outcomes; namely steps/day, movement intensity and patients experience of PA, demonstrated in the current study

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compared to previous studies in patients exhibiting low baseline PA levels (de Blok et al., 2006; Holland et al., 2017; Nolan et al., 2017), several arguments towards this behavioural modification intervention can be made. Firstly, the implementation of greater weekly step goal targets (weekly increase of 10%), that were deemed acceptable and compliant by COPD patients in this study, may have encouraged greater improvements in overall PA compared to the 5% step goal target administered by (Nolan et al., 2017). Secondly, the greater emphasis placed on face-to-face consultations (twice weekly) throughout this PA behavioural modification intervention may have empowered and motivated patients to engage in more daily PA, supporting the greater improvement in PA outcomes demonstrated in this study. Specifically, the twice weekly face-to-face consultations provided more opportunities to contact/engage with the patient on behaviour change techniques which have been shown to benefit patients readiness, motivation and confidence to engage in PA and were associated with significant improvements in PA behaviour (Bourbeau et al., 2021). Finally, measuring objective PA measures (steps/day and movement intensity) at baseline and post-PR using an accelerometer validated for use in COPD patients increased the validity and accuracy of the PA measures reported across this study.

By incorporating these novel approaches as part of a PA behavioural modification intervention to modify patient's behaviour towards greater levels of PA, in conjunction with improvements in exercise capacity and health-related quality of life through PR, it is argued that patients with low baseline PA levels can in-fact improve steps/day, movement intensity and PA experiences by significant and clinically important margins similar to the improvements reported in patients with greater baseline PA levels reported in previous literature (Altenburg et al., 2015; Cruz et al., 2016; Varas et al., 2018).

7.4.3 Exercise capacity

The findings of the current study indicate that both the PR+PA intervention and PR alone group reported significant and clinically important improvements in the 6MWT in patients with COPD following completion of PR. These findings are important as they support the BTS (Bolton et al., 2013) and ATS/ERS (Spruit et al., 2013) recommendations for PR, that exercise training as part of supervised PR elicit gains in exercise capacity. Previous literature has reported improvements in the 6MWT equating to 12% and 10% following PR+PA and PR alone respectively (Altenburg et al., 2015; Cruz et al., 2016; Holland et al., 2017; Kawagoshi et al., 2015). This was similar to the 19% and 14% improvements following PR+PA and PR alone, respectively across the current study. Interestingly, not all published RCT's investigating the effects of PR+PA have assessed exercise capacity using the 6MWT, with Nolan et al. (2017) using the Incremental Shuttle Walk Test (ISWT) and Varas et al. (2018) using the Endurance Shuttle Walk Test (ESWT). Similar improvements in ISWT equating to 23% were reported across both groups in the Nolan et al. (2017) study, coinciding with the findings of the current study that improvements in exercise capacity are reported regardless of study allocation in UK based PR. However, Varas et al. (2018) found a significant between group difference in ESWT distance following completion of its 3 month programme. This was most likely a cause of the control group not receiving any specific supervised exercise training, with only informative sessions about the benefits of exercise provided. The implementation of externally paced field tests including the ISWT are becoming a more common measure in studies assessing exercise performance and exercise capacity in COPD, with the ATS/ERS guidelines (Spruit et al., 2013) considering paced tests more standardised than the 6MWT as the walking speeds are less influenced by motivating and self-selected pacing. However, the 6MWT remains the most established and implemented field test to assess exercise capacity in COPD patients (Spruit et al., 2013).

7.4.4 Muscular strength and endurance

In terms of muscle strength and endurance outcomes, significant improvements in both lower body muscle strength and endurance were reported across both groups, however upper body muscle strength was only significantly improved in the PR+PA intervention.

Limited data on muscle strength and endurance outcomes are available from previous literature implementing PR+PA. Two RCT's (Cruz et al., 2016; Kawagoshi et al., 2015) reported similar improvements in lower body muscle strength across both PR+PA and PR alone groups. In terms of lower body muscle endurance, only a single RCT (de Blok et al., 2006) investigated this outcome, with similar, clinically important improvements documented across groups (de Blok et al., 2006). Reporting improvements in lower body muscle strength and endurance is important as muscle dysfunction of the lower extremities has been identified as a specific cause of exercise impairment, causing many patients to avoid activities of daily living (Singer et al., 2011). Moreover, as detailed in Chapter 6, a significant correlation between improvements in lower body muscle strength and levels of PA were demonstrated in COPD patients in the North East of England.

This is the first study to date exploring the benefits of PR+PA on upper body muscle strength, with significant and clinically important improvements demonstrated. A 12 week exercise counselling programme by Hospes et al. (2009), that incorporated pedometers as a tool to feedback steps/day, reported small insignificant improvements in upper body muscle strength measured via handgrip strength in patients with COPD. The combined approach of PR+PA may be a plausible reason for the significant improvements in upper body muscle strength reported in the current study, because of PR induced improvements in exercise capacity and PA due to the behavioural modification interventions most likely involved more daily activities involving the upper limbs.

7.4.5 Health related quality of life

Significant and clinically important improvements in health-related quality of life, documented by the CAT questionnaire, were found following completion of the PR+PA intervention and PR alone group. Interestingly, a significant and clinically important between group difference in CAT scores were shown.

This is the only study to date that incorporated the CAT questionnaire as a tool to assess health related quality of life in COPD patients conducting an PR+PA intervention. The main reason for this may, in part, be due to many studies incorporating the most widely used disease-specific questionnaires; SGRQ and CRQ (Spruit et al., 2013). However, as detailed in Chapter 4, the CAT questionnaire was developed as a shorter tool which would be easier and quicker to complete, making it more applicable in clinical settings than the SGRQ and CRQ.

A number of studies utilising PA counselling as a standalone intervention have included the CAT questionnaire to assess health related quality of life (Arbillaga-Etxarri et al., 2018; Demeyer et al., 2017; Mendoza et al., 2015). Significant improvements were only found in patients who underwent the PA counselling intervention, with a significant between group difference reported in two of the published RCT's (Arbillaga-Etxarri et al., 2018; Mendoza et al., 2015). Findings of this nature comes as no surprise as specific exercise training was not provided to the control groups in either of the two published RCTs (Arbillaga-Etxarri et al., 2018; Mendoza et al., 2015).

In terms of the CCQ questionnaire, one published RCT implementing PR+PA and four published RCT's implementing PA counselling alone used this questionnaire to assess health related quality of life in patients with COPD (Altenburg et al., 2015; Arbillaga-Etxarri et al., 2018; Demeyer et al., 2016; Hospes et al., 2009; Tabak et al., 2014). In the study by Altenburg et al. (2015), clinically important improvements in the CCQ total domain were reported, while

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results of the other CCQ domains were unavailable. Interestingly, the current study reported minimal changes across all CCQ domains. Regarding the RCT's implementing PA counselling as a standalone intervention, only one study reported significant improvement in the CCQ total domain, with the remaining three documenting minimal effects. Therefore, further research is required to understand the true impact of these interventions on the various domains of the CCQ questionnaire.

7.4.6 The importance of CBT

Incorporation of CBT as part of standard care PR in patients who reported elevated baseline levels of anxiety and/or depression had yet to be investigated alongside PR or alongside PA behavioural modification interventions prior to this study. As detailed earlier, the novel approach of incorporating CBT in this group of patients was based on the theory that alleviating psychological difficulties in those with elevated levels of anxiety and/or depression who are typically less able to manage symptoms and improve levels of PA (Thew et al., 2017; Yohannes & Alexopoulos, 2014), may support an improved mood and better physical conditioning. Such support alongside behaviour change techniques and PR induced improvements in exercise capacity may improve the effectiveness of a PA behavioural modification intervention alongside PR in improving levels of PA. As demonstrated, those with elevated anxiety and/or depression across the current study had reduced baseline levels of PA, with a clinically important mean difference in steps/day between patients who completed PR with ≥ 8 HADS compared to those with < 8 HADS.

Interestingly, following completion of the combined PR+PA+CBT intervention, those patients with elevated anxiety and/or depression reported significant and clinically important improvements in steps/day, movement intensity and total and amount domains of the C-PPAC instrument, that matched the improvements demonstrated by the overall group. Accordingly,

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providing patients with elevated levels of anxiety and/or depression and typically lower PA, with a combination of CBT, PR and PA behavioural modification strategies may yield improvements in PA that mimic in magnitude those in COPD patients with greater levels of PA at baseline. This finding was of significant importance as it may provide a solution to the major finding of the systematic review and meta-analysis (Chapter 3), that patients with low baseline levels of PA report inferior improvements in PA following PA counselling interventions. Interestingly, it seems that in those deconditioned COPD patients with elevated anxiety and/or depression and lower PA, CBT added to PR is not effective in terms of improving PA outcomes unless PA behavioural modification interventions are added to PR+CBT. This is likely because CBT, aiming to alleviate the psychological difficulties associated with activity related symptoms, does not provide any means of directing an increase in PA. The incorporation of PA behavioural modification interventions alongside CBT may provide this missing component, directing an increase in PA, through several behaviour change techniques (Bourbeau et al., 2021).

CBT added to both PR+PA and PR alone in this subgroup of patients was associated with a comparable, clinically important improvement in exercise capacity, health status and depression scores. This finding is important as it demonstrates that the addition of CBT provided no negative impact towards either intervention. However, it must be acknowledged that anxiety scores following PR+CBT failed to reach clinical significance, which may be a result of the small sample size in this subgroup but should be considered when moving forward with future CBT alongside PR and PA behavioural modification interventions.

As detailed above, previous literature has yet to incorporate CBT into PR and/or PA behavioural modification interventions, with only one ongoing RCT protocol available (Sohanpal et al., 2020). Within this ongoing RCT by Tandem investigators, a tailored, cognitive behavioural approach has been developed, issued weekly alongside PR. Their hypothesis is

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that the inclusion of a tailored, cognitive behavioural approach will optimise the benefits of standard care PR. However, Sohanpal et al. (2020) have missed the opportunity to include any objective PA measures, meaning the current study remains the only research providing data on the effects of PR and CBT on PA levels in patients with COPD.

It is important that future research studies incorporate the findings of the current study with that of the Tandem study investigators when their research becomes available, to comprehensively investigate the overall effects of CBT alongside PR and PA behavioural modification interventions in patients with COPD.

7.4.7 Targets for recruitment, randomisation, and completion rates

In terms of the targets for recruitment, randomisation, and completion rates of this PR+PA intervention, the proportion of eligible patients who were recruited into the study (45%), met the recruitment target set prior to initiation (30%). This percentage of recruitment was found to be similar to the majority of other PR+PA RCTs (Altenburg et al., 2015; Cruz et al., 2016; Holland et al., 2017) and was greater than the UK based PR+PA study from Nolan et al. (2017). In addition, the randomisation target rate of 80% was just achieved (86%) and was slightly lower than the rate achieved by Nolan et al. (2017). Finally, following completion of the 8-week PR programme, 80% of patients completed the overall study, which met the pre-defined completion rate of 80%. In terms of the study groups, the completion rate was just missed in the PR+PA group (77%) but met in the PR alone group (83%), with similar rates achieved by Nolan et al. (2017). Meeting these targets set for recruitment, randomisation and completion rates highlights that the inclusion of a PA behavioural modification intervention to standard PR delivered across NuTH is feasible to patients with COPD living across the North East of England.

7.4.8 Patient acceptability and adherence to the PA behavioural modification intervention

The implementation of this 8-week PR+PA intervention was well received by those patients who rated their satisfaction in line with several previous PA interventions in COPD and type-2 diabetes populations (Loeckx et al., 2018a; Verwey et al., 2016). Specifically, when patients were asked to document their opinions on the overall intervention, aspects such as “enjoyment”, “coaching” and the “experience” of receiving weekly increases in PA, were all positively acknowledged through the patient satisfaction form. Interestingly, when asked whether the intervention “coached” patients to increase PA, the majority indicated that it either “helped a lot” or “a little bit”. These findings suggest that the aim of including feedback on PA through a behavioural modification intervention added to PR was effective, in that, patients were aware of their activity levels through PA feedback and were able to motivate themselves to achieve greater PA levels through the step goal targets provided. In terms of how this compares to other published studies, unfortunately, patient’s satisfaction regarding PR+PA interventions has not been provided. However, as the project-tailored satisfaction questionnaire was based on a previous RCT, it was possible to compare findings with a PA tele coaching intervention for patients with COPD (Loeckx et al., 2018a). Similar patient satisfaction scores were reported between the current intervention and the tele-coaching programme by Loeckx et al. (2018a), with the enjoyment of taking part in the intervention and the coaching aspects both receiving high acceptability. Interestingly, when indicating whether the weekly goals were reasonable, patients in the current study reported much higher acceptability than that of Loeckx et al. (2018a). The step goal target provided by Loeckx et al. (2018a) involved increasing patient median weekly step counts by 500 through a ‘yes’ or ‘no’ option on the app, whereas in the current study a 10% increase in mean weekly step counts was administered during the weekly face-to-face consultations. It may be plausible that the lower usefulness score for daily

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feedback reported by Loeckx et al. (2018a) may have influenced the lower acceptability scores, however, it was difficult to fully interpret the true meaning of these figures and thus further research is needed to determine how they influenced other components of the programme. The overall ability to appreciate patients' acceptability perspectives regarding the current PR+PA intervention may be crucial in the design and implementation of future PA interventions and may provide a greater perspective on why previous studies have failed to consistently report effective improvements in PA.

In terms of adherence to the PA behavioural modification components used in the current study, the step count diary and pedometer, both key components of this intervention, achieved high average adherence (over 90%). This is an important finding as the foundations of an effective PA behavioural modification intervention are based upon patients being able to accurately record and report their PA habits (Mantoani et al., 2016). High adherence to both the step count diary and pedometer can be linked to the high acceptability scores demonstrated by patients, with 96% of patients deeming the useability of the pedometer as "easy". Furthermore, the usefulness of both the pedometer and step count diary were high, when reported through the project-tailored satisfaction questionnaire. This confirms that while patients were using the pedometer and step count diary a great deal, they were also able to appreciate its usefulness in regard to supporting their improvements in PA. Adherence to the step count diary in the current study was similar to that of a pilot study from de Blok et al. (2006), who demonstrated adherence of 95% across a 10-week programme alongside PR.

In addition, the adherence and achievability of the weekly step goal targets were reasonably high, with patients on average not meeting the 10% target on only 3 occasions across the 8-week PR programme. This finding offers further evidence that the planned 10% weekly step goal target used during this PR+PA intervention was both feasible and achievable in this group of COPD patients. As detailed earlier, the 10% target set in the current study was achieved

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more often by patients than the 5% target set by the Nolan et al. (2017) group, which may support the negative findings alongside UK based PR documented in that study. It is thus plausible to suggest that the greater achievement of step goal targets reported in the current study may have linked to the individualised approach of each face-to-face behavioural modification session, where patients influenced their own goals, providing a sense of ownership that may have stimulated greater self-motivation and self-efficacy.

Finally, the positive patient acceptability and adherence to this 8-week PR+PA intervention is supported by all 24 patients, indicating that they would take part in at least the PA behavioural modification intervention in the future. Specifically, 58% stated they would use the PA behavioural modification intervention alongside PR and the remaining 42% stated they would use aspects of the behavioural modification intervention (pedometer and step count diary) as a standalone intervention in the future. This was similar to the tele coaching intervention from Loeckx et al. (2018a), with almost half indicating they were “willing to continue” with the intervention. Unfortunately, Loeckx et al. (2018a) did not provide additional data regarding patients willingness to use specific components of the intervention moving forward.

With an overall lack of research regarding patient’s willingness to use PA interventions of this nature, further research is necessary in order to fully investigate patient facilitators and barriers towards PA behavioural modification interventions prior to the initiation of fully powered RCTs.

7.4.9 Strengths and limitations

The strengths of this study include novel data on the effectiveness of a PA behavioural modification intervention alongside a UK based PR programme to improve PA levels in patients with COPD who report low baseline levels of PA. Previous literature from Nolan et al. (2017) was the first and only RCT prior to this study to examine PA counselling alongside

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UK based PR, with negative findings reported. In addition, novel data on the inclusion of CBT as a psychological behavioural modification tool in this study was the first to demonstrate its effectiveness alongside both PA behavioural modification interventions and PR.

This study also strengthens the evidence base for assessing patients' experiences of PA through the C-PPAC instrument, with novel data highlighting significant and clinically important improvements in all domains of the C-PPAC tool following the PR+PA intervention. With this additional evidence, the C-PPAC instrument has now shown clinically important improvements in patients experiences of PA across PA counselling/behavioural modification interventions alone and alongside PR and an interval training exercise programme (Garcia-Aymerich et al., 2021). As a result, the C-PPAC instrument is becoming a useful tool, both for future rehabilitation trials of this nature and other clinical trials, for investigating patients' experiences of PA.

Regarding limitations, the inability to blind patients to the study allocation may have impacted on the overall quality of evidence and increased the risk of bias towards the intervention. Failure to blind patients was based on several reasons. Firstly, it would require a pedometer being issued to the PR alone group. Although the simple addition of a pedometer alongside generic advice on PA provided during PR doesn't necessary provide any form of behavioural modification, the stimulus and incentive to self-manage and increase steps/day with the availability of a pedometer may impact upon the steps/day of the PR alone group. Secondly, in order to remain comparable with previous literature, we followed the procedure of several previous studies that implemented PA counselling alongside standard care PR (Altenburg et al., 2015; de Blok et al., 2006; Holland et al., 2017; Nolan et al., 2017), of which pedometers were not provided to the control group. In future studies however, they may wish to follow the blinding procedure of two recent studies in COPD (Arbillaga-Etxarri et al., 2018; Varas et al., 2018). Varas et al. (2018) blinded patients by allocating a pedometer to both intervention and

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control groups but provided no pedometer specific instructions to the control group. Meanwhile, Arbillaga-Etxarri et al. (2018) took a different approach by refraining the existence of an alternative group to patients. The latter would be difficult to incorporate into the current study due to the lack of resources available to run two separate PR programmes simultaneously, in order to refrain the existence of groups from one another.

Due to all measures being administered in a face-to-face manner by a single researcher, bias related to the researcher providing the PA counselling intervention could be avoided and blinding of the assessor was not possible.

Within this chapter, the intention-to-treat principle was used to analyse the primary outcome while the per-protocol principle was used to analyse secondary outcomes. The intention-to-treat analysis is the recommended method in superiority trials to avoid any significant bias, which can often be found in per-protocol analyses (Tripepi, Chesnaye, Dekker, Zoccali, & Jager, 2020). Furthermore, the intention-to-treat principle can be seen as a better overall analysis of a treatment as it considers all individuals randomised to the protocol instead of only considering those who strictly adhered to the protocol (Tripepi et al., 2020).

Although an adequate sample size calculation was used in this chapter, it was a small-scale study, therefore, generalisability of the results to clinical practice may be limited. Finally, the present PA counselling intervention alongside PR were well received by the vast majority of patients, however such an intervention may require significant health care resources as they are more time consuming compared to PA tele-coaching interventions.

7.5 Conclusion

The findings of this study suggest that for COPD patients who report predominantly low baseline levels of PA, an intervention including a PA behavioural modification intervention, PR and CBT induces significant and clinically important improvements in several PA

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outcomes including, steps/day, movement intensity and patients' experiences of PA. These findings are supported by feasible recruitment, randomisation, and completion rates in response to the combined intervention, high patient acceptability and adherence to the components of the PA behavioural modification intervention, including the pedometer and step count diary to self-monitor and report daily step counts. Importantly, significant, and clinically important improvements in both steps/day, movement intensity and PA experiences were demonstrated in those patients with ≥ 8 HADS who received CBT alongside PR+PA. These findings are of significance due to the typically low baseline daily activity levels reported by these patients. Therefore, this may provide a solution to one of the major research findings of this thesis, that prior to these findings, patients with low baseline levels of PA reported inferior improvements in PA following PA counselling interventions. Importantly this study has shown that in COPD patients with low baseline exercise capacity and PA levels, improvements in exercise capacity induced during PR may be translated into improvements in PA levels only when a tailored behavioural modification intervention is added to PR alongside CBT for those with profound anxiety and/or depression.

Further development and delivery of this combined PA behavioural modification intervention alongside PR and CBT in future RCT's may support those patients with low baseline levels of PA to achieve greater improvements in PA alongside PR induced improvements in exercise capacity, with the main end goal of lowering the risks of increased hospital admissions, morbidity and mortality associated with physical inactivity in patients with COPD.

CHAPTER 8

Chapter 8: General Discussion

CHAPTER 8: GENERAL DISCUSSION

8.1 Overview

Overall, this thesis explored the current literature on PA counselling as a standalone intervention and alongside PR (**Chapter 3**), determined the criterion validity and test-retest reliability of a commercially available pedometer (**Chapter 5**), evaluated PA, muscle function and anxiety and depression in patients with COPD living in the North East of England in comparison to healthy individuals from the same region (**Chapter 6**), and investigated the feasibility, acceptability and efficacy of a novel intervention combining PA behavioural modification strategies, PR and CBT in patients with COPD living in the North East of England (**Chapter 7**).

8.2 Summary of Key Findings

The systematic review and meta-analysis in **Chapter 3** explored the current literature on PA counselling as a standalone intervention and alongside PR on its effectiveness towards improving PA in patients with COPD. Overall, significant and clinically important improvements in steps/day were documented across PA counselling interventions alone and alongside PR. However, important novel evidence was presented showing that compared to patients with greater baseline levels of PA (≥ 4000 steps/day), those patients with low baseline levels of PA (< 4000 steps/day), typically failed to achieve clinically important improvements in steps/day following a PA counselling intervention alongside PR. Therefore, a greater emphasis on those with low levels of PA were urgently needed in order to prevent the decline in PA and the associated risk of hospitalisation and mortality consequent to physical inactivity (Garcia-Aymerich et al., 2006; Garcia-Aymerich et al., 2009; Garcia-Rio et al., 2012; Vaes et al., 2014; Waschki et al., 2011).

