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Exploring Pulmonary Rehabilitation Strategies for those with Respiratory Conditions

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Dedication

This thesis is dedicated to my father, Peter McCreery.

They say never meet your heroes, but I had the fortunate pleasure to call mine dad.

Thank you for everything.

"My father gave the greatest gift anyone could give another person, he believed in me."

- *Jim Valvano*

Abstract

Effective rehabilitation strategies are paramount to improve physiological and psychological health in pulmonary disease. The aim of this thesis was to investigate traditional and alternative pulmonary rehabilitation strategies in those with chronic respiratory disease.

Chapter Four found that traditional pulmonary rehabilitation (PR) was physiologically and psychologically effective, regardless of respiratory disease, with socioeconomic status being a key determinant of adherence. **Chapter Five** investigated the feasibility and acceptability of IMT. Children aged 10.8 ± 0.8 years with Cystic Fibrosis (CF) enjoyed the IMT intervention, perceiving improvements in their physical ability and psychosocial health. The care team highlighted that future interventions needed to be longer and to monitor engagement and adherence. **Chapter Six** assessed the effectiveness of an alternative rehabilitation strategy, using a four-week inspiratory muscle training (IMT) intervention, on lung function and heart rate variability in children with CF aged 10.8 ± 1.1 years. There were significant and clinically meaningful increases in respiratory muscle strength, a clinically meaningful decrease in sympathetic modulation, and decreases in respiratory symptoms. Subsequently, utilising the formative, physiological and psychological findings derived from **Chapters Five and Six,** an eight-week IMT intervention with live biofeedback, performed at 80% maximal inspiratory pressure, three times a week was implemented, with an eight-week optional IMT top-up. Overall, **Chapter Seven** found that eight weeks of IMT elicited significant increases in respiratory muscle strength, aerobic capacity and in CF-specific questionnaire domains in children (11.0 ± 2.2 years) with CF, which were maintained following the eight-week top-up period. **Chapter Eight** demonstrated significant improvements in inspiratory muscle strength and endurance after eight weeks, with sustained improvements in physiological health after 16-weeks in adults with bronchiectasis (64.5 ± 10.3 years). CF and bronchiectasis participants demonstrated high levels of adherence and reported competency and autonomy. Overall, IMT may be an effective and feasible alternative to pulmonary rehabilitation.

Declarations and Statements

Statement 1

I, Jessica Louise McCreery, hereby declare that the work presented in this thesis has not previously been accepted in substance for any degree and is not being concurrently in candidature for any degree.

Statement 2

I, Jessica Louise McCreery hereby declare that the thesis is the result of my own investigation, except where otherwise stated and that other sources are acknowledged by footnotes giving explicit references and that a bibliography is appended.

Statement 3

I, Jessica Louise McCreery, hereby gives consent for the thesis, if accepted, to be available for photocopying and for inter-library load, and for the title and summary to be made available to outside organisations.

Statement 4

I, Jessica Louise McCreery, hereby declare that all University ethical procedures have been followed and, where appropriate, ethical procedure has been granted.

Signed: _  _____(candidate)

Date: _____14/08/2020_____

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Abbreviations, Units and Symbols

Abbreviations

ATP	adenosine triphosphate
ANS	automatic nervous system
ANOVA	analysis of variance
BMI	body mass index
CF	cystic fibrosis
CFCS	cystic fibrosis clinical score
CFTR	cystic fibrosis transmembrane conductance regulator
CFQ	cystic fibrosis questionnaire
CFQ-R	cystic fibrosis questionnaire-revised
CI	confidence interval
CO_2	carbon dioxide
COPD	chronic obstructive pulmonary disease
CPET	cardiopulmonary exercise test
CRQD	chronic respiratory disease questionnaire
CT	computed tomography
ECG	electrocardiogram
EEG	electroencephalogram
ERS	European Respiratory Society
FFM	free fat mass
FEV_1	forced expiratory volume in 1 second