Based on these findings, it was important to investigate the baseline PA habits of COPD patients living in the North East of England prior to their inclusion in a PA behavioural

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modification intervention added to PR in order to support the design and delivery of this combined intervention (**Chapter 7**). Based on this concept, **Chapter 6** confirmed that patients with COPD living in the North East of England experienced significantly lower levels of PA compared to healthy age-matched individuals living in the same region. A major concern arising from **Chapter 6** was the substantial deterioration in levels of PA reported in patients living in the North East of England compared to COPD patients living in other regions of the UK and Europe. With the combined findings of **Chapters 3 and 6**, it was apparent that COPD patients living in the North East of England would not benefit from a standard PA counselling intervention alongside a PR programme. Accordingly, the PA behavioural modification intervention implemented in **Chapter 7** incorporated motivational interviewing, face-to-face twice weekly goal setting, step count monitoring and feedback, alongside psychological support in those patients with anxiety and depression (≥ 8 HADS).

Chapter 7 assessed the feasibility, acceptability, and efficacy of combining PR, designed to improve exercise capacity, with a comprehensive PA behavioural modification intervention, designed to translate PR-induced improvements in exercise capacity into improved daily PA (and CBT in those with profound anxiety and depression) in patients with COPD exhibiting low baseline PA and exercise capacity. The delivery of this PA behavioural modification intervention demonstrated significant and clinically important improvements in PA levels (steps/day, movement intensity and time spent in light PA) and PA experiences using the C-PPAC instrument compared to PR alone. These findings were supported by evidence of adequate intervention completion rates, high patient acceptability and adherence to the components of the PA behavioural modification intervention, including the pedometer and step count diary to self-monitor and report daily step counts. One of the most interesting findings of **Chapter 7** was demonstrated in the subgroup analysis of COPD patients with $HADS \geq 8$ who received CBT alongside either PA behavioural modification interventions and PR or PR alone.

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In these anxious and/or depressed patients, who typically reported lower baseline PA levels compared to those without anxiety and/or depression, significant and clinically important improvements in both steps/day and patients' experiences of PA were reported following PR+PA+CBT compared to PR+CBT. Accordingly, it becomes apparent that in patients with profound anxiety and depression, PA behavioural modification strategies need to compliment CBT approaches in order to translate PR-induced improvements in exercise capacity into enhanced PA levels and PA experiences. CBT added to PR without the inclusion of a PA behavioural modification intervention does not convey PR-induced improvements in exercise capacity into enhanced levels of daily PA in anxious and or/depressed COPD patients.

Importantly, the findings of the present thesis suggest that in COPD patients with low baseline exercise capacity and PA levels, improvements in exercise capacity induced during PR may be translated into improvements in PA levels only when a tailored behavioural modification intervention is added to PR alongside CBT for those with profound anxiety and/or depression. These may present a solution to one of the major research findings of this thesis, demonstrated in the systematic review and meta-analysis in **Chapter 3**, that patients with low baseline levels of PA typically reported inferior improvements in PA following PA counselling interventions. Furthermore, the adequate completion rates, high patient acceptability and adherence to components of the PA behavioural modification intervention provide vital evidence that this combined intervention can be rolled out without difficulty across PR outpatient and community-based centres in the UK.

These findings also provide essential evidence to support the NHS long term plan, that proposes the need for new models of PR, including digital tools, so that patients have the support they need to best self-manage their condition and live as independently as possible. By supporting patients to use digital tools like pedometers to self-manage their condition, it

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goes a long way to reducing the demand on healthcare utilisation and the spiralling costs associated with the long-term management of respiratory conditions.

8.3 Future Directions and Recommendations

With the use of wearables and mobile applications that support tele-coaching becoming more popular, it is important to consider how the results of this thesis may impact the use of these applications and how technological advances may be beneficial in future research and clinical practice. Benefits of using telemedicine and/or tele-coaching include the possibility of decreasing the burden placed on clinicians and patients, the ability to standardise interventions and making such interventions available to patients who live in remote locations where access to healthcare is limited (Demeyer et al., 2017; Institute of Medicine Committee on Evaluating Clinical Applications of, 1996). Interestingly, the PA tele-coaching studies from Loeckx et al. (2018a) and Demeyer et al. (2017) have demonstrated several similar characteristics to the current face-to-face PA behavioural modification intervention, including similar patient acceptability (Loeckx et al., 2018a) and similar improvements in PA levels (Demeyer et al., 2017). Therefore, based on these similarities it is plausible to suggest that the PA behavioural modification strategies implemented in this thesis (motivational interviewing, goal setting, feedback, encouragement, and advice to overcome barriers) could be developed and delivered as a telemedicine or comprehensive tele-coaching intervention. With this in mind the following recommendation can be explored in future research projects. Firstly, the key component of this PA behavioural modification intervention was the face-to-face consultation between patient and researcher that aimed to empower and motivate patients to engage in more daily PA, supporting a continuous improvement in PA. With the development of a tele-coaching alternative, this face-to-face consultation needs to be replaced by other virtual means of consultation via telephone or video consultation (e.g., NHS attend anywhere). Secondly, PA

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tele-coaching supported by virtual consultation may be employed to accelerate recovery of functional capacity following hospital discharge for an acute exacerbation of COPD and thus facilitate enrolment in PR within the critical 90-day post hospital discharge period (Spruit et al., 2013). Furthermore, an effective approach may involve a comprehensive programme, with face-to-face PA behavioural modification strategies used alongside PR as demonstrated in this thesis followed by PA tele-coaching as a maintenance intervention on completion of PR (Demeyer et al., 2017; Loeckx et al., 2018a; Vasilopoulou et al., 2017). This approach provides an opportunity for future studies to investigate whether sufficient follow-up interventions are required to facilitate the maintenance of enhanced PA levels following completion of a PR programme.

Given the positive responses of this combined PA behavioural modification intervention alongside PR and CBT, future studies need to incorporate and deliver this combined intervention throughout standard PR programmes to support patients with COPD who report low baseline PA levels in order to mitigate the increased risk of hospitalisation and mortality associated with physical inactivity. Furthermore, with the clear benefits of CBT as a psychological behavioural modification tool, future research should expand the delivery of CBT alongside both PR and PA behavioural modification interventions particularly in cases where patients have elevated levels of anxiety and depression. As with PA tele-coaching, CBT can be delivered via virtual consultations to address the impact of depression and anxiety on physical inactivity.

Finally, it is important to consider the best available tools for measuring PA in a COPD population. Triaxial accelerometers continue to be recommended as the most accurate and reliable tools and offer more detailed PA data (movement intensity and time spent in domains of PA) than pedometers or step counters. However, purchase costs vary considerably between devices which may impact the ability of research projects with a large sample size to use

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accelerometers moving forward. Furthermore, accelerometers do not provide patients with real-time feedback of PA levels, making them unfeasible for self-monitoring patients' PA. Alternatively, simple low-cost pedometers, step counting devices smartphones and watches are becoming more popular and affordable. As a result, future research should look to investigate the accuracy, reliability and usability of low-cost pedometers, smartphones and watches that provide a step counting application. By providing more clarity on these devices, new avenues for accurately measuring PA may arise and provide a greater outreach for measuring PA in COPD.

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Appendices

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Chapter 3: Systematic Review and Meta-Analysis

Appendix 3a) Characteristics of included studies

Chapter 4: General Methods

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Appendix 4c) Completed IRAS document

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Appendix 4f) Capacity and Capability Approval

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Appendix 4h) GP Letter

Appendix 4i) Chapter 7 Participant Information Sheet

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Appendix 4m) Chapter 5 & 6 Informed Consent Form

Appendix 4n) Patient project tailored questionnaire

Appendix 4o) C-PPAC Instrument

Appendix 4p) Modified Borg Scale

Appendix 4q) Hospital Anxiety and Depression Scale

Appendix 4r) COPD Assessment Test

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Appendix 4t) Medical Research Council Breathlessness Scale

Chapter 7: Randomised Controlled Trial

Appendix 7a) Randomisation Template

Appendix 7b) Step diary

Appendix 3A: Characteristics of included studies (Systematic review & Meta-Analysis)

Author	Y	N (I/C)	Age, years; mean (SD)	FEV ₁ % predicted L; mean	Gender (male/ female)	Patient recruitment	Intervention arm	Control arm	Type of feedback	Weekly goals (Y or N)	Time points/outcomes
^(A) (Altenburg, Wempe, Greef, Hacken, & Kerstjens, 2014)	2014	24/24	65 (58-72)	78 (66-95)	32/16	General practices (primary care)	PA counselling 30 min x5sessions using MI, GS, and pedometer- 12 weeks.	Received care appropriate to their health status.	Face-to-face	<i>N</i>	3 months: daily steps.
^(B) (Altenburg et al., 2014)	2014	23/23	68 (61-72)	58 (40-69)	34/12	Outpatient hospital clinics (secondary care)	PA counselling 30 min x5sessions using MI, GS, and pedometer- 12 weeks. Patients were recruited from outpatient hospital clinics (secondary care).	Received care appropriate to their health status.	Face-to-face	<i>N</i>	3 months: daily steps.
^(C) (Altenburg et al., 2014)	2014	22/15	54 (9.6)	43 (25.9)	32/25	Pulmonary rehabilitation centre	PA Counselling (30 min x5 sessions using MI, GS and pedometer- 12 weeks added to PR (2h x3 times/week- 9 weeks).	PR (2h x3 times/week- 9 weeks)	Face-to-face	<i>N</i>	3 months, daily steps
(Arbillaga-Etxarri et al., 2018)	2018	220/293	69±9	58±17	448/65	Primary care and five hospital care centres	Six components: MI, UT walking, pedometer and personalised calendar, Phone updates, exercise leaflet, group walking sessions.	General health counselling and info booklet	Remote	<i>N</i>	12 months, daily steps

(Bender et al., 2016)	2016	57/58	65±7	54.3±11	48/67	Pulmonary outpatient clinics	Pedometer and personally selected goals involving enjoyed activities of daily living. A target of increasing 15% daily steps per month for 3 months.	Pedometer with no goal setting or communication about physical activity. A small 1-1 telephone call to communicate daily steps.	Remote	<i>N</i>	3 months, daily steps.
(Cruz et al., 2016)	2016	16/16	66.5 (8.4)	66.9 (20.1)	27/5	3 primary care centres and a district hospital	PA- focused behavioural counselling (average 25 minx8 sessions using SCT: SE, MI and pedometer and diary feedback- 6M) added to PR (1h x3 times/week ET and 1.5h x1 times/week EDU sessions- 3 months)	PR (1h x3 times/week ET and 1.5h x 1 time/week EDU sessions- 3 months)	Face-to-face	<i>Y</i>	3 months: daily steps
(Blok et al., 2005)	2005	10/11	64±11	46±18	9/12	Hospital outpatients	Lifestyle PA counselling (30 min x4 sessions using MI, GS and pedometer- 9 weeks) added to PR (9 weeks)	PR (9 weeks)	Face-to-face	<i>N</i>	9 weeks: daily steps
(Demeyer et al., 2017)	2017	172/171	67±8	56±20	219/124	6 rehabilitation centres across Europe	Received the usual care plus the tele coaching platform. This includes a one-to-one interview, a step counter and smartphone	Received a standard leaflet explaining the importance of PA in COPD as well as information	Remote	<i>Y</i>	3 months: daily steps

(Holland et al., 2017)	2017	80/86	69±11	50±19	99/67	Pulmonary rehabilitation waiting list	coaching application. Home rehabilitation, which involved a pedometer and 7 weekly structured telephone calls based around motivational interviewing to improve walking fitness.	about PA recommendations. Centre-based rehabilitation with encouragement to exercise at home, no pedometer issued.	Remote	<i>N</i>	12 months, daily steps
(Hornikx et al., 2015)	2015	15/15	67±7	43±17	17/13	Hospitalised exacerbation patients	Pedometer worn with telephone calls 3 times per week for 1 month to motivate and stimulate patients to increase their PA levels.	No contact nor received any motivational messages. Just advice about increasing PA before hospital discharge.	Remote	<i>Y</i>	1-month, daily steps.
(Hospes et al., 2009)	2009	18/17	62±8	64±15	21/14	Outpatient clinic	12-week customised exercise counselling to enhance daily physical activity. Based on principles of goal setting and implementation of goals.	No counselling programmes.	Face-to-face	<i>N</i>	3 months, daily steps.
(Kawagoshi et al., 2015)	2015	12/15	75±9	59.3±22	24/3	N/A	Home-based rehabilitation in addition to monitored daily physical activity	Multidisciplinary home-based PR programme for 12 months.	Face-to-face	<i>N</i>	12 months, daily steps.

							using pedometer and received monthly feedback on physical activity levels.				
(Kohlbrener et al., 2020)	2020	37/37	65±9	35.7±9	50/24	Outpatients	Pedometer used as a motivational and feedback tool and PA diary to record step counts	Regular visits at their respiratory physician.	Remote	<i>N</i>	3-12 months, daily steps.
(Mendoza et al., 2015)	2015	52/50	68±8	66±19	62/40	Outpatient clinics at private and public hospitals	Received pedometer and physical activity diary alongside counselling to improve physical activity.	Received counselling at each visit to increase their physical activity levels and advised to walk for at least 30 min per day.	Face-to-face	<i>N</i>	3 months, daily steps.
(Moy et al., 2015)	2015	154/84	66±9	/	223/15	National database of veterans	Pedometer and access to a website with components including step count feedback, weekly goals, motivational content to enhance activity levels.	Wore pedometer and recorded steps. Received no instruction about exercise and were not assigned step goals or website.	Remote	<i>Y</i>	4 months, daily steps.
(Nolan et al., 2017)	2017	76/76	69.0 (9.0)	50.5 (21.2)	110/42	Hospital based PR unit	Lifestyle PA counselling (30mins x8sessions using GS and pedometer- 8 weeks) added to PR (1h x2 times/week 8 weeks)	PR (1h x2 times/week 8 weeks)	Face-to-face	<i>Y</i>	9 weeks: daily steps

(Tabak et al., 2014)	2014	14/16	66±7	52±13	19/11	Hospital clinic	Tele-rehabilitation intervention for 4 weeks	Received no tele-rehabilitation. Usual care was defined as usual medication/physiotherapy	Remote	Y	1-month daily steps
(Varas et al., 2018)	2018	21/19	67±8	49±16	31/9	Pulmonology consultants	5 group physiotherapy sessions, 8 weeks counselling to increase DAL, through telephone meetings	Informative sessions on the benefits of exercise, pedometer issued but no additional support	Remote	Y	8 weeks daily steps
(Vorrink et al., 2016)	2016	84/73	62±9	55±17	78/79	Outpatient physiotherapy practises	Consisted of two compartments 1) smartphone application 2) physiotherapist-based website for providing real-time goals and feedback for 6 months.	No intervention	Remote	Y	3 months, daily steps
(Wan et al., 2017)	2017	57/52	68±8	61±21	95/14	General pulmonary clinics	Pedometer and received access to a website which provided four key components: individualised goal setting, iterative step-count feedback, motivational content and online community forum for 3 months.	Received a pedometer and written material about exercise but weren't assigned step-count goals.	Remote	Y	3months, daily steps.

(Wootton et al., 2019)	2019	42/44	70±7	43±16	53/33	PR program referrals	Pedometer and received telephone calls with feedback of pedometer step counts.	No pedometer or feedback received	Remote	<i>N</i>	12 months/daily steps
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Data are presented as n, means or mean (range). Abbreviations: FEV₁: Forced Expiratory Volume in 1 second; PA: Physical Activity; N/A: Not Applicable; PR: Pulmonary Rehabilitation; MI: Motivational interviewing; GS: Goal Setting; SCT: Social cognitive theory; SE: Self Efficacy; ET: Exercise training; EDU: Education.

Appendix 4a: Northumbria University ethics study protocol (Chapters 5 & 6)

Normative daily physical activity levels in elderly healthy individuals living in the North east of England.

Outline General Aims and Research Objectives

State your research aims/questions (maximum 300 words). This should provide the theoretical context within which the work is placed, and should include an evidence-based background, justification for the research, clearly stated hypotheses (if appropriate) and creative enquiry.

It is recommended that people of all ages complete a minimum of 30 minutes moderate intensity daily physical activity to maintain and develop physical fitness (1). Those not meeting this standard of activity are considered insufficiently active, which may lead to increased levels of disability and deconditioning, which are strong predictors of mortality (2). Therefore, quantifying levels of daily physical activity in sedentary individuals is of great importance (3).

Patients suffering from chronic obstructive pulmonary disease (COPD), report 40-60% lower daily number of steps compared to healthy age-matched individuals (4). Decreased physical activity is due to high levels of dyspnea related to everyday tasks. Therefore, it has been suggested that patients suffering from COPD are in a downward spiral of symptom-induced inactivity, leading to deconditioning and muscle weakness (3). These factors are associated with increased risk for hospital admissions and mortality (5). Previous literature has objectively compared physical activity levels between patients with COPD and age-matched healthy control individuals in both Europe and the UK, however this has not been conducted on a regional basis, within the North East of England (3). Statistics from public health England report that the North East of England has the highest proportion of people with smoking + drinking habits which are associated with a high sedentary lifestyle. Specifically, the region as a whole has the lowest percentage of physically active adults in UK, increasing the need to observe physical activity levels in this population (2). As well as this, the prevalence of COPD and amount of respiratory deaths in people aged over 65 is the highest of all UK regions. This suggests that people with respiratory diseases including COPD will be more deconditioned, increasing the risk of exacerbations leading to hospitalisation and increased mortality.

In order to characterise the degree of physical inactivity in COPD and evaluate the ability of physical activity promotion to normalise daily physical activity levels in COPD patients, we need to evaluate the levels of physical activity in healthy aged-matched individuals from the North East of England region. To do this, we require normative data of daily physical activity from 7 days of triaxial accelerometry monitoring, previously validated in COPD patients (6).

Accordingly, we aim to study elderly (aged 50-75 years) healthy individuals on the basis of comparing steps/day and movement intensity (m/sec^2) to COPD patients who are attending a physical activity promotion programme at the Royal Victoria Infirmary (RVI). This physical activity promotion study is

the main topic of my research of which REC NHS approval (18/YH/0376) and Newcastle upon Tyne healthcare trust R&D sponsorship (08968) has been granted.

Throughout the physical activity promotion study, a pedometer will be used to provide feedback and form goals for improving activity levels. The use of pedometers as opposed to accelerometers to promote physical activity is becoming more and more popular due to its visual display of daily steps and usability. A widely used pedometer is the Fitbug air that is going to be used in my clinical physical activity promotion study. This pedometer has previously been used alongside tele-coaching to improve physical activity, however it has yet to be validated for use (7). Due to this, it is necessary to evaluate the accuracy and reproducibility of the specific pedometer that we plan to use. The accuracy and reproducibility of such pedometer will be investigated in healthy elderly individuals during a standard walking protocol in the University laboratories.

Accordingly, the first aim of the study is to establish normative data for physical activity in healthy elderly people in North East of England in order to evaluate the degree of physical inactivity in age matched COPD patients prior to embarking into a physical activity promotion programme at the RVI.

While the second aim is to examine the accuracy of specific pedometer to report steps/day as well as the reproducibility of step count readings of this pedometer during a standardised walking protocol.

G2: Research activities.

Please give a detailed description of your research activities

Please provide a description of the study design, methodology (e.g. quantitative, qualitative, practice based), the sampling strategy, methods of data collection (e.g. survey, interview, experiment, observation, participatory), and analysis. Do sensitive topics such as trauma, bereavement, drug use, child abuse, pornography, extremism or radicalisation inform the research? If so have these been fully addressed?

Study design:

This will be a cross-sectional study to establish the average daily steps and movement intensity of elderly healthy participants to compare with patients who suffer from COPD undergoing a physical activity promotion intervention in the North East of England. The accuracy of a pedometer relative to visual monitoring and reproducibility of the pedometer in reporting consistent step counts during execution of a standardised task will be studied. Experiments will be performed over three visits to the Northumbria University exercise laboratory.

During visit 1, participants will confirm eligibility with the inclusion/exclusion criteria and sign an informed consent form. They will then be required to provide demographic data and complete a spirometry assessment to assess lung function prior to beginning the study. On completion of this, an Actigraph accelerometer will be fitted with the participant required to wear over 7 consecutive days during every day activities to assess mean daily steps and movement intensity.

During visit 2, patients will return the accelerometer to the University. An analysis of the accelerometer data will be performed. An establishment for each individual person of a range of walking speeds on the treadmill which reproduce the median, lower and upper movement intensities outdoors will be conducted using an incremental walking protocol on the treadmill.

During visit 3, participants will be asked to walk at three walking speeds (km/h) corresponding with the median, lower and upper movement intensities which were obtained during their treadmill testing in visit 2. Each of the three speeds will be conducted for 3 minutes. While conducting the walking protocol, participants will wear the pedometer (Fitbug) throughout. Visual interpretation of steps while walking will be assessed using a video camera attached to a tripod beside the treadmill. Comparison of step/counts between the pedometer and the video recording will examine the accuracy of the pedometer to report step counts. After completing all three pre-defined walking speeds, participants will be asked to take a 30 minute break before repeating the same walking protocol. Test-retest variability in daily steps recorded by the step counter will serve the purpose of establishing the reproducibility of the pedometer to a given physical activity task.

Methodology:

Assessment 1- Daily steps/day and movement intensity during daily life activities.

Participant demographic data will be collected during this first testing session. Demographic data will include age, height, mass and gender and measure of walking stride length will be taken.

Participants will then be required to perform a spirometry measurement to assess lung function, which will be conducted using a metabolic cart. An Actigraph accelerometer will be initiated based on specific required information. An overview of how to wear and the usability of the accelerometer will be conducted. Each participant will be asked to attach the accelerometer around their waist with the device attached to their dominant side and wear it for 7 consecutive days between the hours of 08:00 and 22:00 (wakefulness). For valid assessment of daily physical activity, each participant will require at least 3 acceptable days with over 8 hours of activity, excluding days with less than 8 hours of wear time.

Assessment 2- Establish walking protocol on the treadmill.

Participants will return to the University after wearing the accelerometer for 7 consecutive days. The aim of this second visit is to establish for each participant, a range of walking speeds on a treadmill which will reproduce the movement intensity registered during daily living via accelerometer monitoring. This will provide a correspondence between movement intensity recorded outdoors (m/sec^3) and the speed of the treadmill (km/h) and produce a regression analysis for each

participant (Figure 1), so as to reproduce in the laboratory the representative movement intensity experienced by each participant in daily life. The walking protocol will involve an incremental design, with participants required to walk at speeds beginning at 1km/h and increasing by 1km/h every minute up to 6km/h, meaning a total of 6 minutes worth of walking as previously published (8). While walking, the accelerometer will be attached to the participant to record the movement intensity of each speed throughout the increments.

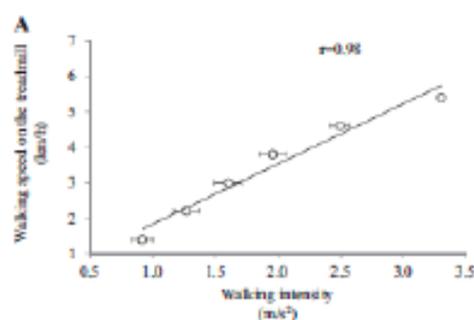


Figure 1: Relationship between mean walking intensity at each treadmill walking speed in patients from Louvaris et al. 2013 (8).

Assessment 3- Establish accuracy and measurement reproducibility of pedometer.

Participants will return to the exercise laboratory on a day which is suitable to them. During this visit participants will undergo an individualised walking protocol on the treadmill. They will be required to walk at three walking speeds (km/h). The walking speeds will correspond to movement intensities reported from the accelerometer data and matched to the correct walking speeds using the regression analysis from visit 2. To cover a range of walking speeds, the median movement intensity value will be used alongside a lower and upper quartile of median. Participants will be asked to wear the pedometer throughout and will have their walking gait videoed using a camera and tripod mounted to the side of the treadmill.

A warm-up of 1 minute at a speed corresponding to 1.5 km/h will occur before the walking protocol begins. Each of the pre-defined speeds will have a duration of 3 minutes with a 1 minute rest period between each speed.

Once the three walking speeds have been completed a 30 minute break will occur followed by the same walking protocol, to evaluate the reproducibility of the pedometer to report daily steps.

Method of data collection:

Information on demographics to inform analysis collected through self-reports will include:

Demographic characteristics collected will include: Stature, body mass, BMI, Spirometry (FEV₁/FVC & FEV₁ % Pred) and daily physical activity

Assessment of daily physical activity:

Assessment of Daily Physical Activity will be performed for one week (7 days) between visits 1 and 2, using a triaxial accelerometer (Actigraph GT3X; Actigraph LLC, Pensacola, FL, USA). Participants will be asked to wear the activity monitor during wakefulness for 7 consecutive days. Daily step count will be performed over 7 days, with at least 3 acceptable days' data, excluding days with less than 8 hours of wear time (Table 1).

Assessment of accuracy and test re-test reliability of pedometer:

To assess the accuracy of the pedometer, step counts on a treadmill will be compared using the pedometer and visual interpretation (video camera). The test re-test reliability of the pedometer will be measured over two tests on the same day. A measurement of steps will be taken from the pedometer for both tests and an interclass correlation of step counts between tests will be calculated.

Assessment of pulmonary function:

Pulmonary function assessment will be performed during the first assessment visit. The assessment will include comprehensive spirometry evaluation for the determination of Forced Expiratory Volume at the 1st second (FEV₁) and Forced Vital Capacity (FVC).

Statistical Analysis:

Analyses will be conducted in SPSS v22. Descriptive statistics such as percentages, mean + standard deviations will be used to present participant demographic characteristics. An independent t-test will also be used to assess the difference in daily physical activity (assessed by the Actigraph) between elderly aged-matched individuals in the North east of England and COPD patients at the RVI.

The accuracy of the pedometer will be analysed using a two-way anova with repeated measures, comparing the number of steps reported by the pedometer with the visual count from a video camera across different walking speeds. Bland and Altman plots will be constructed to visually inspect the data and to assess agreement with the criterion measures. The percent relative error of the Fitbug air pedometer step counts will be calculated in order to facilitate comparison with previous pedometers/activity monitors studied. This will be calculated using the following equation:

$$\text{Percent relative error} = \frac{|\text{Fitbug output} - \text{observer count}|}{\text{observer count}} \times 100$$

The test-retest reliability of the pedometer will be analysed using the intraclass correlation coefficient (ICC). Specifically, we will use the ICC (2,1), random effects model and standard error of measurement (SEM), respectively.

M1: People and/or Personal Data.

Sample Groups

Provide details of the sample groups that will be involved in the study and include details of their location (whether recruited in the UK or from abroad) and any organisational affiliation. For most research studies, this will cover: the number of sample groups; the size of each sample group; the criteria that will be used to select the sample group(s) (e.g. gender, age, sexuality, health conditions). If the sample will include NHS staff or patients please state this clearly.

All participants will be recruited from the North East of England and will be general members of the public.

Key inclusion criteria:

- Sedentary males and females aged 50-75 years old.
- Normal spirometry results (FEV₁/FVC >0.70 & FEV₁ >80% predicted).
- Stable condition with no comorbidities which would affect levels of daily physical activity.
- Able to provide informed consent.

Key exclusion criteria:

- Orthopaedic, neurological or other concomitant diseases that significantly impair normal biomechanical movement patterns, as judged by the investigator.
- Spirometry suggesting symptoms of COPD or other lung conditions.
- Unstable ischaemic heart disease, including myocardial infarction within 6 weeks.
- Moderate or severe aortic stenosis or hypertrophic obstructive cardiomyopathy.
- Uncontrolled hypertension.
- Another condition likely to limit life expectancy to less than one year (principally metastatic malignancy).

Sample size:

This sample size calculation aims to establish sufficient number of healthy age-matched individuals who provide normative data for daily physical activity (steps/day) to be utilised as reference when comparing this data to patients with COPD. Sample size has been calculated from a recent study that took place in Leicester (9), comparing steps/day recorded in COPD patients (n=19) with healthy age-matched volunteers (n=10). Using the mean difference in steps/day (1995) between COPD patients and healthy volunteers and a standard deviation (2088), with an alpha significance level of 0.05 (2-sided) of 80% power, a minimum total sample size of 16 participants will be sufficient to detail

significant differences in daily physical activity levels (steps/day) between healthy and COPD participants.

Nature of data pertaining to Living Individuals

If you will be including personal data of living individuals, including still or moving images, please specify the nature of this data, and (if appropriate) include details of the relevant individuals who have provided permission to utilise this data, upload evidence of these permissions in the supporting documentation section.

Details of any Special Category Data - If you will be collecting data revealing racial or ethnic origin, political opinions, religious or philosophical beliefs, trade union membership, data concerning health or data concerning a natural person's sex life or sexual orientation, please specify which categories you will be using.

Personal data of participants will include basic demographic characteristics data namely: date of birth, height, weight. The only information considering current health status will be current physical activity levels and any history of lung conditions.

Recruitment

Describe the step by step process of how you will contact and recruit your research sample and name any organisations or groups that will be approached. Your recruitment strategy must be appropriate to the research study and the sensitivity of the subject area. You must have received written permission from any organisations or groups before you begin recruiting participants. Copies of draft requests for organisational consent must be included in the 'Supporting Documentary Evidence'. You must also provide copies of any recruitment emails/posters that will be used in your study.

Adult participants will be recruited through one of five methods of recruitment:

1. Recruitment posters advertising the research study will be placed around Northumbria University, both at City and Coach Lane campus, to stimulate interest.
2. Through the use of social media tools and social networking sites, where details of the study will be uploaded.
3. An email containing the study information/ recruitment post will be sent to university staff members.
4. Word of mouth.
5. Staff from University of Northumbria.

Researcher and Participant Safety Issues

If there are any risks the research could cause any discomfort or distress to participants (physical, psychological or emotional) describe the measures that will be put in place to alleviate or minimise them. Please give details of the support that will be available for any participants who become distressed during their involvement with the research.

The only risks associated with the research for participants will be during the walking protocol on the treadmill. Even at low walking speeds participants may become slightly fatigued which may cause low levels of muscle soreness. Throughout the walking protocol participants will be asked to wear a pulse oximeter in order for the researcher to observe heart rate and oxygen saturation levels.

Data Gathering Materials Used

Provide a detailed description of what the participants will be asked to do for the research study, including details about the process of data collection (e.g. completing how many interviews / assessments, when, for how long, with whom). Add any relevant documentation to the 'Supporting Documentary Evidence' section of this form.

Participants will be asked to complete three assessment visits at the University, with each session lasting no longer than 90 minutes. The data gathered during these assessment visits will be from the following pieces of equipment:

- Accelerometer: Daily steps (steps/day) and movement intensity (m/sec^2).
- Pedometer: Step counts.
- Video Camera: Video coverage of walking to allow analysis of step counts made during walking protocols
- K4 breath by breath analyser: Spirometry assessment before familiarisation

Potential Ethical Issues

Please describe any potential ethical issues the project may have which are not covered above, and how you have sought to minimise these.

There aren't any additional potential ethical issues.

G3: Research Data Management Plan

Anonymising Data (mandatory)

Describe the arrangements for anonymising data and if not appropriate explain why this is and how it is covered in the informed consent obtained.

All data collected will conform to university guidelines, the EU General Data Protection Regulations (GDPR) and Data Protection Act (2018). Paper records such as consent forms, completed questionnaires and clinical measurements will be stored in numerical order and kept secure in a locked cabinet in Northumbria University. To ensure quality data, all outcome data such as completed questionnaires will be checked manually by an investigator for completeness, clarity of answers and consistency before being entered electronically into Microsoft Excel. Data entry will involve labelling numeric codes so data can be filtered and easier to understand.

Storage Details (mandatory)

Describe the arrangements for the secure transport and storage of data collected and used during the study.

You should explain what kind of storage you intend to use, e.g. cloud-based, portable hard drive, USB stick, and the protocols in place to keep the data secure.

If you have identified the requirement to collect 'Special category data', please specify any additional security arrangements you will use to keep this data secure.

Electronic data will be stored on a password-protected computer will be treated in accordance with the Data Protection Act (2018). Personal data necessary for scientific research will be treated in accordance with safeguards, transparency and fairness. Only the researcher will have access to any identifiable information which will be kept separate from any data that can identify the participant. A complete back up of the electronic database will be performed once a month, via a password protected hard drive, this storage device will be stored off-site. Incremental data back-ups will be performed on a daily basis. Passwords will be changed on a regular basis.

Table 1: Assessment of variables prior to and following the rehabilitation programme.

	STUDY PERIOD			
	Visits- Northumbria University			
TIMEPOINT	Enrolment/ Screening	Visit One	Visit Two (8 days apart, +/- 1 day)	Visit Three
Participant information sheet	X			
Informed consent	X			
Participant ID number	X			
Demographical and Clinical information: Age, Gender	X			
DATA COLLECTION				
Demographics		X		
Stature and body mass		X		
Spirometry		X		
Triaxial accelerometer issued		X		
Incremental walking protocol			X	
Triaxial accelerometer returned			X	
Three speed walking protocol				X

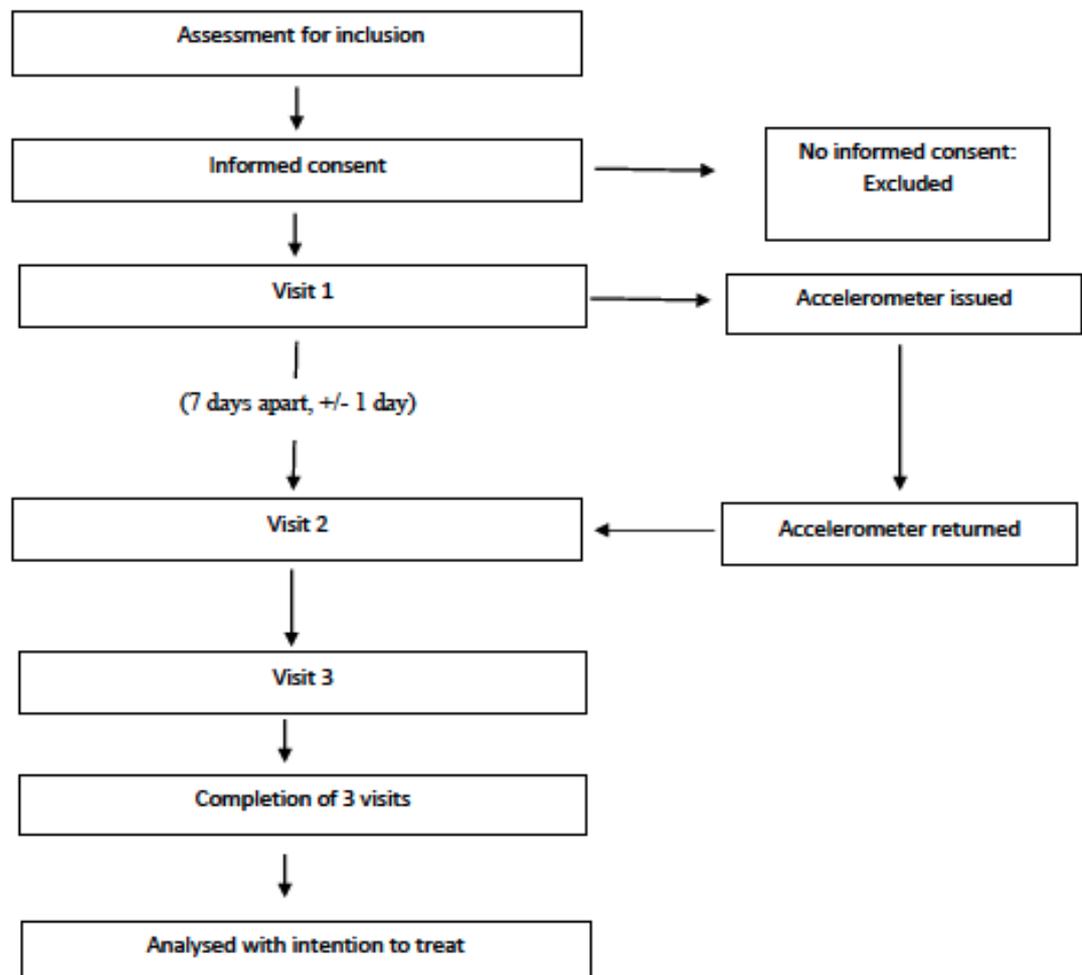


Figure 1: Consort diagram.

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Appendix 4b: NHS ethics study protocol (Chapter 7)



Study Title: A feasibility study assessing the inclusion of Physical Activity Promotion to standard care pulmonary rehabilitation and cognitive behavioural therapy in patients with COPD.

Summary:

In patients with COPD, daily physical activity is reduced compared with that in healthy age-matched individuals. Furthermore, it is well documented that reduced levels of physical activity in patients with COPD are associated with a faster rate of disease progression, greater risk for exacerbation of COPD (ECOPD), leading to increased rates of hospital admissions and mortality. Global guidelines endorse pulmonary rehabilitation as an integral non-pharmacological component in COPD management. However, while supervised pulmonary rehabilitation programs improve exercise capacity and health related quality of life in people with COPD, these findings have not consistently progressed into improvements in daily physical activity.

Physical activity is a complex health behaviour that is modified by behavioural change interventions such as identification of barriers, goal setting, self-efficacy, motivation, self-monitoring and feedback. Physical activity promotion through interventions, which combine the use of wearable monitors (i.e. pedometers, accelerometers) with goal setting, can increase daily physical activity in COPD patients. A recent systematic review and meta-analysis addressed the addition of physical activity promotion strategies to standard pulmonary rehabilitation, failing to demonstrate consistent improvements in daily physical activity along with improvements in exercise capacity and quality of life. This is principally due to diverse interventions that have lacked an emphasis on individualised goal setting and patient feedback, with only a small number of contact sessions to discuss strategies for consistently improving activity levels and affecting motivation towards behaviour change.

Alongside physical activity promotion, the incorporation of cognitive behavioural modification (CBM) strategies is also important in terms of reversing physical inactivity in COPD. CBM addresses several behavioural barriers including anxiety, depression and physical inactivity, an important component in the management of COPD to improve engagement with pulmonary rehabilitation and physical activity promotion strategies.

Accordingly, we propose to perform a feasibility study assessing patient adherence to a pulmonary rehabilitation programme that concomitantly promotes daily physical activity and behavioural changes. We will compare patients' adherence to pulmonary rehabilitation including physical activity promotion and behavioural changes with pulmonary rehabilitation alone. Our major outcome will be adherence to the combined intervention over 16 sessions of PR.

Literature background:

COPD is a debilitating and progressive disease, primarily affecting the respiratory system. In many patients, it also has adverse extra-pulmonary effects, such as skeletal muscle dysfunction and weakness [1]. Pulmonary and skeletal muscle metabolic abnormalities enhance the ventilatory requirement during exercise, resulting in exercise-associated symptoms such as breathlessness and leg discomfort. These symptoms make every day physical activity an unpleasant experience, which many patients try to avoid [2]. Physical activity levels are therefore remarkably lower in COPD patients than healthy age-matched individuals, presenting a major predictor of mortality and hospitalisation in these patients [3]& [4]. Implementation of exercise training as part of Pulmonary Rehabilitation aims to reserve the systemic consequences of COPD, in particular skeletal muscle dysfunction and weakness [2]. Currently pulmonary

rehabilitation programs have shown substantial improvements in exercise tolerance; however, these findings have not consistently progressed into improvements in daily physical activity [5]. One reason for this may link to physical activity in COPD being a complex health behaviour [2].

Physical activity promotion is an intervention employed to influence physical inactivity in patients with COPD [5]. The main aim of the intervention is to stimulate patients to increase their daily physical activity levels by incorporating lifestyle activities into daily life. Patients receive counselling in order to modify their behaviour towards enhanced physical activity through the application of a pedometer, which allows patient monitoring and feedback of their daily steps along with frequently adjusted goal setting. Previous research has shown that remote coaching of physical activity (tele coaching) improves daily steps over a three-month period [6]. Studies incorporating physical activity promotion during pulmonary rehabilitation have, however, failed to find consistent improvements in daily physical activity along with improvements in exercise capacity and quality of life [7]. This is principally due to diverse interventions that have lacked an emphasis on individualised goal setting and patient feedback, with only a small number of contact sessions to discuss strategies for consistently improving activity levels and affecting motivation towards behaviour change. No study to date has comprehensively incorporated both a behavioural change intervention (physical activity promotion along with some form of behavioural modification therapy) and pulmonary rehabilitation to facilitate progression of improved physical functioning to enhanced daily physical activity levels. Primarily adherence to the behavioural physical promotion intervention alongside pulmonary rehabilitation has been inconsistent [8]. Consequently, more evidence is required to understand the true benefits of the intervention. The current study aims to provide regular feedback of daily steps (twice weekly), with a pre-intervention interview enabling the research team to understand patient concerns and preferences around daily physical activity. This will provide the healthcare team with information, which can be incorporated into individualised goals, allowing patients to receive physical activity support tailored to their own specific needs, capabilities and daytime habits.

Alongside the physical barriers influencing daily physical activity, the distressing nature of COPD has a significant impact on patients' psychological wellbeing. Major focusing points for COPD patients are the sense of feeling unwell, the inability to perform everyday activities and the emotional consequences of the condition (British Lung Foundation, 2006). These symptoms can promote anxiety and depression, which are prevalent in patients with COPD and are associated with poorer treatment outcomes and reduced survival [9]. Cognitive Behavioural modification (CBM) strategies is a psychological intervention that focuses on understanding how experiences are interpreted. It provides an interaction between thoughts, mood, behaviour and physical sensations, which are intrinsically linked. [10] conducted a small case study involving 10 COPD patients. They used CBM strategies in COPD patients who were anxious or depressed, assessed using the hospital anxiety and depression scale. Techniques used for anxiety included; education on anxiety and COPD, distraction techniques, breathing control and relaxation. These techniques help to break the vicious cycle of anxiety and can reduce patients' distress. Similar techniques for patients suffering mainly from depression include; education about depression and inactivity and planning and recording activities each day, while rating these for achievement or pleasure. These techniques help to break patient inactivity, which can lead to low mood and poor physical condition. A key treatment for depression can involve encouragement to increase activities within the patients' physical capabilities. The study found clinical and statistically significant improvements in anxiety and depression scores and a statistically significant reduction in hospital admissions following CBM strategies [10]. CBM is therefore an important approach to incorporate into COPD management to improve engagement with pulmonary rehabilitation and the effectiveness of a physical activity promotion strategy. [10].