$FEV_{1\%predicted}$	forced expiratory volume in 1 second expressed as a percentage of predicted normative values
FIT	fatigue index test
FVC	forced vital capacity
$FVC_{\%predicted}$	forced vital capacity expression as a percentage of predicted normative values
GET	gas exchange threshold
HADS	hospital anxiety and depression scale
HF	high frequency
HR	heart rate
HR_{peak}	peak heart rate
HRQoL	health related quality of life
HRV	heart rate variability
ICC	interclass correlation coefficient
IME	inspiratory muscle endurance
IMS	inspiratory muscle strength
IMT	inspiratory muscle training
ISWT	intermittent shuttle walk test
LF	low frequency
LPA	light physical activity
MEP	mean expiratory pressure
METs	metabolic equivalents
MIP	mean inspiratory pressure
MPA	moderate physical activity
MVPA	moderate-to- vigorous physical activity

MVV	maximum voluntary ventilation
NHS	National Health Service
NREM	non-rapid eye movement
O_2	oxygen
OSA	obstructive sleep apnea
PA	physical activity
P.*aeuringosa*	pseudomonas aeruginosa
$PaCO_2$	arterial pressure of carbon dioxide
PaO_2	arterial pressure of oxygen
PEF	peak expiratory flow
P_{Imax}	maximal inspiratory pressure
PR	pulmonary rehabilitation
PWC	physical work capacity
PSQI	Pittsburgh sleep quality index
QoL	quality of life
REM	rapid eye movement
RER	respiratory exchange ratio
RMF	respiratory muscle function
RMMSD	root mean square of successive RR interval differences
RMT	respiratory muscle training
RPD	rating of perceived dyspnoea
RPE	rating of perceived exertion
RPM	revolutions per minute
SD	standard deviation

SDANN	standard deviation of the average NN intervals
SDNN	standard deviation of NN intervals
SDT	self-determination theory
SES	socioeconomic status
SGRQ	St George's respiratory questionnaire
S.Index	strength index
S_{max}	supramaximal verification
SMIP	sustained maximal inspiratory pressure
SP_{Imax}	sustained inspiratory muscle strength
SV	stroke volume
TLC	total lung capacity
TR	diaphragm thickening ratio
UK	United Kingdom
VC	vital capacity
$\dot{V}CO_2$	carbon dioxide output
$\dot{V}E$	minute ventilation
$\dot{V}_E/\dot{V}O_2$	ventilatory equivalent for oxygen
$\dot{V}_E/\dot{V}CO_2$	ventilatory equivalent of carbon dioxide
VIDD	ventilator-induced diaphragm dysfunction
VPA	vigorous physical activity
$\dot{V}O_2$	oxygen uptake
$\dot{V}O_{2max}$	maximal oxygen uptake
$\dot{V}O_{2peak}$	peak oxygen uptake
VT	ventilatory threshold

W	watts
WASO	wake after sleep onset
WHO	World Health Organisation
WHR	Waist to hip ratio
WIMD	Welsh index of multiple deprivation
W_{peak}	peak workload
WR	work rate
6MWT	six-minute walk test
5RM	five rep max

Units and Symbols

cm	centimetres
d	Cohen's effect size
kg	kilograms
$kg.m^2$	kilogram per metre squared
$l \cdot min^{-1}$	litres per minute
m	metres
min	minutes
$ml \cdot kg^{-1} \cdot min^{-1}$	millilitres per kilogram per minute
n	sample size
p	significance value
r	Pearson's correlation coefficient
s	seconds
$W \cdot min^{-1}$	watts per minute
~	approximately

Scientific Output

Publications

McCreery, J.L., Mackintosh, K.A., Cox, N.S., McNarry, M.A. (2018). Assessing the perceptions of inspiratory muscle training in children with cystic fibrosis and their multidisciplinary team: Mixed-methods study. *JMIR Paediatrics and Parenting*, 1(2). Chapter 5 99

McCreery, J.L., Mackintosh, K.A., McNarry, M.A. (2020). Effects of inspiratory muscle training on heart rate variability in children with cystic fibrosis: A pilot study. *Journal of Science in Sport and Exercise*. Chapter 6.....112

Published Abstracts

McCreery, J.L., Mackintosh, K.A., Duckers, J., Lines, T., Chamberlain, J., Jones, M., McNarry, M.A. (2019). P21 Influence of attendance rate on pulmonary rehabilitation in those with respiratory disease. *Thorax*, 74: A100. Chapter 4.....82

Conferences

McCreery, J.L., Mackintosh, K.A., McNarry, M.A. (2017). Qualitative study determining the views and opinions of cystic fibrosis children and their clinical care team on an inspiratory muscle intervention. Oral presentation at the 1st Pan Wales Postgraduate Conference in Sport, Health and Exercise Science, Swansea, Wales. Chapter 5 99