The addition of CBM strategies to structured pulmonary rehabilitation is currently under investigation (TANDEM COPD trial). The feasibility of assessing patient adherence to a pulmonary rehabilitation programme that concomitantly promotes daily physical activity and behavioural changes is still unknown. Accordingly, it is proposed that it is necessary to incorporate standard pulmonary rehabilitation and physical activity promotion along with behavioural modification strategies to induce both functional and behavioural changes including anxiety, depression and physical inactivity in those patients suffering from anxiety and depression. Furthermore, a recently concluded systematic review carried out as part of my Ph.D. studies indicated that there is limited and inconclusive evidence of the added benefit of incorporating a physical activity promotion consultation programme into standard pulmonary rehabilitation in COPD patients not suffering from anxiety and depression. Hence, an additional aim of the study will be to investigate the addition of physical activity promotion to standard pulmonary rehabilitation on daily physical activity levels in COPD patients not expressing evidence of anxiety and depression.

Research question:

The project will investigate whether patients adhere well to an intervention combining standard pulmonary rehabilitation sessions (including exercise training and education), instructions on promoting daily physical activity and behavioural modification strategies to combat physical inactivity.

Aims:

The primary objective is to investigate patient adherence to the regular use of activity trackers to monitor and adjust daily physical activity levels during the course of a standard pulmonary rehabilitation programme (16 sessions) that includes behavioural modification consultancy sessions.

The secondary aims are to assess:

- Change in physical activity using a validated triaxial accelerometer.
- Mean change in Hospital Anxiety and Depression Score assessed by the HADS questionnaire.
- Mean change in quality of life assessed by clinical COPD questionnaire (CCQ) and COPD assessment test (CAT).
- Exercise capacity assessed by the 6-min walking test (6MWT),

Project plan:

This is a single centre feasibility, single blind, parallel, randomised controlled trial. We will investigate patient adherence, and acceptability of a physical activity promotion programme by the patients and the multidisciplinary respiratory team.

Study population:

We will recruit 80 stable COPD patients.

Key inclusion criteria:

- 1) COPD confirmed by obstructive spirometry.
- 2) Clinically stable male or female COPD patients aged 40 years or older.
- 3) Optimised medical therapy
- 4) Able to provide informed consent.
- 5) Valid HADS score.

Key exclusion criteria:

- 1) Orthopaedic, neurological or other concomitant diseases that significantly impair normal biomechanical movement patterns, as judged by the investigator.
- 2) Moderate or severe COPD exacerbation (AECOPD) within 4 weeks.

- 3) Unstable ischaemic heart disease, including myocardial infarction within 6 weeks.
- 4) Moderate or severe aortic stenosis or hypertrophic obstructive cardiomyopathy.
- 5) Uncontrolled hypertension.
- 6) Another condition likely to limit life expectancy to less than one year (principally metastatic malignancy).

Planned interventions:

Following confirmation of eligibility, informed consent (Appendix 1) and baseline assessment (Table 1), 80 patients will be evenly randomised to one of the following four groups : i) Group A: 8 weeks of standard pulmonary *rehabilitation alone* ii) Group B: 8 weeks of standard pulmonary rehabilitation *alongside physical activity promotion* iii) Group C: 8-weeks of standard pulmonary rehabilitation *alongside cognitive behavioural therapy* [11] and iv) Group D: 8 weeks of standard pulmonary rehabilitation *alongside Cognitive behavioural therapy and physical activity promotion* [6], (Fig. 1). Randomisation will be performed independently for groups 1 and 2 (not anxious or depressed based on HADS<8) and groups 3 and 4 (anxious and depressed based on HADS≥8), with 1:1 allocation using the 6MWT for stratification, (above or below 350m) [6] & [12], (Fig. 2).

Standard Care Pulmonary rehabilitation;

Exercise Sessions:

All patients will attend a group programme running twice weekly for 8 weeks (16 sessions) for approximately 50 minutes of exercise and 20 minutes of education or relaxation. The exercises include an individualised programme of aerobic (cycling and walking) and strengthening exercises were each patient would be progressed at each session as able.

Cognitive behavioural modification (CBM):

CBM strategies are part of standard care pulmonary rehabilitation at the Royal Victoria Infirmary for those patients presenting with a HADS score ≥8. Made up of four elements: behaviour, cognition/thoughts, feelings/emotions, and physical sensations [13]. A number of techniques will be used to aid symptoms of anxiety and depression including; education on anxiety and depression and COPD, distraction techniques, breathing control and relaxation and rating achievement/pleasure of physical activities [10] (Figure 1). CBM will be administered once at study entry (week 1 for 45 min session), and three times during weeks 2, 3 and 4 for 30 min each time.

Physical activity Promotion:

The physical activity (PA) promotion intervention, will include: 1) a step-counter with a digital display, 2) a semi-structured interview discussing motivation issues, favourite activities, and strategies to become more active; 3) a tailored physical activity coaching plan including an individualized daily activity goal (steps/day) revised weekly. Patients' targets during the course of PR will be revised every 7 days, based on performance in the preceding week. The aim is to increase physical activity by 10% each week. The goal can be altered if required. Patients will be asked to wear the step counter during waking hours for a minimum of 8 hours after waking up on a daily basis. Patients will log their daily steps on a diary provided by the PR team. On a weekly basis, staff at the pulmonary rehabilitation programme will download

manually the data from the activity monitor to keep a record. The patient's goal will be adjusted to the patient's performance of the previous week and to their willingness to increase their goal [6], (Figure 1).

Follow up:

Following the PR programme, participants will be invited to participate in a 6-month follow up period. Patients in the intervention group will keep the step counter and activity diaries given to them during PR. Every 2 weeks, patients will be contacted via telephone to report their weekly steps, check progress and provide guidance if required. Those in the control group should continue with their usual daily activities as per usual care.

Trial Outcomes:

The primary outcome is to investigate patient adherence to the regular use of activity trackers to monitor and adjust daily physical activity levels during the course of a standard pulmonary rehabilitation programme (16 sessions) that includes behavioral modification consultancy sessions to adopt an active lifestyle.

Secondary outcomes include:

- Change in physical activity at 9 weeks and following a 12 and 24 week follow up period
- Change in hospital anxiety and depression score at 9 weeks and following a 12 and 24 week follow up period
- Change in 6MWT at 9 weeks;
- Change in incremental shuttle walk test at 9 weeks;
- Change in QOL at 9 weeks and following a 12 and 24 week follow up period

Assessment Procedures:

Pulmonary function:

Pulmonary function assessment will be performed before and after completion of the PR program. The assessment will include comprehensive evaluation for the determination of Forced Expiratory Volume at the 1st second (FEV1) and Forced Vital Capacity (FVC) (Table 1).

Functional capacity:

The six-minute walk test (6 MWT) will be performed according to the instructions of the American Thoracic Society [14], in order to assess the functional capacity of the patients. Intensity of dyspnoea and leg discomfort will be assessed by the modified Borg scale, whereas cardiac frequency (fc), and oxygen saturation will be recorded every min and at the end of 6 MWT. In addition, patients will undertake the incremental shuttle walk test (ref). The 6 MWT and shuttle walk tests will be performed within 1 week before and one week after the end of the rehabilitation program (Table 1).

Daily physical activity:

Assessment of Daily Physical Activity will be performed one week before starting the PR program, one week after the completion of the PR program (9th week) and after a 12 and 24 week follow-up, using a triaxial accelerometer (Actigraph GT3X; Actigraph LLC, Pensacola, FL, USA). Patients will be asked to wear the activity monitor during wakefulness for 7 consecutive days. Daily step count will be performed over 7 days, with at least 3 acceptable days' data, excluding days with less than 8 hours of wear time (Table 1).

Health-related Quality of Life:

Quality of Life (QoL) will be assessed at the onset and following completion of the PR program. Patients will be asked to complete different questionnaires in order to evaluate their emotional condition and symptoms. The assessment of QoL will include 3 different questionnaires namely: Hospital Anxiety and Depression Score (HADS), Clinical COPD Questionnaire (CCQ), COPD Assessment test (CAT). The questionnaires will be administered 1 week before and 1 week after the end of the rehabilitation programme as well as after a 12 and 24 week follow up period.

Statistical plan

Statistical analyses will be supported by standard statistical software (e.g. SPSS, SAS) as required. This is a feasibility study and key outcomes of interest relate to adherence, attendance and drop out rather than clinical outcomes. However, clinical outcome data (steps/day) will be collected and reported to help inform a future randomized controlled trial. Feasibility data will be summarized using standard descriptive statistics, depending on the level of the data (e.g. mean, median, standard deviation, range). Baseline characteristics between groups will be assessed by t-tests for independent samples. Differences between groups across different time points will be assessed by a two-way ANOVA with repeated measures followed by appropriate post-hoc analysis. The Level of significance is set at $p < 0.05$.

Table 1: Assessment of variables prior to and following the rehabilitation programme

Visit number (Assessments)	1	2	3	4	5 (Via Post)	6 (Via post)
	Week 0	Week 1	Week 9	Week 10	Week 21	Week 33
Inclusion/Exclusion criteria	x					
Information & Informed consent	x					
Physical examination	x					
mMRC evaluation	x					
Current medication review	x					
Pulmonary Function Assessment		x				
Heart Function Assessment (resting ECG)		x				
BMI (body composition)		x		x		
Oximetry & Blood Pressure		x				
6 Minute Walk Test		x	x			
Shuttle walk test		x	x			
Daily Physical Activity Assessment	x		x	x	x	x
Quality of Life Assessment		x		x	x	x

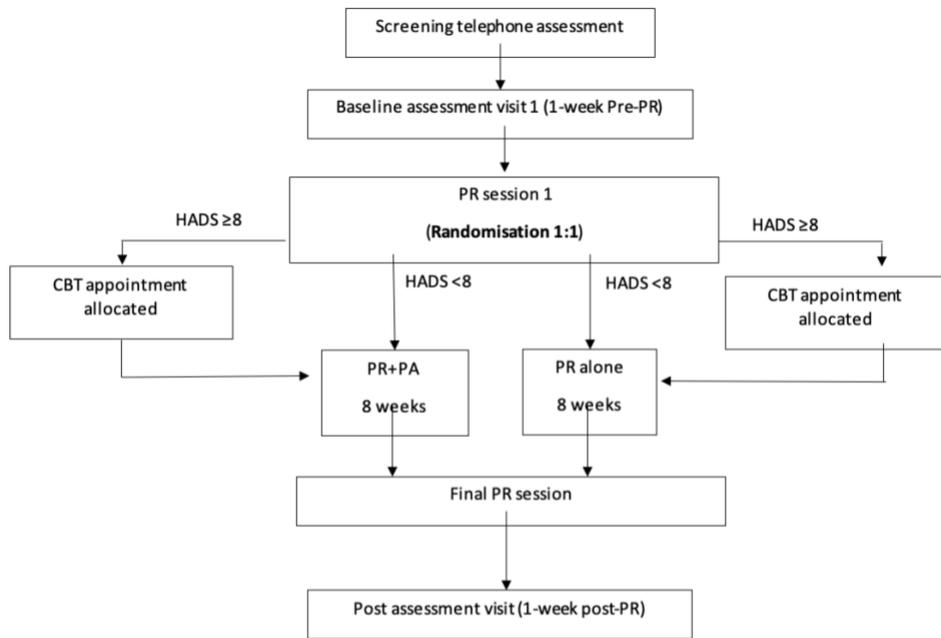


Figure 1: Study design



Figure 2: Consort Diagram.

References:

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2. Troosters, T., et al., *Improving physical activity in COPD: towards a new paradigm*. Respiratory research, 2013. **14**(1): p. 115.
3. Pitta, F., et al., *Characteristics of physical activities in daily life in chronic obstructive pulmonary disease*. American journal of respiratory and critical care medicine, 2005. **171**(9): p. 972-977.
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11. Bolton, C.E., et al., *British Thoracic Society guideline on pulmonary rehabilitation in adults: accredited by NICE*. Thorax, 2013. **68**(Suppl 2): p. ii1-ii30.
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13. Greenberger, D. and C.A. Padesky, *Mind over Mood: a cognitive therapy treatment manual for clients*. 1995: Guilford press.
14. Laboratories, A.C.o.P.S.f.C.P.F., *Statement AT: guidelines for the six-minute walking-test*. Am J Respir Crit Care Med, 2002. **166**: p. 111-117.

Appendix 4c: Completed IRAS document

IRAS Form

Reference:
18/YH/0376

IRAS Version 5.9.1

Welcome to the Integrated Research Application System

IRAS Project Filter

The integrated dataset required for your project will be created from the answers you give to the following questions. The system will generate only those questions and sections which (a) apply to your study type and (b) are required by the bodies reviewing your study. Please ensure you answer all the questions before proceeding with your applications.

Please complete the questions in order. If you change the response to a question, please select 'Save' and review all the questions as your change may have affected subsequent questions.

Please enter a short title for this project (maximum 70 characters)
An Intervention to improve physical activity in COPD

1. Is your project research?

Yes No

2. Select one category from the list below:

- Clinical trial of an investigational medicinal product
- Clinical investigation or other study of a medical device
- Combined trial of an investigational medicinal product and an investigational medical device
- Other clinical trial to study a novel intervention or randomised clinical trial to compare interventions in clinical practice
- Basic science study involving procedures with human participants
- Study administering questionnaires/interviews for quantitative analysis, or using mixed quantitative/qualitative methodology
- Study involving qualitative methods only
- Study limited to working with human tissue samples (or other human biological samples) and data (specific project only)
- Study limited to working with data (specific project only)
- Research tissue bank
- Research database

If your work does not fit any of these categories, select the option below:

Other study

2a. Will the study involve the use of any medical device without a CE Mark, or a CE marked device which has been modified or will be used outside its intended purposes?

Yes No

2b. Please answer the following question(s):

- a) Does the study involve the use of any ionising radiation? Yes No
- b) Will you be taking new human tissue samples (or other human biological samples)? Yes No
- c) Will you be using existing human tissue samples (or other human biological samples)? Yes No

Date: 07/09/2018

1

248697/1252281/37/146

3. In which countries of the UK will the research sites be located?(Tick all that apply)

- England
 Scotland
 Wales
 Northern Ireland

3a. In which country of the UK will the lead NHS R&D office be located:

- England
 Scotland
 Wales
 Northern Ireland
 This study does not involve the NHS

4. Which applications do you require?

IMPORTANT: If your project is taking place in the NHS and is led from England select 'IRAS Form'. If your project is led from Northern Ireland, Scotland or Wales select 'NHS/HSC Research and Development Offices' and/or relevant Research Ethics Committee applications, as appropriate.

- IRAS Form
 Confidentiality Advisory Group (CAG)
 Her Majesty's Prison and Probation Service (HMPPS)

For NHS/HSC R&D Offices in Northern Ireland, Scotland and Wales the CI must create NHS/HSC Site Specific Information forms, for each site, in addition to the study wide forms, and transfer them to the PIs or local collaborators.

For participating NHS organisations in England different arrangements apply for the provision of site specific information. Refer to IRAS Help for more information.

5. Will any research sites in this study be NHS organisations?

- Yes No

5a. Are all the research costs and infrastructure costs (funding for the support and facilities needed to carry out research e.g. NHS Support costs) for this study provided by a NIHR Biomedical Research Centre, NIHR Biomedical Research Unit, NIHR Collaboration for Leadership in Health Research and Care (CLAHRC), NIHR Patient Safety Translational Research Centre or a Diagnostic Evidence Co-operative in all study sites?

Please see information button for further details.

- Yes No

Please see information button for further details.

5b. Do you wish to make an application for the study to be considered for NIHR Clinical Research Network (CRN) Support and inclusion in the NIHR Clinical Research Network Portfolio?

Please see information button for further details.

- Yes No

The NIHR Clinical Research Network provides researchers with the practical support they need to make clinical studies happen in the NHS e.g. by providing access to the people and facilities needed to carry out research "on the ground".

If you select yes to this question, you must complete a NIHR Clinical Research Network (CRN) Portfolio Application Form (PAF) immediately after completing this project filter question and before submitting other applications. Failing to complete the PAF ahead of other applications e.g. HRA Approval, may mean that you will be unable to access NIHR CRN Support for your study.

6. Do you plan to include any participants who are children?

Yes No

7. Do you plan at any stage of the project to undertake intrusive research involving adults lacking capacity to consent for themselves?

Yes No

Answer Yes if you plan to recruit living participants aged 16 or over who lack capacity, or to retain them in the study following loss of capacity. Intrusive research means any research with the living requiring consent in law. This includes use of identifiable tissue samples or personal information, except where application is being made to the Confidentiality Advisory Group to set aside the common law duty of confidentiality in England and Wales. Please consult the guidance notes for further information on the legal frameworks for research involving adults lacking capacity in the UK.

8. Do you plan to include any participants who are prisoners or young offenders in the custody of HM Prison Service or who are offenders supervised by the probation service in England or Wales?

Yes No

9. Is the study or any part of it being undertaken as an educational project?

Yes No

Please describe briefly the involvement of the student(s):
This study will be used as part of a PhD research thesis

9a. Is the project being undertaken in part fulfilment of a PhD or other doctorate?

Yes No

10. Will this research be financially supported by the United States Department of Health and Human Services or any of its divisions, agencies or programs?

Yes No

11. Will identifiable patient data be accessed outside the care team without prior consent at any stage of the project (including identification of potential participants)?

Yes No

Integrated Research Application System
Application Form for Other clinical trial or investigation
IRAS Form (project information)

Please refer to the E-Submission and Checklist tabs for instructions on submitting this application.

The Chief Investigator should complete this form. Guidance on the questions is available wherever you see this symbol displayed. We recommend reading the guidance first. The complete guidance and a glossary are available by selecting [Help](#).

Please define any terms or acronyms that might not be familiar to lay reviewers of the application.

Short title and version number: (maximum 70 characters - this will be inserted as header on all forms)
An Intervention to improve physical activity in COPD

Please complete these details after you have booked the REC application for review.

REC Name:
Yorkshire & The Humber - Sheffield Research Ethics Committee

REC Reference Number:
18/YH/0376

Submission date:
07/09/2018

PART A: Core study information
1. ADMINISTRATIVE DETAILS
A1. Full title of the research:

A feasibility study assessing the inclusion of Physical Activity Promotion to standard care pulmonary rehabilitation and cognitive behavioural therapy in patients with COPD who are anxious or depressed.

A2-1. Educational projects

Name and contact details of student(s):

Student 1

	Title Forename/Initials Surname
	Mr Matthew Armstrong
Address	158 Whitefield Terrace
	Heaton
	Newcastle Upon Tyne
Post Code	NE65SS
E-mail	matthew.armstrong@northumbria.ac.uk
Telephone	07495155142
Fax	

Give details of the educational course or degree for which this research is being undertaken:

Name and level of course/ degree:

Post graduate research (PhD)	
Name of educational establishment: Northumbria University	
Name and contact details of academic supervisor(s):	
Academic supervisor 1	
	Title Forename/Initials Surname Prof Ioannis Vogiatzis
Address	Northumbria University Northumberland Building
Post Code	NE1 8ST
E-mail	ioannis.vogiatzis@northumbria.ac.uk
Telephone	01913495446
Fax	
Please state which academic supervisor(s) has responsibility for which student(s): Please click "Save now" before completing this table. This will ensure that all of the student and academic supervisor details are shown correctly.	
Student(s)	Academic supervisor(s)
Student 1 Mr Matthew Armstrong	<input checked="" type="checkbox"/> Prof Ioannis Vogiatzis
A copy of a <u>current CV</u> for the student and the academic supervisor (maximum 2 pages of A4) must be submitted with the application.	

A2-2. Who will act as Chief Investigator for this study?

- Student
 Academic supervisor
 Other

A3-1. Chief Investigator:

	Title Forename/Initials Surname Dr Karen Heslop-Marshell
Post	Respiratory Research Nurse
Qualifications	BSc, MSc, PhD
ORCID ID	
Employer	Newcastle Upon Tyne NHS Foundation Trust
Work Address	Royal Victoria Infirmary Queen Victoria Road Newcastle Upon Tyne
Post Code	NE14LP
Work E-mail	Karen.Heslop@nuth.nhs.uk
* Personal E-mail	Karen.Heslop@nuth.nhs.uk

Work Telephone 07753884774
 * Personal Telephone/Mobile 07753884774
 Fax

* This information is optional. It will not be placed in the public domain or disclosed to any other third party without prior consent.

A copy of a current CV (maximum 2 pages of A4) for the Chief Investigator must be submitted with the application.

A4. Who is the contact on behalf of the sponsor for all correspondence relating to applications for this project?

This contact will receive copies of all correspondence from REC and HRA/R&D reviewers that is sent to the CI.

Title Forename/Initials Surname
 Mr Aaron Jackson
 Address Joint research Office
 The Newcastle Upon Tyne NHS Foundation Trust
 Regent point (Level 1)
 Post Code NE33HD
 E-mail Aaron.jackson@nuth.nhs.uk
 Telephone 01912825789
 Fax

A5-1. Research reference numbers. Please give any relevant references for your study:

Applicant's/organisation's own reference number, e.g. R & D (if available): n/a
 Sponsor's/protocol number: 1.0
 Protocol Version: 1.2
 Protocol Date: 17/07/2018
 Funder's reference number (enter the reference number or state not applicable): n/a
 Project website: n/a

Registry reference number(s):

The UK Policy Framework for Health and Social Care Research sets out the principle of making information about research publicly available. Furthermore: Article 19 of the World Medical Association Declaration of Helsinki adopted in 2008 states that "every clinical trial must be registered on a publicly accessible database before recruitment of the first subject"; and the International Committee of Medical Journal Editors (ICMJE) will consider a clinical trial for publication only if it has been registered in an appropriate registry. Please see guidance for more information.

International Standard Randomised Controlled Trial Number (ISRCTN):

ClinicalTrials.gov Identifier (NCT number):

Additional reference number(s):

Ref.Number	Description	Reference Number

A5-2. Is this application linked to a previous study or another current application?

Yes No

Please give brief details and reference numbers.

2. OVERVIEW OF THE RESEARCH

To provide all the information required by review bodies and research information systems, we ask a number of specific questions. This section invites you to give an overview using language comprehensible to lay reviewers and members of the public. Please read the guidance notes for advice on this section.

A6-1. Summary of the study. *Please provide a brief summary of the research (maximum 300 words) using language easily understood by lay reviewers and members of the public. Where the research is reviewed by a REC within the UK Health Departments' Research Ethics Service, this summary will be published on the Health Research Authority (HRA) website following the ethical review. Please refer to the question specific guidance for this question.*

In patients with Chronic Obstructive Pulmonary Disease (COPD) daily physical activity is reduced compared to healthy age-matched individuals. Reduced levels of physical activity in patients with COPD are associated with increased risk for exacerbations, hospital admissions and mortality.

Pulmonary rehabilitation (PR) constitutes standard care for patients with COPD as it improves exercise capacity, quality of life and reduces the risk for exacerbations and hospitalisation. Participation in PR, however, does not necessarily translate into improved daily physical activity levels. It is currently unknown whether addition of physical activity promotion strategies to standard PR programs induces an improvement in daily physical activity along with exercise capacity and quality of life compared to pulmonary rehabilitation alone.

Physical activity (PA) is a complex health behaviour that is modified by behavioural change interventions. PA promotion programs through the use of wearable monitors (i.e. pedometers, accelerometers) with goal setting and feedback, have shown to increase daily physical activity, but not exercise capacity or quality of life in COPD patients. Therefore, combination of both PR and PA promotion strategies is necessary to translate PR-induced improvements in functional capacity into improved daily physical activity levels.

We propose to perform a feasibility study assessing patient adherence to PA promotion incorporated into a standard PR program. To enhance adherence to the PA promotion strategy, Cognitive Behavioural Modification Strategies (CBM) will be provided to patients undertaking PR. CBM strategies facilitate the goals of PR as they address several behavioural barriers including anxiety, depression and physical inactivity, and constitutes an important component in the management of COPD to improve engagement with PR and promote a physically active lifestyle.

We will divide patients into two programs: one including PR, PA promotion and CBM and the other comprising standard PR and CBM provision. We will compare patients' adherence (16 sessions of PR) to both programs.

A6-2. Summary of main issues. *Please summarise the main ethical, legal, or management issues arising from your study and say how you have addressed them.*

Not all studies raise significant issues. Some studies may have straightforward ethical or other issues that can be identified and managed routinely. Others may present significant issues requiring further consideration by a REC, HRA, or other review body (as appropriate to the issue). Studies that present a minimal risk to participants may raise complex organisational or legal issues. You should try to consider all the types of issues that the different reviewers may need to consider.

Patients will be required to undertake exercise training sessions twice a week for one hour each time over 8 weeks as part of the standard pulmonary rehabilitation program at RVI. The program is delivered by an experienced respiratory physiotherapist (LM). As part of standard management of COPD, patients will be provided with 3 sessions of cognitive behavioural modification strategies by a respiratory nurse consultant(KHM).

In addition, patients in the intervention arm will be given an activity tracker that captures daily steps to assess physical activity levels. On a weekly basis the number of steps will be reviewed and a weekly goal will be determined, facilitating improvement in daily/steps every week. We do envisage any ethical, legal or management issues as the physical activity intervention requires minimal contact and interaction with the patients.

3. PURPOSE AND DESIGN OF THE RESEARCH

A7. Select the appropriate methodology description for this research. Please tick all that apply.

- Case series/ case note review
- Case control
- Cohort observation
- Controlled trial without randomisation

- Cross-sectional study
- Database analysis
- Epidemiology
- Feasibility/ pilot study
- Laboratory study
- Metanalysis
- Qualitative research
- Questionnaire, interview or observation study
- Randomised controlled trial
- Other (please specify)

A10. What is the principal research question/objective? Please put this in language comprehensible to a lay person.

The project will investigate whether patients adhere to an intervention of physical activity promotion incorporated within a standard pulmonary rehabilitation programme (including exercise training, education and behavioural modification strategies).

The primary objective is to investigate patient compliance with the physical activity promotion intervention which entails daily use of a step counter for a period of 8 weeks.

A11. What are the secondary research questions/objectives if applicable? Please put this in language comprehensible to a lay person.

The secondary aims are to assess:

- Change in levels of physical activity (steps/day) measured by a validated triaxial accelerometer.
- Change in symptoms of anxiety and depression assessed by the HADS questionnaire.
- Change in quality of life assessed by St' Georges Respiratory Questionnaire (StGRQ).
- Improve exercise capacity assessed by the 6-min walking test (6MWT).

A12. What is the scientific justification for the research? Please put this in language comprehensible to a lay person.

Chronic Obstructive Pulmonary Disease (COPD) is a debilitating and progressive disease, primarily affecting the respiratory system. In many patients, it also has adverse extra-pulmonary effects, such as skeletal muscle dysfunction and weakness. Pulmonary and skeletal muscle metabolic abnormalities enhance the ventilatory requirement during exercise, resulting in exercise-associated symptoms such as breathlessness and leg discomfort. These symptoms make every day physical activity an unpleasant experience, which many patients try to avoid. Physical activity levels are therefore remarkably lower in COPD patients than healthy age-matched individuals, presenting a major predictor of exacerbations, hospitalisations and mortality and in these patients.

Implementation of exercise training as part of Pulmonary Rehabilitation aims to reverse the systemic consequences of COPD, in particular skeletal muscle dysfunction and weakness. Currently pulmonary rehabilitation programs have shown substantial improvements in exercise capacity; however, these findings have not consistently progressed into improvements in daily levels of physical activity. One reason for this may link to physical activity in COPD being a complex health behaviour.

Recently, physical activity coaching, including weekly targets and feedback, has shown to be effective in patients with COPD in terms of improving daily steps over a period of three months. Accordingly, activity coaching may be added to standard pulmonary rehabilitation to facilitate the rehabilitation-induced improvements in exercise capacity to progress into improvements in physical activity.

Alongside the physical barriers influencing daily physical activity, the distressing nature of COPD has a significant impact on patients' psychological well-being. Major focusing points for COPD patients are the sense of feeling unwell, the inability to perform everyday activities and the emotional consequences of the condition. These symptoms can promote anxiety and depression, which are prevalent in patients with COPD, are associated with poorer treatment outcomes, and reduced survival.

Cognitive Behavioural Modification (CBM) strategies constitute an intervention that focuses on understanding how experiences are interpreted. It provides an understanding of the interaction between thoughts, mood, behaviour and

physical sensations, which are intrinsically linked. Techniques used for anxiety include education on anxiety and COPD, planning/pacing, distraction techniques, breathing control, relaxation and managing worry. These techniques help to break the vicious cycle of anxiety and can reduce patients' distress.

Similar techniques for patients suffering mainly from depression include education about depression and physical inactivity and planning and recording activities each day, while rating these for achievement or pleasure. These techniques help to break patient inactivity, which can lead to low mood and poor physical condition. A key treatment for depression can involve encouragement to increase activities within the patients' physical capabilities. A study found clinical and statistically significant improvements in anxiety and depression scores and a statistically significant reduction in hospital admissions following CBM. CBM is therefore an important approach to incorporate into COPD management to improve engagement with both pulmonary rehabilitation and the physical activity promotion programme.

The feasibility of incorporating a physical activity promotion program to standard care pulmonary rehabilitation along with CBM strategies is still unknown.

Accordingly, it is proposed to study patient compliance with the physical activity promotion programme comprising weekly goals in terms of daily step counts measured by a commercially available step counter. Compliance to the intervention is defined as at least 4 days per week with valid step count data (>70 steps/day) ensuring that patients use the step counter on a daily basis. Over the 8-week program patients should have a minimum of 6 weeks (75%) compliance with the physical activity intervention. If patients adhere adequately to this programme, a randomised controlled trial will be designed to study the long-term effects of adding physical activity promotion to Pulmonary Rehabilitation (including exercise training, education, physical activity promotion and behavioural modification strategies) on the risk for COPD exacerbations and hospitalisations.

A13. Please summarise your design and methodology. It should be clear exactly what will happen to the research participant, how many times and in what order. Please complete this section in language comprehensible to the lay person. Do not simply reproduce or refer to the protocol. Further guidance is available in the guidance notes.

Project plan

This is a single centre feasibility, single blind, parallel, randomised controlled study. We will investigate compliance to an intervention of physical activity consultation, with the aim to promote physical activity, incorporated within a standard pulmonary rehabilitation programme (including exercise training, education and behavioural modification strategies).

Planned interventions

Following confirmation of eligibility, informed consent and baseline assessment, 40 patients will be randomised to: 1) an 8-week standard care pulmonary rehabilitation programme including 16 exercise training sessions, and 3 sessions of cognitive behavioural modification (CBM) strategies or 2) a standard care pulmonary rehabilitation programme including 16 exercise training, 3 sessions of cognitive behavioural modification (CBM) strategies and 16 sessions of physical activity consultation. Randomisation will be performed independently, with 1:1 allocation using stratification variables: HADS (8 or above) and 6MWT (above or below 350m). Stratification will ensure that patients in the two groups are well matched in terms of baseline psychological and functional conditions.

Pulmonary rehabilitation

As part of standard care for COPD patients, a referral will be made to pulmonary rehabilitation by consultants and nurses from the RVI Chest Clinic, physiotherapists on acute wards and the COPD Chest Team. All patients will be assessed at study entry by the pulmonary rehabilitation team including senior physiotherapists. During this assessment, patients will be screened for any contraindications, they will perform a 6 minute walk test and will complete questionnaires (HADS & CAT) assessing anxiety, depression, and symptoms. In addition, all patients will be given an accelerometer to record daily activity levels for one week prior to the initiation of the pulmonary rehabilitation programme.

Following baseline assessment all patients will attend a group programme running twice weekly for 8 weeks (16 sessions) for approximately 50 minutes of exercise and 20 minutes of education or relaxation. The exercises include an individualised programme of aerobic (cycling and walking) and strengthening exercises where each patient will be progressed at each session as able. In addition, the rehabilitation programme will include 3 sessions of cognitive behavioural modification (CBM) strategies that is a standard feature for the management of patients with COPD at RVI with a Hospital Anxiety & Depression Score of >8 and implemented by a respiratory nurse consultant. CBM strategies are made up of four elements: behaviour, cognition/thoughts, feelings/emotions, and physical sensations. A number of techniques will be used to aid symptoms of anxiety and depression including; education on anxiety and depression and COPD, distraction techniques, breathing control and relaxation, activity diary and rating achievement/pleasure of physical activities. CBM will be administered once at study entry (week 1 for 45 min session), and three times during weeks 2, 3 and 4 for 30 min each time.

Physical activity Promotion

The physical activity (PA) promotion intervention will be provided only to the intervention group, and will include: 1) a step-counter with a digital display, 2) an interview discussing motivational issues, favourite daily activities and strategies to become more physically active; and 3) a tailored physical activity coaching plan including an individualised activity goal (in steps/day) revised twice weekly through consultation sessions (16 sessions in total). Patients' targets will be revised twice weekly during the consultation sessions which will be incorporated into the Pulmonary rehabilitation sessions. The aim is to increase physical activity by 10% each week. The goal can be altered if required. Patients will be asked to wear the step counter during waking hours for a minimum of 8 hours after waking up on a daily basis. Compliance to the intervention is defined as at least 4 days per week with valid step count data (>70 steps/day). The step count recordings will be reviewed twice weekly during the rehabilitation sessions and new step goals will be set during consultation sessions.

Within a week following completion of the pulmonary rehabilitation programme, all patients will complete the aforementioned questionnaires to assess improvements in quality of life, and disease related symptoms. In addition exercise capacity will be assessed by the 6 min walk test and average weekly physical activity by a triaxial accelerometer.

Accordingly patients will be required to visit the hospital on 18 different occasions: twice for assessment (one week before and one week following completion of the rehabilitation programme) and 16 times to attend the rehabilitation sessions.

Statistical plan

Statistical analyses will be supported by standard statistical software (e.g. SPSS, SAS) as required. This is a feasibility study and key outcomes of interest relate to adherence, attendance and drop out rather than clinical outcomes. However, clinical outcome data (steps/day) will be collected and reported to help inform a future randomized controlled trial. Feasibility data will be summarized using standard descriptive statistics, depending on the level of the data (e.g. mean, median, standard deviation, range). Baseline characteristics between groups will be assessed by t-tests for independent samples. Differences between groups across different time points will be assessed by a two-way ANOVA with repeated measures followed by appropriate post-hoc analysis. The Level of significance is set at $p < 0.05$.

A14-1. In which aspects of the research process have you actively involved, or will you involve, patients, service users, and/or their carers, or members of the public?

- Design of the research
- Management of the research
- Undertaking the research
- Analysis of results
- Dissemination of findings
- None of the above

Give details of involvement, or if none please justify the absence of involvement.
Taking part in the Pulmonary rehabilitation and physical activity promotion

4. RISKS AND ETHICAL ISSUES**RESEARCH PARTICIPANTS****A15. What is the sample group or cohort to be studied in this research?**

Select all that apply:

- Blood
- Cancer

- Cardiovascular
- Congenital Disorders
- Dementias and Neurodegenerative Diseases
- Diabetes
- Ear
- Eye
- Generic Health Relevance
- Infection
- Inflammatory and Immune System
- Injuries and Accidents
- Mental Health
- Metabolic and Endocrine
- Musculoskeletal
- Neurological
- Oral and Gastrointestinal
- Paediatrics
- Renal and Urogenital
- Reproductive Health and Childbirth
- Respiratory
- Skin
- Stroke

Gender: Male and female participants
 Lower age limit: 40 Years
 Upper age limit: 75 Years

A17-1. Please list the principal inclusion criteria (list the most important, max 5000 characters).

- 1) COPD confirmed by obstructive spirometry
- 2) Clinically stable male or female COPD patients aged 40 years or older
- 3) Optimised medical therapy
- 4) Able to provide informed consent
- 5) HADS score of 8 and above

A17-2. Please list the principal exclusion criteria (list the most important, max 5000 characters).

- 1) Orthopaedic, neurological or other concomitant diseases that significantly impair normal biomechanical movement patterns, as judged by the investigator.
- 2) Moderate or severe COPD exacerbation (AECOPD) within 4 weeks.
- 3) Unstable ischaemic heart disease, including myocardial infarction within 6 weeks.
- 4) Moderate or severe aortic stenosis or hypertrophic obstructive cardiomyopathy.
- 5) Uncontrolled hypertension.
- 6) Another condition likely to limit life expectancy to less than one year (principally metastatic malignancy).

RESEARCH PROCEDURES, RISKS AND BENEFITS

A18. Give details of all non-clinical intervention(s) or procedure(s) that will be received by participants as part of the research protocol. These include seeking consent, interviews, non-clinical observations and use of questionnaires.

Please complete the columns for each intervention/procedure as follows:

1. Total number of interventions/procedures to be received by each participant as part of the research protocol.
2. If this intervention/procedure would be routinely given to participants as part of their care outside the research, how many of the total would be routine?
3. Average time taken per intervention/procedure (minutes, hours or days)
4. Details of who will conduct the intervention/procedure, and where it will take place.

Intervention or procedure	1	2	3	4
Informed consent form	1	1	10 minutes	By a member of the respiratory team at the RVI
Interview discussing baseline activity levels	1	0	30 minutes	By a member of the respiratory team at the RVI
Consultations of daily steps captured by activity trackers and goal setting	16	0	15 minutes	By a member of the research team
Completion of questionnaires (HADS & CATS)	2	2	30 minutes	By a member of the respiratory team at the RVI

A19. Give details of any clinical intervention(s) or procedure(s) to be received by participants as part of the research protocol. These include uses of medicinal products or devices, other medical treatments or assessments, mental health interventions, imaging investigations and taking samples of human biological material. Include procedures which might be received as routine clinical care outside of the research.

Please complete the columns for each intervention/procedure as follows:

1. Total number of interventions/procedures to be received by each participant as part of the research protocol.
2. If this intervention/procedure would be routinely given to participants as part of their care outside the research, how many of the total would be routine?
3. Average time taken per intervention/procedure (minutes, hours or days).
4. Details of who will conduct the intervention/procedure, and where it will take place.

Intervention or procedure	1	2	3	4
Exercise training as part of pulmonary rehabilitation	16	16	50 minutes	Physiotherapist at the RVI
Cognitive Behavioural Modification sessions	3	3	45 minutes	Specialised nurse in delivering cognitive behavioural therapy
6 minute walk test	2	2	6 minutes	Physiotherapist at the RVI
Assessment of daily physical activity in steps/day using triaxial accelerometer	2	2	7 days	Physiotherapist at the RVI

A20. Will you withhold an intervention or procedure, which would normally be considered a part of routine care?

Yes No

A21. How long do you expect each participant to be in the study in total?

10 weeks

0-1 week: baseline assessment
2-9 week: pulmonary rehabilitation
9-10 week: follow up assessment

A22. What are the potential risks and burdens for research participants and how will you minimise them?

For all studies, describe any potential adverse effects, pain, discomfort, distress, intrusion, inconvenience or changes to lifestyle. Only describe risks or burdens that could occur as a result of participation in the research. Say what steps would be taken to minimise risks and burdens as far as possible.

Patients participating to the study will be among those referred to pulmonary rehabilitation sessions at Royal Victoria Infirmary Hospital. All exercise training sessions and exercise capacity assessments will be performed under the supervision of a physiotherapist, who will take into consideration patients' symptoms (such as dizziness, drop of blood pressure, arrhythmias, chest pain, etc). Oxygen saturation will be monitored. Oxygen will be supplied to those patients who experience moderate de-saturation. A physician will be available to manage any adverse events, although the absolute risk is exceptionally small. During the rehabilitation sessions patients may feel breathless and/or leg muscle discomfort. These are common symptoms during exercise and there is not any potential risks for the patients.

No risks will be taken using either the accelerometer to assess physical activity prior to and following completion of the rehabilitation programme or use of activity trackers to assess daily step counts over the 8-week rehabilitation period.

A23. Will interviews/ questionnaires or group discussions include topics that might be sensitive, embarrassing or upsetting, or is it possible that criminal or other disclosures requiring action could occur during the study?

Yes No

A24. What is the potential for benefit to research participants?

Participants will be enrolled on standard care pulmonary rehabilitation, meaning they will receive the same benefits as any patient referred by the chest clinic at the Royal Victoria Infirmary. Furthermore patients in the physical activity promotion programme will experience the opportunity of monitoring their own physical activity levels and receive guidance on how to improve daily steps. The results of the trial will inform clinical services in the future, which may be of benefit to participants during future pulmonary rehabilitation courses, as well as other patients.

A25. What arrangements are being made for continued provision of the intervention for participants, if appropriate, once the research has finished? May apply to any clinical intervention, including a drug, medical device, mental health intervention, complementary therapy, physiotherapy, dietary manipulation, lifestyle change, etc.

Patients will be taught to monitor their daily activity levels and adjust these levels weekly. Following completion of the intervention, patients will be advised to maintain an active lifestyle and further improve the time spent during activities of daily living.

A26. What are the potential risks for the researchers themselves? (if any)

There aren't any potential risks for the researchers.

RECRUITMENT AND INFORMED CONSENT

In this section we ask you to describe the recruitment procedures for the study. Please give separate details for different study groups where appropriate.

A27-1. How will potential participants, records or samples be identified? Who will carry this out and what resources will be used? For example, identification may involve a disease register, computerised search of GP records, or review of medical records. Indicate whether this will be done by the direct healthcare team or by researchers acting under arrangements with the responsible care organisation(s).

Potential participants will be recruited from patients referred to pulmonary rehabilitation as standard care. Specifically patients who give a HADS score of 8 and above would receive cognitive behavioural modification therapy as standard care and would therefore be eligible to take part in this study. Patients will receive full information about the trial, be given the opportunity to ask any questions and appropriate time to consider whether they wish to take part. Written informed consent will be obtained.

A27-2. Will the identification of potential participants involve reviewing or screening the identifiable personal information of patients, service users or any other person?

Yes No

Please give details below:

Potential participants will be identified by the respiratory team.

A27-3. Describe what measures will be taken to ensure there is no breach of any duty of confidentiality owed to patients, service users or any other person in the process of identifying potential participants. Indicate what steps have been or will be taken to inform patients and service users of the potential use of their records for this purpose. Describe the arrangements to ensure that the wishes of patients and service users regarding access to their records are respected. Please consult the guidance notes on this topic.

As potential participants will be identified by the respiratory care team, there are no concerns in this regard.

A27-4. Will researchers or individuals other than the direct care team have access to identifiable personal information of any potential participants?

Yes No

A28. Will any participants be recruited by publicity through posters, leaflets, adverts or websites?

Yes No

A29. How and by whom will potential participants first be approached?

Potential patients would be informed of the opportunity to take part in this study while being enrolled to usual care pulmonary rehabilitation. This would be conducted by a healthcare professional who would undertake a pre screening assessment regardless of enrolment to this study.

A30-1. Will you obtain informed consent from or on behalf of research participants?

Yes No

If you will be obtaining consent from adult participants, please give details of who will take consent and how it will be done, with details of any steps to provide information (a written information sheet, videos, or interactive material). Arrangements for adults unable to consent for themselves should be described separately in Part B Section 6, and for children in Part B Section 7.

If you plan to seek informed consent from vulnerable groups, say how you will ensure that consent is voluntary and fully informed.

Informed consent will be conducted by the research Nurse or primary investigator who will be running the study. This will involve eligible patients receiving a "participant information sheet" and "informed consent form", which are both attached below.