McCreery, J.L., Mackintosh, K.A., McNarry, M.A. (2018). An 8-week Inspiratory Muscle Training programme on the physiological and psychological health in those with Cystic Fibrosis. Poster presentation at the 7th International Society for Physical Activity and Health Congress, London, UK. Chapter 7 127

McCreery, J.L., Mackintosh, K.A., Duckers, J., Lines, T., Chamberlain, J., Jones, M., McNarry, M.A. (2019). Determination of pulmonary rehabilitation efficacy in those with respiratory disease. Poster presentation at the British Thoracic Society Winter Meeting 2019, London, UK. Chapter 4.....82

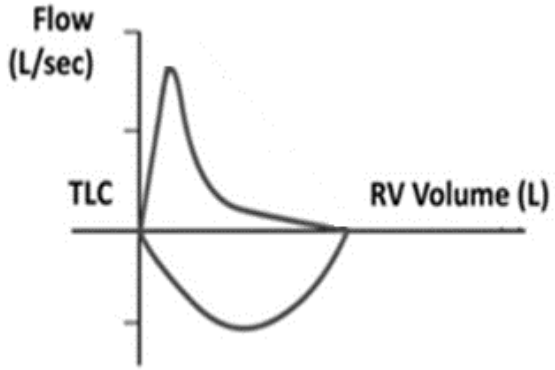
Chapter 1

Introduction

Respiratory diseases impose a significant health problem across the world, with more than 1 billion people worldwide suffering from either acute or chronic respiratory conditions (WHO, 2012). Whilst, globally, approximately 4 million people die prematurely from chronic respiratory diseases annually (Ferkol & Schraufnagel, 2014; WHO, 2014), the United Kingdom (UK) has the highest mortality rate from respiratory diseases in Europe (Salciccioli et al., 2018). Respiratory disease therefore represents a significant burden to individuals, to society and to the health service; it was recently estimated that respiratory diseases cost the NHS £11.1 billion annually (Trueman, Woodcock, & Hancock, 2017).

Chronic respiratory conditions can be separated into two categories; obstructive or restrictive lung disease (Figure 1.1). Obstructive lung diseases are characterised by increased airway resistance, airway secretions and ventilatory demand, dynamic hyperinflation, abnormalities of gas exchange and cardiovascular dysfunction (Dhand, 2005; Figure 1.1, A). Examples of obstructive lung disease include chronic obstructive pulmonary disease (COPD), asthma, bronchiectasis and cystic fibrosis (CF). Conversely, restrictive lung diseases, such as interstitial lung disease, sarcoidosis, pulmonary fibrosis and silicosis typically present as dyspnoeic with an increased respiratory centre drive resulting from decreased lung elasticity (Dimarco, Kelsen, Cherniack, & Gothe, 1983; Renzi, Milic-Emili, & Grassino, 1982; Figure 1.1, B). Despite having inherently different pathophysiologies, both obstructive and restrictive lung disease share a number of common manifestations, such as dyspnoea, coughing, fatigue and physical inactivity (Varadi & Goldstein, 2010). Additionally, those with chronic respiratory disease often experience secondary peripheral muscular, as well as cardiac, nutritional and psychologic impairments, which both individually and in combination with the primary respiratory condition can further limit exercise capacity and health-related quality of life (HRQoL; Varadi & Goldstein, 2010). This subsequently impacts on personal and family health, as well as necessitating increased health-care use.

A. Obstructive Lung Disease



B. Restrictive Lung Disease

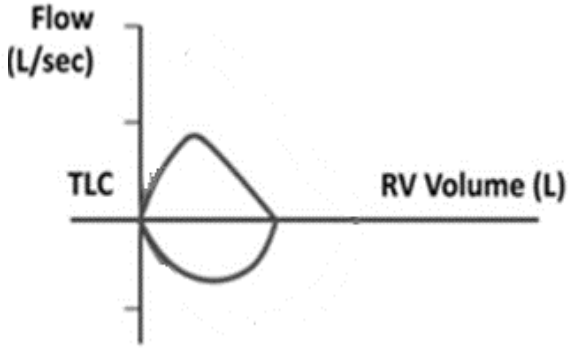


Figure 1.1 Example of A) obstructive and B) restrictive disease flow volume loops.