If you are not obtaining consent, please explain why not.

Please enclose a copy of the information sheet(s) and consent form(s).

A30-2. Will you record informed consent (or advice from consultees) in writing?

Yes No

A31. How long will you allow potential participants to decide whether or not to take part?

Participants will be informed by hospital's multidisciplinary respiratory team working within the Trust (usual care team, including physicians, physiotherapists and specialist nurses) and an information sheet will be provided to them. If potential participants need more time to decide if they want to take part in the study, they will be able to return home, discuss about the protocol with their families and/or their GP and inform the recruiting physicians about their decision.

A32. Will you recruit any participants who are involved in current research or have recently been involved in any research prior to recruitment?

- Yes
 No
 Not Known

If Yes, please give details and justify their inclusion. If Not Known, what steps will you take to find out?

We will not exclude patients who have recently completed a research study (particularly observational studies) unless there is concern that this influences the trial.

We will not include patients who are currently participating in any interventional research study.

A33-1. What arrangements have been made for persons who might not adequately understand verbal explanations or written information given in English, or who have special communication needs?(e.g. translation, use of interpreters)

The Trust's R&D department has access to both interpreters and a full translation service

A34. What arrangements will you make to ensure participants receive any information that becomes available during the course of the research that may be relevant to their continued participation?

We have searched for relevant registered clinical trials; we do not expect new data to become available during this study that would influence patient participation, but will repeat the search prior to commencing the trial. Should relevant information come to light, this will be communicated with participants (verbally and in writing).

A35. What steps would you take if a participant, who has given informed consent, loses capacity to consent during the study? Tick one option only.

- The participant and all identifiable data or tissue collected would be withdrawn from the study. Data or tissue which is not identifiable to the research team may be retained.
- The participant would be withdrawn from the study. Identifiable data or tissue already collected with consent would be retained and used in the study. No further data or tissue would be collected or any other research procedures carried out on or in relation to the participant.
- The participant would continue to be included in the study.
- Not applicable – informed consent will not be sought from any participants in this research.
- Not applicable – it is not practicable for the research team to monitor capacity and continued capacity will be assumed.

Further details:

CONFIDENTIALITY

In this section, personal data means any data relating to a participant who could potentially be identified. It includes pseudonymised data capable of being linked to a participant through a unique code number.

Storage and use of personal data during the study

A36. Will you be undertaking any of the following activities at any stage (including in the identification of potential participants)?(Tick as appropriate)

- Access to medical records by those outside the direct healthcare team
- Access to social care records by those outside the direct social care team
- Electronic transfer by magnetic or optical media, email or computer networks
- Sharing of personal data with other organisations
- Export of personal data outside the EEA
- Use of personal addresses, postcodes, faxes, emails or telephone numbers
- Publication of direct quotations from respondents
- Publication of data that might allow identification of individuals
- Use of audio/visual recording devices
- Storage of personal data on any of the following:
 - Manual files (includes paper or film)
 - NHS computers
 - Social Care Service computers
 - Home or other personal computers
 - University computers
 - Private company computers
 - Laptop computers

Further details:

A37. Please describe the physical security arrangements for storage of personal data during the study?

Computers will either be NHS or University supplied and registered, and will be password protected with encryption software. Paper files will be kept in a secured locked filing cabinet.

A38. How will you ensure the confidentiality of personal data?Please provide a general statement of the policy and procedures for ensuring confidentiality, e.g. anonymisation or pseudonymisation of data.

All data will be anonymised, with patients identified using a unique trial number.

A40. Who will have access to participants' personal data during the study? Where access is by individuals outside the direct care team, please justify and say whether consent will be sought.

Members of the research team will have access to participants' personal data if required and only with consent.

Storage and use of data after the end of the study

A41. Where will the data generated by the study be analysed and by whom?

Data will be analysed by the applicant in collaboration with his PhD student, Mr Matthew Armstrong, and clinical colleagues from the Trust, namely Dr. Graham Burns and Dr. Karen Heslop.

A42. Who will have control of and act as the custodian for the data generated by the study?

	Title Forename/Initials Surname
	Dr Karen Heslop-Marshall
Post	Respiratory Research Nurse
Qualifications	BSc, MSc, PhD
Work Address	Royal Victoria Infirmary Queen Victoria Road Newcastle Upon Tyne
Post Code	NE14LP
Work Email	Karen.Heslop@nuth.nhs.uk
Work Telephone	07753884774
Fax	

A43. How long will personal data be stored or accessed after the study has ended?

- Less than 3 months
 3 – 6 months
 6 – 12 months
 12 months – 3 years
 Over 3 years

A44. For how long will you store research data generated by the study?

Years: 15
Months: 0

A45. Please give details of the long term arrangements for storage of research data after the study has ended. Say where data will be stored, who will have access and the arrangements to ensure security.

Data which is anonymised will be retained on password protected encrypted computers. Paper records will be stored securely by the R&D department.

INCENTIVES AND PAYMENTS**A46. Will research participants receive any payments, reimbursement of expenses or any other benefits or incentives for taking part in this research?**

- Yes No

A47. Will individual researchers receive any personal payment over and above normal salary, or any other benefits or incentives, for taking part in this research?

- Yes No

A48. Does the Chief Investigator or any other investigator/collaborator have any direct personal involvement (e.g. financial, share holding, personal relationship etc.) in the organisations sponsoring or funding the research that may give rise to a possible conflict of interest?

- Yes No

NOTIFICATION OF OTHER PROFESSIONALS

A49-1. Will you inform the participants' General Practitioners (and/or any other health or care professional responsible for their care) that they are taking part in the study?

Yes No

If Yes, please enclose a copy of the information sheet/letter for the GP/health professional with a version number and date.

PUBLICATION AND DISSEMINATION

A50. Will the research be registered on a public database?

The UK Policy Framework for Health and Social Care Research sets out the principle of making information about research publicly available. Furthermore: Article 19 of the World Medical Association Declaration of Helsinki adopted in 2008 states that "every clinical trial must be registered on a publicly accessible database before recruitment of the first subject"; and the International Committee of Medical Journal Editors (ICMJE) will consider a clinical trial for publication only if it has been registered in an appropriate registry. Please see guidance for more information.

Yes No

Please give details, or justify if not registering the research.
Clinicaltrials.gov

Please ensure that you have entered registry reference number(s) in question A5-1.

A51. How do you intend to report and disseminate the results of the study? Tick as appropriate:

- Peer reviewed scientific journals
 Internal report
 Conference presentation
 Publication on website
 Other publication
 Submission to regulatory authorities
 Access to raw data and right to publish freely by all investigators in study or by Independent Steering Committee on behalf of all investigators
 No plans to report or disseminate the results
 Other (please specify)

A52. If you will be using identifiable personal data, how will you ensure that anonymity will be maintained when publishing the results?

We will not use identifiable data in this study

A53. Will you inform participants of the results?

Yes No

Please give details of how you will inform participants or justify if not doing so.
By holding a patient forum. We anticipate that the participants will value the opportunity to not only be informed of the results, but to discuss the implications with the investigators.

5. Scientific and Statistical Review

A54. How has the scientific quality of the research been assessed? Tick as appropriate:

- Independent external review
- Review within a company
- Review within a multi-centre research group
- Review within the Chief Investigator's institution or host organisation
- Review within the research team
- Review by educational supervisor
- Other

Justify and describe the review process and outcome. If the review has been undertaken but not seen by the researcher, give details of the body which has undertaken the review:

A review of previous literature and a number of systematic reviews have suggested that physical activity alongside pulmonary rehabilitation was unable to provide significant improvements in daily physical activity due to a lack of a behavioural intervention to relay the relevant information around improving everyday activities.

For all studies except non-doctoral student research, please enclose a copy of any available scientific critique reports, together with any related correspondence.

For non-doctoral student research, please enclose a copy of the assessment from your educational supervisor/ institution.

A56. How have the statistical aspects of the research been reviewed? Tick as appropriate:

- Review by independent statistician commissioned by funder or sponsor
- Other review by independent statistician
- Review by company statistician
- Review by a statistician within the Chief Investigator's institution
- Review by a statistician within the research team or multi-centre group
- Review by educational supervisor
- Other review by individual with relevant statistical expertise
- No review necessary as only frequencies and associations will be assessed – details of statistical input not required

In all cases please give details below of the individual responsible for reviewing the statistical aspects. If advice has been provided in confidence, give details of the department and institution concerned.

	Title	Forename/Initials	Surname
	Professor	Ioannis	Vogiatzis
Department	Sport, Exercise and Rehabilitation, Faculty of Health and Life Sciences		
Institution	Northumbria University of Newcastle		
Work Address	Northumberland Building Newcastle		
Post Code	NE1 8ST		
Telephone	01913496446		
Fax			
Mobile			
E-mail	ioannis.vogiatzis@northumbria.ac.uk		

Please enclose a copy of any available comments or reports from a statistician.

A57. What is the primary outcome measure for the study?

The primary outcome is patient compliance with the physical activity promotion intervention. Compliance is defined as a minimum of 4 days per week with valid step count data (>70 steps/day).

A58. What are the secondary outcome measures?(if any)

The secondary aims are to assess:

- Change in physical activity using a validated accelerometer.
- Mean change in Hospital Anxiety and Depression Scores assessed by the HADS questionnaire.
- Mean change in quality of life scores assessed by St' Georges Respiratory Questionnaire (StGRQ).
- Exercise capacity assessed by the 6-min walking test (6MWT).

A59. What is the sample size for the research? How many participants/samples/data records do you plan to study in total? If there is more than one group, please give further details below.

Total UK sample size: 40

Total international sample size (including UK):

Total in European Economic Area:

Further details:

We are going to allocate 40 patients into two groups of 20 patients. Group A will undertake physical activity promotion alongside standard care pulmonary rehabilitation, whilst Group B will undertake standard care pulmonary rehabilitation only.

A60. How was the sample size decided upon? If a formal sample size calculation was used, indicate how this was done, giving sufficient information to justify and reproduce the calculation.

This is a feasibility study and key outcomes of interest relate to adherence to using a step counter a means to increase daily physical activity. However, clinical outcome data will be collected and reported to help inform a future randomised controlled trial. Feasibility data will be summarised using standard descriptive statistics, depending on the level of data (e.g. mean, median, standard deviation, range). Inferential analysis to assess the significance of differences between groups will be used sparingly. The inferential tests used will also reflect the nature of the data.

A61. Will participants be allocated to groups at random?

Yes No

If yes, please give details of the intended method of randomisation:

Randomisation will be performed independently, with 1:1 allocation using stratification, variables: HADS (8 or above) and 6MWT (above or below 350m).

A62. Please describe the methods of analysis (statistical or other appropriate methods, e.g. for qualitative research) by which the data will be evaluated to meet the study objectives.

Statistical analyses will be supported by standard statistical software (e.g. SPSS, SAS) as required. This is a feasibility study and key outcomes of interest relate to adherence, attendance and drop out rather than clinical outcomes. However, clinical outcome data (steps/day) will be collected and reported to help inform a future randomized controlled trial. Feasibility data will be summarized using standard descriptive statistics, depending on the level of the data (e.g. mean, median, standard deviation, range). Baseline characteristics between groups will be assessed by t-tests for independent samples. Differences between groups across different time points will be assessed by a two-way ANOVA with repeated measures followed by appropriate post-hoc analysis. The Level of significance is set at $p < 0.05$.

6. MANAGEMENT OF THE RESEARCH

A63. Other key investigators/collaborators. Please include all grant co-applicants, protocol co-authors and other key members of the Chief Investigator's team, including non-doctoral student researchers.

	Title	Forename/Initials	Surname
	Professor	Ioannis	Vogiatzis
Post	Professor of Rehabilitation Sciences		
Qualifications	Ph.D. (Glasgow University), M.Sc. (University of Sheffield), B.Sc. (University of Athens)		
Employer	Northumbria University		
Work Address	Northumberland Building Newcastle		
Post Code	NE1 8ST		
Telephone	01913495446		
Fax			
Mobile			
Work Email	ioannis.vogiatzis@northumbria.ac.uk		
	Title	Forename/Initials	Surname
	Dr	Karen	Heslop
Post			
Qualifications	BSc, MSc, PhD		
Employer	Newcastle Upon Tyne Health Care Trust		
Work Address	Royal Victoria Infirmary Queen Victoria Road		
Post Code	NE14LP		
Telephone	07753884774		
Fax			
Mobile			
Work Email	Karen.Heslop@nuth.nhs.uk		

A64. Details of research sponsor(s)

A64-1. Sponsor

Lead Sponsor	
Status:	Commercial status:
<input checked="" type="radio"/> NHS or HSC care organisation <input type="radio"/> Academic <input type="radio"/> Pharmaceutical industry <input type="radio"/> Medical device industry <input type="radio"/> Local Authority <input type="radio"/> Other social care provider (including voluntary sector or private organisation) <input type="radio"/> Other	Non-Commercial
<i>If Other, please specify:</i>	

Contact person

Name of organisation The Newcastle upon Tyne NHS foundation trust R&D
Given name Aaron Jackson
Family name Jackson
Address Regent Point (Level 1)
Town/city Gosforth
Post code NE33HD
Country UNITED KINGDOM
Telephone 01912825789
Fax
E-mail Aaron.jackson@nuth.nhs.uk

A65. Has external funding for the research been secured?

Please tick at least one check box.

- Funding secured from one or more funders
 External funding application to one or more funders in progress
 No application for external funding will be made

What type of research project is this?

- Standalone project
 Project that is part of a programme grant
 Project that is part of a Centre grant
 Project that is part of a fellowship/ personal award/ research training award
 Other

Other – please state:

A66. Has responsibility for any specific research activities or procedures been delegated to a subcontractor (other than a co-sponsor listed in A64-1)? Please give details of subcontractors if applicable.

- Yes No

A67. Has this or a similar application been previously rejected by a Research Ethics Committee in the UK or another country?

- Yes No

Please provide a copy of the unfavourable opinion letter(s). You should explain in your answer to question A6-2 how the reasons for the unfavourable opinion have been addressed in this application.

A68-1. Give details of the lead NHS R&D contact for this research:

	Title Forename/Initials Surname Mr Aaron Jackson
Organisation	Newcastle Upon Tyne Health Care Trust
Address	Newcastle Joint Research Office Level 1 Regent Point Regent Farm Road
Post Code	NE33HD
Work Email	aaron.jackson@nuth.nhs.uk
Telephone	01912825059
Fax	
Mobile	

Details can be obtained from the NHS R&D Forum website: <http://www.rdforum.nhs.uk>

A69-1. How long do you expect the study to last in the UK?

Planned start date: 01/10/2018
 Planned end date: 30/09/2019
 Total duration:
 Years: 1 Months: 0 Days: 0

A71-1. Is this study?

- Single centre
 Multicentre

A71-2. Where will the research take place? (Tick as appropriate)

- England
 Scotland
 Wales
 Northern Ireland
 Other countries in European Economic Area

Total UK sites in study 1

Does this trial involve countries outside the EU?

- Yes No

A72. Which organisations in the UK will host the research? Please indicate the type of organisation by ticking the box and give approximate numbers if known:

- NHS organisations in England 1
 NHS organisations in Wales
 NHS organisations in Scotland
 HSC organisations in Northern Ireland
 GP practices in England
 GP practices in Wales
 GP practices in Scotland

<input type="checkbox"/> GP practices in Northern Ireland	
<input type="checkbox"/> Joint health and social care agencies (eg community mental health teams)	
<input type="checkbox"/> Local authorities	
<input type="checkbox"/> Phase 1 trial units	
<input type="checkbox"/> Prison establishments	
<input type="checkbox"/> Probation areas	
<input type="checkbox"/> Independent (private or voluntary sector) organisations	
<input checked="" type="checkbox"/> Educational establishments	1
<input type="checkbox"/> Independent research units	
<input type="checkbox"/> Other (give details)	
Total UK sites in study:	2

A73-1. Will potential participants be identified through any organisations other than the research sites listed above?

Yes No

A74. What arrangements are in place for monitoring and auditing the conduct of the research?

Trial Steering Committee - with an independent chair.
Internal monitoring to ensure compliance with GCP.

A75-1. What arrangements will be made to review interim safety and efficacy data from the trial? Will a formal data monitoring committee or equivalent body be convened?

The proposed project is standard clinical practice at RVI

If a formal DMC is to be convened, please forward details of the membership and standard operating procedures to the Research Ethics Committee when available. The REC should also be notified of DMC recommendations and receive summary reports of interim analyses.

A75-2. What are the criteria for electively stopping the trial or other research prematurely?

Unwillingness of patients to use step counters that is part of the physical activity promotion programme.

A76. Insurance/ indemnity to meet potential legal liabilities

Note: in this question to NHS indemnity schemes include equivalent schemes provided by Health and Social Care (HSC) in Northern Ireland

A76-1. What arrangements will be made for insurance and/or indemnity to meet the potential legal liability of the sponsor(s) for harm to participants arising from the management of the research? Please tick box(es) as applicable.

Note: Where a NHS organisation has agreed to act as sponsor or co-sponsor, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For all other sponsors, please describe the arrangements and provide evidence.

- NHS indemnity scheme will apply (NHS sponsors only)
 Other insurance or indemnity arrangements will apply (give details below)

Please enclose a copy of relevant documents.

A76-2. What arrangements will be made for insurance and/ or indemnity to meet the potential legal liability of the sponsor(s) or employer(s) for harm to participants arising from the design of the research? Please tick box(es) as applicable.

Note: Where researchers with substantive NHS employment contracts have designed the research, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For other protocol authors (e.g. company employees, university members), please describe the arrangements and provide evidence.

- NHS indemnity scheme will apply (protocol authors with NHS contracts only)
 Other insurance or indemnity arrangements will apply (give details below)

Please enclose a copy of relevant documents.

A76-3. What arrangements will be made for insurance and/ or indemnity to meet the potential legal liability of investigators/collaborators arising from harm to participants in the conduct of the research?

Note: Where the participants are NHS patients, indemnity is provided through the NHS schemes or through professional indemnity. Indicate if this applies to the whole study (there is no need to provide documentary evidence). Where non-NHS sites are to be included in the research, including private practices, please describe the arrangements which will be made at these sites and provide evidence.

- NHS indemnity scheme or professional indemnity will apply (participants recruited at NHS sites only)
 Research includes non-NHS sites (give details of insurance/ indemnity arrangements for these sites below)

Please enclose a copy of relevant documents.

A77. Has the sponsor(s) made arrangements for payment of compensation in the event of harm to the research participants where no legal liability arises?

- Yes No

Please enclose a copy of relevant documents.

A78. Could the research lead to the development of a new product/process or the generation of intellectual property?

- Yes No Not sure

PART C: Overview of research sites

Please enter details of the host organisations (Local Authority, NHS or other) in the UK that will be responsible for the research sites. For further information please refer to guidance.

Investigator identifier	Research site	Investigator Name	
IN1	<input checked="" type="radio"/> NHS/HSC Site	Forename	Karen
	<input type="radio"/> Non-NHS/HSC Site	Middle name	
		Family name	Heslop-Marshell
		Email	Karen.Heslop@nuth.nhs.uk
	Organisation name	Qualification (MD...)	BSc, MSc, PhD
	Address	Country	UNITED KINGDOM
	Post Code		
	Country		
IN2	<input type="radio"/> NHS/HSC Site	Forename	Ioannis
	<input checked="" type="radio"/> Non-NHS/HSC Site	Middle name	
		Family name	Vogiatzis
		Email	ioannis.vogiatzis@northumbria.ac.uk
	Institution name	Qualification (MD...)	Ph.D.
	Department name	Country	UNITED KINGDOM
	Street address		
	Town/city		
	Post Code		
	Country		

PART D: Declarations**D1. Declaration by Chief Investigator**

1. The information in this form is accurate to the best of my knowledge and belief and I take full responsibility for it.
2. I undertake to fulfil the responsibilities of the chief investigator for this study as set out in the UK Policy Framework for Health and Social Care Research.
3. I undertake to abide by the ethical principles underlying the Declaration of Helsinki and good practice guidelines on the proper conduct of research.
4. If the research is approved I undertake to adhere to the study protocol, the terms of the full application as approved and any conditions set out by review bodies in giving approval.
5. I undertake to notify review bodies of substantial amendments to the protocol or the terms of the approved application, and to seek a favourable opinion from the main REC before implementing the amendment.
6. I undertake to submit annual progress reports setting out the progress of the research, as required by review bodies.
7. I am aware of my responsibility to be up to date and comply with the requirements of the law and relevant guidelines relating to security and confidentiality of patient or other personal data, including the need to register when necessary with the appropriate Data Protection Officer. I understand that I am not permitted to disclose identifiable data to third parties unless the disclosure has the consent of the data subject or, in the case of patient data in England and Wales, the disclosure is covered by the terms of an approval under Section 251 of the NHS Act 2006.
8. I understand that research records/data may be subject to inspection by review bodies for audit purposes if required.
9. I understand that any personal data in this application will be held by review bodies and their operational managers and that this will be managed according to the principles established in the Data Protection Act 1998.
10. I understand that the information contained in this application, any supporting documentation and all correspondence with review bodies or their operational managers relating to the application:
 - ◊ Will be held by the REC (where applicable) until at least 3 years after the end of the study; and by NHS R&D offices (where the research requires NHS management permission) in accordance with the NHS Code of Practice on Records Management.
 - ◊ May be disclosed to the operational managers of review bodies, or the appointing authority for the REC (where applicable), in order to check that the application has been processed correctly or to investigate any complaint.
 - ◊ May be seen by auditors appointed to undertake accreditation of RECs (where applicable).
 - ◊ Will be subject to the provisions of the Freedom of Information Acts and may be disclosed in response to requests made under the Acts except where statutory exemptions apply.
 - ◊ May be sent by email to REC members.
11. I understand that information relating to this research, including the contact details on this application, may be held on national research information systems, and that this will be managed according to the principles established in the Data Protection Act 1998.
12. I understand that the main REC or its operational managers may share information in this application or supporting documentation with the Medicines and Healthcare products Regulatory Agency (MHRA) where it is relevant to the Agency's statutory responsibilities.
13. Where the research is reviewed by a REC within the UK Health Departments Research Ethics Service, I understand that the summary of this study will be published on the website of the National Research Ethics Service (NRES), together with the contact point for enquiries named below. Publication will take place no earlier than 3 months after issue of the ethics committee's final opinion or the withdrawal of the application.