Bronchiectasis is a chronic airway disease characterised by permanent destruction and dilation of large airways, bronchi and bronchioles (Cohen & Sahn, 1999; Martínez-García, Soler-Cataluña, Perpiñá-Tordera, Román-Sánchez, & Soriano, 2007). A vicious cycle of persistent bacterial colonisation, chronic inflammation of the bronchial mucosa and progressive tissue destruction is evident due to the dysfunction of mucociliary clearance (Barker, 2002). Impaired lung function in bronchiectasis leads to chronic airflow obstruction (Barker, 2002; Martínez-García, Perpiñá-Tordera, Román-Sánchez, & Soler-Cataluña, 2005; Wilson, Jones, O'Leary, Cole, & Wilson, 1997), with the degree of hyperinflation and lung diffusion capacity being independent predictors of mortality in this population (Loebinger et al., 2009). It has been reported that the presence of bronchiectasis worsens underlying disease prognosis and accelerates loss of pulmonary function (King et al., 2005; Mannino & Davis, 2006), with frequent exacerbations associated with a rapid decline in lung function (Martinez-Garcia, Soler-Cataluña, Perpiñá-Tordera, Roman-Sanchez, & Soriano, 2007), increased mortality and significantly reduced quality of life (Martínez-García et al., 2005; Martińez-García et al., 2013). There is an urgent need to identify long-term therapies that retard, or ameliorate, this decline in lung function and concomitant decrements in quality of life, as well as reduce exacerbations in those with bronchiectasis (Gibson, Loddenkemper, Sibille, Lundback, & Flecther, 2013). Bronchiectasis is a common feature of a variety of pulmonary diseases, with CF being the major inherited disease associated with bronchiectasis (Schafer et al., 2018). Indeed, CF is the most common cause of childhood bronchiectasis, with 50-70% of CF patients having computed tomography (CT) defined bronchiectasis by three to five years of age (Stick et al., 2009). Globally, in up to half of all cases of bronchiectasis

the cause cannot be identified (idiopathic; Schafer et al., 2018). These cases, in combination with several other known aetiologies, collectively fall under the category of 'non-cystic fibrosis' (non-CF) bronchiectasis (Boyton et al., 2016).

CF is a multisystem genetic disease and the most common monogenetic disease in Caucasian populations (Rowe, Hoover, Solomon, & Sorscher, 2016). The disease is caused by mutations in the *cystic fibrosis transmembrane conductance regulator* (CFTR) protein, which results in abnormal ion transport (Cutting, 2015). The altered fluid and salt transport properties alter cell-lining fluid and mucous qualities, leading to chronic upper and lower respiratory tract infection, bronchiectasis and end-stage lung disease (Molina & Hunt, 2017; Rowe et al., 2016). The progressive decline in lung function in those with CF has been linked to inflammatory-mediated airflow obstruction, yet emerging evidence suggests that inspiratory muscle weakness plays a key role (Sovtic, Minic, Markovic-Sovtic, & Trajkovic, 2018). Specifically, mechanical disadvantage is evident in those with CF due to airflow obstruction, which engenders hyperinflation, leading to sub-optimal shortening of the inspiratory muscles (Sharma et al., 2001). Therefore, strategies to address this inspiratory muscle weakness and mechanical disadvantage are of vital importance to improve quality of life (QoL; Zemanick et al., 2010) and even life expectancy (Cohen-Cymberknoh, Shoseyov, & Kerem, 2011).

Physical activity (PA) has been shown to positively impact the health and well-being of those with chronic respiratory conditions (Arne et al., 2009; O'Donovan et al., 2010). Indeed, in CF, increased PA levels have been associated with slower rates of decline in lung function (Wilkes, Scheniderman-Walker, Corey, 2007) and, consequently, longer survival (Nixon, Orenstein, Kelsey, & Doershuk, 1992). Moreover, those with bronchiectasis who undertake PA show improved physiological and psychological health compared to their peer who didn't partake (Lee, Hill, McDonald, & Holland, 2017; Mandal et al., 2012; Patel et al., 2019b). However, despite the importance of PA, there is little consensus regarding PA levels in those with CF, especially in children, with some reporting lower volumes of habitual PA (Aznar et al., 2014; Nixon, Orenstein, & Kelsey, 2001) whilst others found no significant differences (Jantzen et al., 2016; Mackintosh, Ridgers, Evans, & McNarry, 2018; Selvadurai, Blimkie, Cooper, Mellis, & Van Asperen, 2004) compared to their healthy peers. Indeed, current PA promotion in CF is limited to informal discussion