Contact point for publication*(Not applicable for R&D Forms)*

NRES would like to include a contact point with the published summary of the study for those wishing to seek further information. We would be grateful if you would indicate one of the contact points below.

- Chief Investigator
- Sponsor
- Study co-ordinator
- Student
- Other – please give details
- None

Access to application for training purposes *(Not applicable for R&D Forms)*

Optional – please tick as appropriate:

I would be content for members of other RECs to have access to the information in the application in confidence for training purposes. All personal identifiers and references to sponsors, funders and research units would be removed.

This section was signed electronically by Ms karen heslop on 24/09/2018 18:40.

Job Title/Post: Nurse Consultant
Organisation: Newcastle upon Tyne NHS Foundation Trust
Email: karen.heslop@nuth.nhs.uk

D2. Declaration by the sponsor's representative

If there is more than one sponsor, this declaration should be signed on behalf of the co-sponsors by a representative of the lead sponsor named at A64-1.

I confirm that:

1. This research proposal has been discussed with the Chief Investigator and agreement in principle to sponsor the research is in place.
2. An appropriate process of scientific critique has demonstrated that this research proposal is worthwhile and of high scientific quality.
3. Any necessary indemnity or insurance arrangements, as described in question A76, will be in place before this research starts. Insurance or indemnity policies will be renewed for the duration of the study where necessary.
4. Arrangements will be in place before the study starts for the research team to access resources and support to deliver the research as proposed.
5. Arrangements to allocate responsibilities for the management, monitoring and reporting of the research will be in place before the research starts.
6. The responsibilities of sponsors set out in the UK Policy Framework for Health and Social Care Research will be fulfilled in relation to this research.

Please note: The declarations below do not form part of the application for approval above. They will not be considered by the Research Ethics Committee.

7. Where the research is reviewed by a REC within the UK Health Departments Research Ethics Service, I understand that the summary of this study will be published on the website of the National Research Ethics Service (NRES), together with the contact point for enquiries named in this application. Publication will take place no earlier than 3 months after issue of the ethics committee's final opinion or the withdrawal of the application.
8. Specifically, for submissions to the Research Ethics Committees (RECs) I declare that any and all clinical trials approved by the HRA since 30th September 2013 (as defined on IRAS categories as clinical trials of medicines, devices, combination of medicines and devices or other clinical trials) have been registered on a publically accessible register in compliance with the HRA registration requirements for the UK, or that any deferral granted by the HRA still applies.

This section was signed electronically by Mr Aaron Jackson on 24/09/2018 12:50.

Job Title/Post: RM&G Manager
Organisation: The Newcastle upon Tyne Hospitals NHS Foundation Trust
Email: trust.R&D@nuth.nhs.uk

D3. Declaration for student projects by academic supervisor(s)

1. I have read and approved both the research proposal and this application. I am satisfied that the scientific content of the research is satisfactory for an educational qualification at this level.

2. I undertake to fulfil the responsibilities of the supervisor for this study as set out in the UK Policy Framework for Health and Social Care Research.

3. I take responsibility for ensuring that this study is conducted in accordance with the ethical principles underlying the Declaration of Helsinki and good practice guidelines on the proper conduct of research, in conjunction with clinical supervisors as appropriate.

4. I take responsibility for ensuring that the applicant is up to date and complies with the requirements of the law and relevant guidelines relating to security and confidentiality of patient and other personal data, in conjunction with clinical supervisors as appropriate.

Academic supervisor 1

This section was signed electronically by Professor Ioannis Vogiatzis on 24/09/2018 12:50.

Job Title/Post: Professor of Rehabilitation Sciences
Organisation: Northumbria University
Email: ioannis.vogiatzis@northumbria.ac.uk

Appendix 4d: HRA Approval



Ymchwil Iechyd
a Gofal Cymru
Health and Care
Research Wales



Dr Karen Heslop
Newcastle Upon Tyne Health Care Trust
Royal Victoria Infirmary
Queen Victoria Road
NE14LP

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

2 October 2018

Dear Dr Heslop

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

Study title: A feasibility study assessing the inclusion of Physical Activity Promotion to standard care pulmonary rehabilitation and cognitive behavioural therapy in patients with COPD who are anxious or depressed.

IRAS project ID: 248697

Protocol number: 1.0

REC reference: 18/YH/0376

Sponsor Newcastle Upon Tyne NHS Foundation Trust

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

How should I continue to work with participating NHS organisations in England and Wales?
You should now provide a copy of this letter to all participating NHS organisations in England and Wales, as well as any documentation that has been updated as a result of the assessment.

This is a single site study sponsored by the site. The sponsor R&D office will confirm to you when the study can start following issue of HRA and HCRW Approval.

It is important that you involve both the research management function (e.g. R&D office) supporting each organisation and the local research team (where there is one) in setting up your study. Contact details of the research management function for each organisation can be accessed [here](#).

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?

HRA and HCRW Approval does not apply to NHS/HSC organisations within the devolved administrations of Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report (including this letter) has been sent to the coordinating centre of each participating nation. You should work with the relevant national coordinating functions to ensure any nation specific checks are complete, and with each site so that they are able to give management permission for the study to begin.

Please see [IRAS Help](#) for information on working with NHS/HSC organisations in Northern Ireland and Scotland.

How should I work with participating non-NHS organisations?

HRA and HCRW Approval does not apply to non-NHS organisations. You should work with your non-NHS organisations to [obtain local agreement](#) in accordance with their procedures.

What are my notification responsibilities during the study?

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

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

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

I am a participating NHS organisation in England or Wales. What should I do once I receive this letter?

You should work with the applicant and sponsor to complete any outstanding arrangements so you are able to confirm capacity and capability in line with the information provided in this letter.

The sponsor contact for this application is as follows:

Name: Dr Karen Heslop
Tel: 07753884774
Email: Karen.Heslop@nuth.nhs.uk

Who should I contact for further information?

Please do not hesitate to contact me for assistance with this application. My contact details are below.

Your IRAS project ID is 248697. Please quote this on all correspondence.

Yours sincerely

Rachel Heron
Assessor

Email: hra.approval@nhs.net

Appendix 4e: REC Approval



Yorkshire & The Humber - Sheffield Research Ethics Committee
NHS Blood and Transplant Blood Donor Centre
Holland Drive
Newcastle upon Tyne
Tyne and Wear
NE2 4NQ

Telephone: 02071048122

12 September 2018

Dr Karen Heslop
Newcastle Upon Tyne Health Care Trust
Royal Victoria Infirmary
Queen Victoria Road
NE14LP

Dear Dr Heslop

Study title:	A feasibility study assessing the inclusion of Physical Activity Promotion to standard care pulmonary rehabilitation and cognitive behavioural therapy in patients with COPD who are anxious or depressed.
REC reference:	18/YH/0376
Protocol number:	1.0
IRAS project ID:	248697

Thank you for your application for ethical review, which was received on 07 September 2018. I can confirm that the application is valid and will be reviewed by the Proportionate Review Sub-Committee via correspondence.

One of the REC members is appointed as the lead reviewer for each application reviewed by the Sub-Committee. I will let you know the name of the lead reviewer for your application as soon as this is known.

Please note that the lead reviewer may wish to contact you by phone or email between 14.09.18 and 24.09.18 to clarify any points that might be raised by members and assist the Sub-Committee in reaching a decision.

If you will not be available between these dates, you are welcome to nominate another key investigator or a representative of the study sponsor who would be able to respond to the lead reviewer's queries on your behalf. If this is your preferred option, please identify this person to us and ensure we have their contact details.

You are not required to attend a meeting of the Proportionate Review Sub-Committee.

Please do not send any further documentation or revised documentation prior to the review unless requested.

Documents received

The documents to be reviewed are as follows:

Document	Version	Date
GP/consultant information sheets or letters	1.0	12 August 2018
IRAS Application Form [IRAS_Form_07092018]		07 September 2018
IRAS Application Form XML file [IRAS_Form_07092018]		07 September 2018
IRAS Checklist XML [Checklist_10092018]		10 September 2018
Participant consent form [Consort Form]	2.0	21 August 2018
Participant information sheet (PIS)	2.0	21 August 2018
Research protocol or project proposal [Protocol]	2.0	21 August 2018
Summary CV for Chief Investigator (CI) [Chief Investigator CV]		07 August 2018
Summary CV for student [Student CV]		08 August 2018
Summary CV for supervisor (student research) [Supervisor CV]		09 August 2018
Summary, synopsis or diagram (flowchart) of protocol in non technical language [Protocol Diagram]	1.0	08 August 2018

No changes may be made to the application before the meeting. If you envisage that changes might be required, you are advised to withdraw the application and re-submit it.

Notification of the Sub-Committee's decision

We aim to notify the outcome of the Sub-Committee review to you in writing within 21 calendar days from the date of receipt of a valid application.

If the Sub-Committee is unable to give an opinion because the application raises material ethical issues requiring further discussion at a full meeting of a Research Ethics Committee, your application will be referred for review to the next available meeting. We will contact you to explain the arrangements for further review and check they are convenient for you. You will be notified of the final decision within 60 days of the date on which we originally received your application. If the first available meeting date offered to you is not suitable, you may request review by another REC. In this case the 60 day clock would be stopped and restarted from the closing date for applications submitted to that REC.

Setting up sites in the NHS

All researchers and local research collaborators who intend to participate in this study at sites in the National Health Service (NHS) or Health and Social Care (HSC) in Northern Ireland should work with the relevant care organisation to ensure management permission is confirmed before the study begins. Guidance on how to work with sites is provided in the IRAS help section at <https://www.myresearchproject.org.uk/help/hlpnhshscr.aspx>

Final management permission will not be confirmed until after a favourable opinion has been given by this Committee, and all other relevant approvals for the research to begin are in place. Please contact the NHS R&D office at the lead site in the first instance for further guidance.

Communication with other bodies

All correspondence from the REC about the application will be copied to the research sponsor and to the R&D office for Newcastle upon Tyne NHS Foundation Trust. It will be your responsibility to ensure that other investigators, research collaborators and NHS care organisation(s) involved in the study are kept informed of the progress of the review, as necessary.

HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at <http://www.hra.nhs.uk/hra-training/>

18/YH/0376	Please quote this number on all correspondence
------------	--

Yours sincerely



Neil McCaffery
Deputy Regional Manager

Email: nrescommittee.yorkandhumber-sheffield@nhs.net

Copy to: *Dr Karen Heslop*
Mr Aaron Jackson, Newcastle Upon Tyne Health Care Trust

Appendix 4f: Capacity and Capability Approval

From: Caldicott@nuth.nhs.uk [<mailto:Caldicott@nuth.nhs.uk>]
Sent: 10 October 2018 15:09
To: Heslop, Karen (Nurse Consultant, Chest Clinic)
Cc: Trust Research & Development
Subject: Your Caldicott application has been accepted (ID: 6825)

Dear Karen Heslop

The Caldicott application you submitted for the following study has been accepted (ID: 6825)

"A feasibility study of Physical Activity Promotion to standard care pulmonary rehabilitation and cognitive behavioural therapy in patients with COPD who are anxious and/or depressed."

Thank you.

Richard Oliver
Head of Information Governance & Security
The Newcastle upon Tyne Hospitals NHS Foundation Trust
richard.oliver@nuth.nhs.uk
richard.oliver2@nhs.net

Appendix 4g: Research Passport Approval



The Newcastle upon Tyne Hospitals
NHS Foundation Trust

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

Tel: (0191) 233 6161

REF: LOA/SM

15th July 2020

Sent by email only to: matthew.armstrong@northumbria.ac.uk
Mr Matthew Armstrong

Dear Mr Armstrong

Letter of access for research (Research Project No: 8968)

This letter confirms your right of access to conduct research through The Newcastle upon Tyne Hospitals NHS Foundation Trust for the purpose and on the terms and conditions set out below. This right of access commences on 28th November 2018 and ends on 1st September 2020 unless terminated earlier in accordance with the clauses below.

Renewal of this agreement is your responsibility; if you wish to extend this study please apply by the 1st August 2020.

You have a right of access to conduct such research as confirmed in writing in the letter of permission for research from this NHS organisation. Please note that you cannot start the research until the Principal Investigator for the research project has received a letter from us giving permission to conduct the project.

The information supplied about your role in research at The Newcastle upon Tyne Hospitals NHS Foundation Trust has been reviewed and you do not require an honorary research contract with this NHS organisation. We are satisfied that such pre-engagement checks as we consider necessary have been carried out.

You are considered to be a legal visitor to The Newcastle upon Tyne Hospitals NHS Foundation Trust premises. You are not entitled to any form of payment or access to other benefits provided by this NHS organisation to employees and this letter does not give rise to any other relationship between you and this NHS organisation, in particular that of an employee.

While undertaking research through The Newcastle upon Tyne Hospitals NHS Foundation Trust, you will remain accountable to your employer Northumbria University but you are required to follow the reasonable instructions of Karen

Heslop in this NHS organisation or those given on their behalf in relation to the terms of this right of access.

Where any third party claim is made, whether or not legal proceedings are issued, arising out of or in connection with your right of access, you are required to co-operate fully with any investigation by this NHS organisation in connection with any such claim and to give all such assistance as may reasonably be required regarding the conduct of any legal proceedings.

You must act in accordance with The Newcastle upon Tyne Hospitals NHS Foundation Trust policies and procedures, which are available to you upon request, and the Research Governance Framework.

You are required to co-operate with The Newcastle upon Tyne Hospitals NHS Foundation Trust in discharging its duties under the Health and Safety at Work etc Act 1974 and other health and safety legislation and to take reasonable care for the health and safety of yourself and others while on The Newcastle upon Tyne Hospitals NHS Foundation Trust premises. You must observe the same standards of care and propriety in dealing with patients, staff, visitors, equipment and premises as is expected of any other contract holder and you must act appropriately, responsibly and professionally at all times.

You are required to ensure that all information regarding patients or staff remains secure and *strictly confidential* at all times. You must ensure that you understand and comply with the requirements of the NHS Confidentiality Code of Practice (www.dh.gov.uk/assetRoot/04/06/92/54/04069254.pdf) and the Data Protection Act 1998. Furthermore you should be aware that under the Act, unauthorised disclosure of information is an offence and such disclosures may lead to prosecution.

You should ensure that, where you are issued with an identity or security card, a bleep number, email or library account, keys or protective clothing, these are returned upon termination of this arrangement. Please also ensure that while on the premises you wear your ID badge at all times, or are able to prove your identity if challenged. Please note that this NHS organisation accepts no responsibility for damage to or loss of personal property.

We may terminate your right to attend at any time either by giving seven days' written notice to you or immediately without any notice if you are in breach of any of the terms or conditions described in this letter or if you commit any act that we reasonably consider to amount to serious misconduct or to be disruptive and/or prejudicial to the interests and/or business of this NHS organisation or if you are convicted of any criminal offence. Your substantive employer is responsible for your conduct during this research project and may in the circumstances described above instigate disciplinary action against you.

If you wish to terminate your post prior to the expiry date you are required to return your ID Badge and inform Trust Research and Development, the

nominated NHS Representative and the Senior HR Administrator as detailed below.

The Newcastle upon Tyne Hospitals NHS Foundation Trust will not indemnify you against any liability incurred as a result of any breach of confidentiality or breach of the Data Protection Act 1998. Any breach of the Data Protection Act 1998 may result in legal action against you and/or your substantive employer.

If your current role or involvement in research changes, or any of the information provided in your Research Passport changes, you must inform your employer through their normal procedures and inform your NHS Representative.

Yours sincerely



Ashleigh Logan
Workforce Services Team Leader

cc

HR Representative	Paul.Aqnew@northumbria.ac.uk
NHS Representative	Karen.Heslop@nuth.nhs.uk
Applicant Supervisor	Ioannis.Vogietzis@northumbria.ac.uk
R&D Representative	nuth.researchpassports@nhs.net

Enc Confidentiality Statement

Appendix 4h: GP Letter

[Doctor]
[Address]
[date]

Dear [Doctor]

Re [Patient, DOB, Address]

The above patient currently attends Clinic under the care of [Consultant]. [Patient] has agreed to participate in a feasibility study observing the effects of physical activity promotion and cognitive behavioural therapy alongside pulmonary rehabilitation on daily physical activity. The purpose of the study is to identify if physical activity promotion and cognitive behavioural therapy together can help to improve daily physical activity while undergoing standard care pulmonary rehabilitation in patients with COPD. We are following patients up to 8 weeks after randomisation.

[Patient] has been screened for both COPD using spirometry and anxiety and depression using the Hospital Anxiety & Depression Scale. This patient has been randomised and allocated to the [intervention or control] group. The intervention group will undertake weekly physical activity promotion sessions alongside their standard care pulmonary rehabilitation in the Chest Clinic, RVI. This patient will receive a pedometer at the start of the program in order to track daily steps. At every session, this patient will undergo a feedback session where daily step goals will be provided and motivational support to meet these goals will be received. Three sessions of CBT in the Chest Clinic, RVI will be conducted throughout the 8 weeks of rehabilitation. The control group will receive standard care, which includes pulmonary rehabilitation and CBT. If you require further information, please do not hesitate to contact me on the number below.

Yours sincerely

Dr Karen Heslop-Marshall
Nurse Consultant Respiratory Medicine
Chest Clinic, RVI
Tel 0191 - 2829095

Appendix 4i: Chapter 7 Participant Information Sheet

Participant Information Sheet

Title of Project: **A feasibility study assessing the inclusion of Physical Activity Promotion to standard care pulmonary rehabilitation and cognitive behavioural therapy in patients with COPD.**

Name of researcher: Matthew Armstrong MSc, BSc

We would like to invite you to take part in our research study. Joining the study is entirely up to you before you decide we would like you to understand why the research is being undertaken and what it would involve for you. One member of our team will go through this information sheet with you, to help you decide whether you would like to take part and answer any questions, you may have. This should take about 30 minutes. Please feel free to talk to others about the study if you wish.

The first part of the Participant Information Sheet tells you the purpose of the study and what will happen to you if you take part.

Then we give you more detailed information about the conduct of the study.

Do ask if anything is unclear.

What is the purpose of the study?

In patients who suffer COPD, daily physical activity is reduced compared to healthy individuals. Reduced levels of physical activity are associated with increased rates of hospital admission and mortality. Interventions such as physical activity promotion have been found to improve engagement in physical activity and alongside pulmonary rehabilitation have been found to promote a healthy physically active lifestyle. To date no study has incorporated physical activity promotion alongside an intervention to adapt behaviour. Therefore, we aim to incorporate both physical activity promotion and cognitive behavioural therapy to the standard care pulmonary rehabilitation at the Royal Victoria Infirmary.

Why have you been chosen?

You have been chosen because you are a patient with COPD referred from the chest clinic to a programme of pulmonary rehabilitation at the Royal Victoria Infirmary. If you report a score of ≥ 8 on the HADS questionnaire you will be referred to Dr Karen Heslop for sessions of Cognitive Behavioural Therapy, conducted throughout your pulmonary rehabilitation programme. If you don't report a score of ≥ 8 on the HADS questionnaire then you will only be referred to pulmonary rehabilitation. Both Pulmonary rehabilitation and Cognitive behavioural therapy are part of your standard care and will not be affected by your decision in regard to this study.

What the study involves?

The added physical activity promotion intervention will include: 1) a step-counter with a digital display, 2) a semi-structured interview discussing motivation issues, favourite activities, and strategies to become more active; 3) a tailored physical activity coaching plan including an individualized daily activity goal (steps) revised weekly. The physical activity promotion intervention will take place over telephone and will only require a 5-10-minute conversation with a member of the research team each week. During this time a conversation will be held to discuss the previous weeks daily step count (reported from step-counters), leading to a new weekly step goal being set.

Who would usually be admitted?

In this study, the participants will be COPD patients who experience breathlessness and locomotor muscle discomfort during activities of daily living. If a HADS score of ≥ 8 for either anxiety and/or depression is reported then a referral for CBT would be arranged and patients would have shown interest to receive this behavioural intervention. If a HADS score of < 8 for either anxiety and/or depression is reported then patients would be allocated to pulmonary rehabilitation only.

Where the study will be conducted?

The study will take place over telephone as part of your home-based pulmonary rehabilitation programme, part of the Newcastle upon Tyne Health Care Trust.

How long will the study last; when will it start and end?

As per the updated standard practice due to the COVID-19 pandemic, the study will involve one hospital visit prior to the initiation of the pulmonary rehabilitation programme and one hospital visit after completion of the pulmonary rehabilitation program in order to provide questionnaires and complete a number of small tests to assess the effects of pulmonary rehabilitation on your functional capacity and symptoms. The program itself will last a total of 8 weeks. During each home-based rehabilitation session, exercises will be provided using a home-exercise booklet and/or 4G tablet, with example videos and clear explanations of how to safely complete each exercise. The physical activity promotion intervention will take place over telephone once per week in conjunction with telephone calls from the respiratory physiotherapist team.

Do I have to take part?

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

If you decide not to take part, you will continue to receive the same usual care treatment.

What is physical activity promotion?

The physical activity (PA) promotion intervention will include: 1) a step-counter with a digital display, 2) a telephone based semi-structured interview discussing motivation issues, favourite activities, and strategies to become more active; 3) a tailored physical activity coaching plan including an individualized daily activity goal (steps) revised weekly.

Cognitive behavioural modification?

Cognitive behavioural modification is made up of four elements; behaviour, cognition/thoughts, feelings/emotions, physical sensations. A number of techniques will be used to aid symptoms of anxiety and depression including; education on anxiety and depression and COPD, distraction techniques, breathing control and relaxation and rating achievement/pleasure of physical activities.

What are the possible disadvantages and risks to taking part?

It is likely to feel breathless or experience muscle discomfort during the PR programme, nevertheless it is expected to recover very quickly after each session. Exercise is good for you.

What are the advantages to taking part?

You will have the chance to experience the positive effects of pulmonary rehabilitation and your results will contribute to inform clinical service in the future so that an optimal form of exercise training is prescribed to patients in the future.

Will my personal information be kept confidential?

During the study, we will collect information from you about your health and well-being. Your personal information such as your name and date of birth will be kept confidential and only available to the research team. The information given will only be used in a way that cannot be traced back to you, and any personal information will be stored securely. With your permission, we will write to your GP to let him/her know that you are taking part in the study. No one outside the research team will know if you decide not to take part.

What if there is a problem or I need more information?

If you wish to complain, or have any concerns about the study, please ask to speak to the physicians who oversee the study and will do his/her best to answer your questions. If you are still unhappy, you can complain formally using the normal NHS complaints channels.

What will happen with the results of the study?

The results will be discussed at scientific medical meetings and will be published in medical journals so that others can learn from our findings. You can receive a copy of the results by contacting Dr. Karen Heslop-Marshall.

Newcastle upon Tyne Healthcare trust is the sponsor for this study based in England. We will be using information from you and/or your medical records in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. Newcastle upon Tyne Healthcare trust will keep identifiable information about you for three years after the study has finished.

Your rights to access change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we already have obtained. To safeguard your rights, we will use the minimum personally identifiable information possible.

You can find out more about how we use your information by contacting the Respiratory Nurse Consultant in charge of this study, who's contact details can be found below;

Dr. Karen Heslop-Marshall, Chest Clinic, RVI Hospital.

Telephone: 0191 282 29095

Email: karen.heslop@nuth.nhs.uk

Mr Matthew Armstrong, Department for Health and Life Sciences, Northumbria University,

Telephone: 07495155142

Email: matthew.armstrong@northumbria.ac.uk

Appendix 4j: Chapter 7 Informed Consent Form

CONSENT FORM

Title of Project: **A feasibility study assessing the inclusion of Physical Activity Promotion to standard care pulmonary rehabilitation in patients with COPD.**

Name of Researcher: **Matthew Armstrong**

Please read the following statements, placing an initial in each box to confirm that you have read and agreed the terms required. Once complete please provide your name, date of completion and a signature on the lines provided. On completion of this consent form, the original copy will be kept alongside the study documents and a copy will be made for your personal use.

1. / I confirm that I have read the information sheet dated..... (version.....) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.

2. / I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.

/

3. I understand that the information collected about me will be used to support other research in the future and may be shared anonymously with other researchers.

4. / I agree to my General Practitioner being informed of my participation in the study. / I agree to my General Practitioner being involved in the study, including any necessary exchange of information about me between my GP and the research team.

5. / I understand that the information held and maintained by _____ [(enter name of organisation(s) that will be providing you with data, including any NHS/HSC organisations)] may be used to help contact me or provide information about my health status.

/

6. I agree to take part in the above study.

Name of Participant Date Signature

Name of research Date Signature



Participants WANTED

Healthy males and females aged 60-80.

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



Why?

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

What's involved?

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

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

What Next?

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



**Northumbria
University**
NEWCASTLE

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



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

PARTICIPANT INFORMATION SHEET

You have been invited to take part in a research study. Before you decide whether to participate, it is important for you to understand why the research is being carried out and what it will involve. Please take time to read the information carefully, discuss it with others and ask any questions you may have.

1. What is the purpose of the study?

Physical activity can provide immediate and long-term health benefits for everyone. The World Health Organisation recommends that adults should aim to achieve 150

minutes of moderate or 75 minutes of vigorous activity per week. Reaching these guidelines can lead to improvements in many aspects of health including fitness, psychological well-being and reduce the risk of developing chronic conditions such as type 2 diabetes and cancer.

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

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

2. Who can take part?

You have been chosen because you are a healthy individual aged between 18-80 years of age with low to moderate levels of everyday physical activity. Before you can be enrolled onto this research study you must be able to meet the study inclusion criteria which will be outlined by a member of the research team during enrolment/screening over telephone.

3. Do I have to take part?

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

4. What would taking part involve?

If interested in the study, a member of the research team will ask you to provide informed consent. If you chose to take part, you will need to attend Northumbria University on two separate occasions. Each visit should last no longer than 60 minutes.

During visit 1, you will be asked to complete a short physical activity questionnaire and an assessment of your lung function will be conducted. A member of the research team will then check that you meet the study inclusion/exclusion criteria. Following this, you will perform an 8-minute walking protocol on a treadmill, which will involve walking for 2 minutes with no incline at 4 different speeds (2.5, 3, 3.5 and 4 km/h). Whilst walking you will be required to attach a pedometer to your waist and wrist, as well as an activity tracker around your waist. Throughout the walking protocol, a video camera will record the number of steps that you take, so that this number can be compared to the pedometer and activity tracker.

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

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

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

5. Are there any expense of payments involved?

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

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

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

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

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

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

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

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

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

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

10. Who is funding the study?

This study has not received any funding.

11. What happens if I have a complaint?

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

12. Who has reviewed this study?

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

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

Contact Information

For further information please contact:

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

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

Professor Ioannis Vogiatzis (Chief Investigator)

Email: ioannis.vogiatzis@northumbria.ac.uk

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

Appendix 4m: Chapter 5 & 6 Informed Consent Form

Normative daily physical activity levels in elderly healthy individuals living in the North east of England.

INFORMED CONSENT FORM

1. I confirm that I have read and understood the participation information sheet provided for the above study. I have had the opportunity to consider and discuss the information, ask questions and have had these answered satisfactory.

2. I understand that my participation is voluntary, and I am free to withdraw from the study at any time, without having to give any reason and without prejudice

3. I understand that any personal information collected during this study will be anonymised and may be used to support other future research

4. I agree to my General Practitioner (GP) being informed of any results that are indicative of requiring treatment

5. I understand that my participation in this research study involves exposure to radiation in addition to what I may receive as part of my standard care

6. I understand that if I would like to receive feedback on the overall results of the study I must contact the researcher at: matthew.armstrong@northumbria.ac.uk

7. I agree to take part in the above study

Statement by the researcher

I can confirm that the participant was given the information sheet and the opportunity to ask any questions or queries related to this study. All the questions asked by the participant have been answered correctly and to the best of my ability the participant understands what they are required to do. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

Appendix 4n: Project Tailored Patient Questionnaire

A feasibility study assessing the inclusion of Physical activity Promotion to standard care pulmonary rehabilitation and cognitive behavioural therapy in patients with COPD.

Patient satisfaction form

Participant ID:

Completion Date: / /
DAY MONTH YEAR

How much did you enjoy taking part in this activity program?

- I liked it a lot
- I liked it

- Neutral
- I did not like it
- No opinion

Explain why?

.....

.....

.....

.....

Did the intervention **coach you in increasing** your physical activity outside of pulmonary rehabilitation?

- Yes, it helped me a lot
- Yes, a little bit
- Not noticeable
- No, not at all
- No, it rather discouraged me

Explain why?

.....

.....

.....

.....

How did you **experience the weekly increases** proposed during the intervention?

- Much too low
- A little bit too low
- Reasonable
- A little bit to high

- Much too high

Explain why?

.....

.....

.....

.....

How was it for you to work with the **pedometer** provided?

- Very easy
- Easy
- Not easy, but I managed
- Difficult
- Very difficult

Explain why?

.....

.....

.....

.....

How useful did you find the following parts of the intervention for increasing physical activity?

1) The **step counter**

0 1 2 3 4 5 6 7 8 9 10

2) The **step count diary** provided

0 1 2 3 4 5 6 7 8 9 10

3) Daily **step goals** displayed on your step count diary each week

0 1 2 3 4 5 6 7 8 9 10

4) Activity **feedback** during each of the pulmonary rehabilitation sessions
 0 1 2 3 4 5 6 7 8 9 10

5) If your HADS levels were >8, **your sessions of CBT**
 0 1 2 3 4 5 6 7 8 9 10

How often did you (in general) perform the following actions?

	Several times per day	Once per day	Sometimes, but not every day	Once or twice per week	Never
Look at your step counter during the day					
Look and use your daily step diary					

Which part of the intervention would you be willing to use further in the future/recommend to future patients in your position?

- Nothing
- The step counter
- The step counter and daily step diary
- CBT (HADS >8 patients)
- Pulmonary rehabilitation alone
- All of the above interventions together

What component of the intervention would you like to change in the future?

Explain:

.....

.....
.....

.....
.....

Would you like to add a comment?

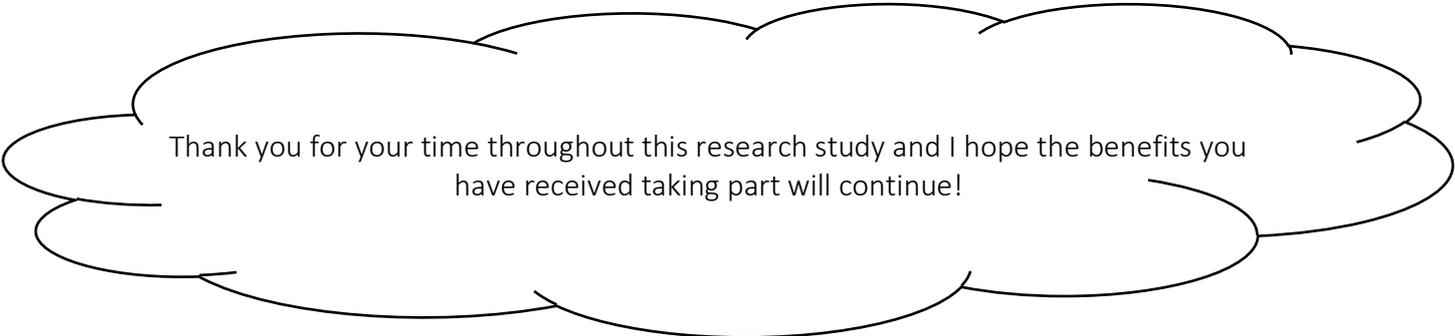
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Appendix 4o: C-PPAC Instrument

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

INSTRUCTIONS TO PATIENTS:

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

Please select the box next to the response that best applies to you **IN THE PAST 7 DAYS**. There are no wrong answers. We very much value your response.

	Difficulty score	Amount score
In the past 7 days, how much walking did you do outside?		
<input type="checkbox"/> None at all		0
<input type="checkbox"/> A little bit (about 10 minutes every day)		1
<input type="checkbox"/> Some (about 30 minutes every day)		2
<input type="checkbox"/> A lot (about 1 hour every day)		3
<input type="checkbox"/> A great deal (more than 1 hour every day)		3
In the past 7 days, how many chores did you do outside the house? Some examples are gardening, taking the rubbish out, or doing small errands.		
<input type="checkbox"/> None at all		0
<input type="checkbox"/> A few		1
<input type="checkbox"/> Some		2
<input type="checkbox"/> A lot		3
<input type="checkbox"/> A large amount		4
In the past 7 days, how much difficulty did you have getting dressed?		
<input type="checkbox"/> None at all	4	
<input type="checkbox"/> A little bit	3	
<input type="checkbox"/> Some	2	
<input type="checkbox"/> A lot	1	
<input type="checkbox"/> A great deal	0	
In the past 7 days, how much difficulty did you have getting out and about?		
<input type="checkbox"/> None at all	4	
<input type="checkbox"/> A little bit	3	
<input type="checkbox"/> Some	2	
<input type="checkbox"/> A lot	1	
<input type="checkbox"/> A great deal	0	
In the past 7 days, how often did you avoid doing activities because of your lung problems?		
<input type="checkbox"/> Not at all	4	
<input type="checkbox"/> Rarely	3	
<input type="checkbox"/> Sometimes	2	
<input type="checkbox"/> Frequently	1	

All the time 0

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

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

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

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

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

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

In the past 7 days, how often did you have to take breaks during your physical activities?

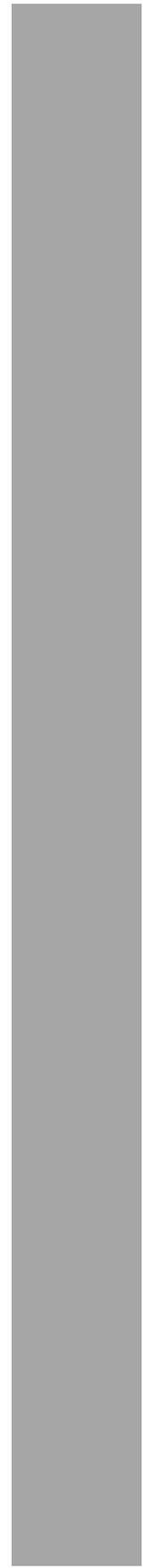
Not at all 4
 Rarely 3
 Sometimes 2
 Frequently 1
 All the time 0

In the past 7 days, how breathless were you when walking on level ground indoors and outdoors?

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

In the past 7 days, how much time did you need to recover from your physical activities?

None at all 4
 A little bit 3
 Some 2
 A lot 1

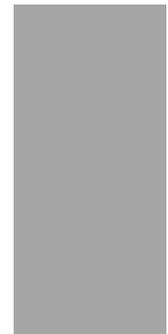


A great deal

In the past 7 days, did you need to consider your lung problems when you planned your activities because of your lung problems? Examples are a trip out, an appointment or expecting visitors.

- No
- A little bit
- Sometimes
- A lot
- A great deal

0
4
3
2
1
0



Weekly steps score

- 0
- 1
- 2
- 3
- 4

Measured by Actigraph

- <1000
- 1000-2000
- 2000-4000
- 4000-6000
- >6000

Measured by Dynaport

- <1500
- 1500-2500
- 2500-4500
- 4500-6500
- >6500

0
1
2
3
4

Weekly VMU score

- 0
- 1
- 2
- 3
- 4

Measured by Actigraph

- <100
- 100-200
- 200-300
- 300-500
- >500

Measured by Dynaport

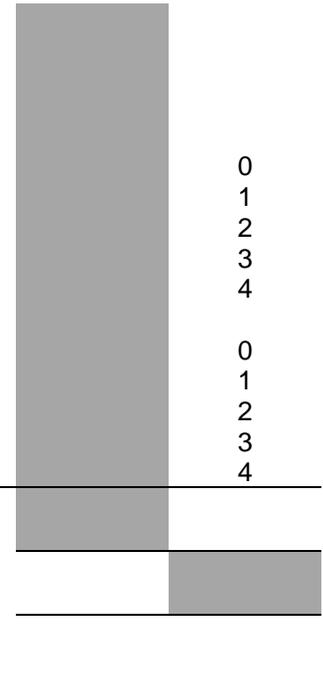
- <60
- 60-130
- 130-210
- 210-370
- >370

0
1
2
3
4

Amount scores (sum above):

Difficulty scores (sum above):

Total scores (sum above):



Appendix 4p: Modified Borg Scale

Shortness of Breath Modified Borg Dyspnea Scale	
0	Nothing at all
0.5	Extremely Slight (just noticeable)
1	Very Slight
2	Slight
3	Moderate
4	Somewhat Severe
5	Severe
6	
7	Very Severe
8	
9	Extremely Severe (almost maximal)
10	Maximal

Appendix 4q: Hospital Anxiety and Depression Scale

Hospital Anxiety and Depression Scale (HADS)

Tick the box beside the reply that is closest to how you have been feeling in the past week.
Don't take too long over you replies: your immediate is best.

D	A		D	A	
		I feel tense or 'wound up':			I feel as if I am slowed down:
	3	Most of the time	3		Nearly all the time
	2	A lot of the time	2		Very often
	1	From time to time, occasionally	1		Sometimes
	0	Not at all	0		Not at all
		I still enjoy the things I used to enjoy:			I get a sort of frightened feeling like 'butterflies' in the stomach:
0		Definitely as much	0		Not at all
1		Not quite so much	1		Occasionally
2		Only a little	2		Quite Often
3		Hardly at all	3		Very Often
		I get a sort of frightened feeling as if something awful is about to happen:			I have lost interest in my appearance:
	3	Very definitely and quite badly	3		Definitely
	2	Yes, but not too badly	2		I don't take as much care as I should
	1	A little, but it doesn't worry me	1		I may not take quite as much care
	0	Not at all	0		I take just as much care as ever
		I can laugh and see the funny side of things:			I feel restless as I have to be on the move:
0		As much as I always could		3	Very much indeed
1		Not quite so much now		2	Quite a lot
2		Definitely not so much now		1	Not very much
3		Not at all		0	Not at all
		Worrying thoughts go through my mind:			I look forward with enjoyment to things:
	3	A great deal of the time	0		As much as I ever did
	2	A lot of the time	1		Rather less than I used to
	1	From time to time, but not too often	2		Definitely less than I used to
	0	Only occasionally	3		Hardly at all
		I feel cheerful:			I get sudden feelings of panic:
3		Not at all		3	Very often indeed
2		Not often		2	Quite often
1		Sometimes		1	Not very often
0		Most of the time		0	Not at all
		I can sit at ease and feel relaxed:			I can enjoy a good book or radio or TV program:
	0	Definitely	0		Often
	1	Usually	1		Sometimes
	2	Not Often	2		Not often
	3	Not at all	3		Very seldom

Please check you have answered all the questions

Scoring:

Total score: Depression (D) _____ Anxiety (A) _____

0-7 = Normal

8-10 = Borderline abnormal (borderline case)

11-21 = Abnormal (case)

Appendix 4r: COPD Assessment Test

CAT Score – COPD Assessment test

NAME: -----

DATE-----

I never cough	1	2	3	4	5	I cough all the time
I have no phlegm (mucus) in my chest at all	1	2	3	4	5	My chest is full of phlegm (mucus)
My chest does not feel tight at all	1	2	3	4	5	My chest feels very tight
When I walk up stairs I am not breathless	1	2	3	4	5	When I walk up a hill or one flight of stairs I am very breathless
I am not limited Doing any Activities at home	1	2	3	4	5	I am very limited doing activities at home
I am confident leaving my home despite my lung condition	1	2	3	4	5	I am not confident at all leaving my home because of my lung condition
I sleep soundly	1	2	3	4	5	I don't sleep soundly because of my lung condition
I have lots of energy	1	2	3	4	5	I have no energy at all

SCORE: -----

Appendix 4s: Clinical COPD Questionnaire

CLINICAL COPD QUESTIONNAIRE							
Please circle the number of the response that best describes how you have been feeling during the past week . (Only one response for each question).							
On average, during the past week , how often did you feel:	never	hardly ever	a few times	several times	many times	a great many times	almost all the time
1. Short of breath at rest ?	0	1	2	3	4	5	6
2. Short of breath doing physical activities ?	0	1	2	3	4	5	6
3. Concerned about getting a cold or your breathing getting worse?	0	1	2	3	4	5	6
4. Depressed (down) because of your breathing problems?	0	1	2	3	4	5	6
In general, during the past week , how much of the time:							
5. Did you cough ?	0	1	2	3	4	5	6
6. Did you produce phlegm ?	0	1	2	3	4	5	6
On average, during the past week , how limited were you in these activities because of your breathing problems :	not limited at all	very slightly limited	slightly limited	moderately limited	very limited	extremely limited	totally limited /or unable to do
7. Strenuous physical activities (such as climbing stairs, hurrying, doing sports)?	0	1	2	3	4	5	6
8. Moderate physical activities (such as walking, housework, carrying things)?	0	1	2	3	4	5	6
9. Daily activities at home (such as dressing, washing yourself)?	0	1	2	3	4	5	6
10. Social activities (such as talking, being with children, visiting friends/relatives)?	0	1	2	3	4	5	6

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Appendix 4t: Medical Research Council Breathlessness Scale

The MRC Breathlessness Scale

Grade	Degree of breathlessness related to activities
1	Not troubled by breathlessness except on strenuous exercise
2	Short of breath when hurrying on the level or walking up a slight hill
3	Walks slower than most people on the level, stops after a mile or so, or stops after 15 minutes walking at own pace
4	Stops for breath after walking about 100 yds or after a few minutes on level ground
5	Too breathless to leave the house, or breathless when undressing

Appendix 7a: Randomisation Template

HADS \geq 8				HADS<8			
1		2		3		4	
6MWT <300M		6MWT >300M		6MWT <300M		6MWT >300M	
1		1		1		1	
2		2		2		2	
3		3		3		3	
4		4		4		4	
5		5		5		5	
6		6		6		6	
7		7		7		7	
8		8		8		8	
9		9		9		9	
10		10		10		10	
11		11		11		11	
12		12		12		12	
13		13		13		13	
14		14		14		14	
15		15		15		15	
16		16		16		16	
17		17		17		17	
18		18		18		18	
19		19		19		19	
20		20		20		20	

Appendix 7b: Step Diary

+

Daily step count									
Week									
Your daily step count was? (Please indicate).									
Your daily step goals were as followed:									
Has your daily step goal been met? (Please tick or cross). Yes ✓ No ✗									
How did you feel today? (Please number based on the faces below).									



1



2



3