and generic advice as current assessments in CF clinics are not sufficient to provide information about habitual PA (Shelley et al., 2018). Habitual PA levels are less equivocal in the bronchiectasis population who are generally reported to be largely inactive, with few meeting PA guidelines (Bradley et al., 2015), and a significant proportion showing marked decreases in exercise tolerance and PA levels (Burtin & Hebestreit, 2015; Pehlivan, Niksarlıoğlu, Balcı, & Kılıç, 2019). Poor engagement in PA in both CF and bronchiectasis could be attributed to numerous factors, including, but not limited to, treatment burden, which increases with age and disease severity (Roberts & Hubbard, 2010; Williams & Stevens, 2013). Further research is important as the impact of disease on mental health and well-being, with mental state shown to affect compliance to treatments and, eventually, morbidity and mortality (de Bruyne, Eg, & Thavagnanam, 2017; Quittner et al., 2014). Therefore, it is imperative to ascertain the views of those with CF and bronchiectasis regarding PA and their involvement in interventions to ensure long-term adherence.

Perhaps one of the most widely implemented, non-pharmacological interventions for those with respiratory disease, pulmonary rehabilitation (PR) is a multi-faceted intervention incorporating education, behaviour change and exercise training components. Considerable research has focused on the utility of PR for those with respiratory diseases, with evidence regarding those with chronic obstructive pulmonary disease (COPD) considered relatively conclusive (Lacasse, Cates, McCarthy, & Welsh, 2015). However, the transferability of traditional PR programmes to other respiratory conditions largely remains to be elucidated. In bronchiectasis, PR is suggested to be associated with improvements in HRQoL, exercise capacity, clinical symptoms and frequency of exacerbations (Lee et al., 2017). In CF, PR may increase aerobic fitness (Klijn et al., 2004; Selvadurai et al., 2002), decrease the rate of decline, or indeed improve, lung function (Moorcroft, Dodd, Morris, & Webb, 2004; Schneiderman-Walker et al., 2000) and improve HRQoL (Selvadurai et al., 2004). However, many of these studies are characterised by potentially biased samples, with many patients either refusing to enrol on, or not completing, the PR programme (Steiner et al., 2017). Whilst the reason for this lack of engagement is unclear, high treatment burdens associated with CF and bronchiectasis may preclude patients from adhering to regular exercise and educational programmes (Metersky & ZuWallack, 2019). Moreover, chronic

respiratory diseases are highly varied, with differing aetiologies; the composition of PR programmes may, therefore, not be transferable from COPD. Indeed, the magnitude of effect in those studies that have reported beneficial effects of PR in other respiratory disease is, in general, considerably smaller than those elicited in COPD (Holland, Wadell, & Spruit, 2013). The considerable inter-study heterogeneities in PR composition, limits the interpretation of PR effectiveness in different respiratory conditions or the identification of whether the varying success is due to programme variations, adherence or disease-specific factors. Therefore, the acceptability and transferability of PR to respiratory diseases, other than COPD, is questionable. Alternative interventions that provide similar physiological and psychological benefits, whilst being time-efficient and, preferably, home-based, would be advantageous for these populations.

One alternative method to PR that has received increasing attention in clinical populations is inspiratory muscle training (IMT), which is a low cost and time-efficient training method (Polkey, Moxham, & Green, 2011). By utilising a restricted airflow breathing technique, IMT increases the load placed on the intercostal muscles and diaphragm, stimulating a hypertrophic response (Enright, Unnithan, Heward, Withnall, & Davies, 2006). Given that the force a skeletal muscle can generate depends on how effective it is at applying tensile force to a cross-sectional area (Rochester, 1988), stimulating a hypertrophic response in the inspiratory muscles and increasing their cross-sectional area may delay, or reverse, the complications of impaired inspiratory muscle function (Enright, Chatham, Ionescu, Unnithan, & Shale, 2004). Furthermore, a reduction in lung function and increased inspiratory muscle fatigue has been associated with an increase in metaboreflex resulting in sympathetic overactivity in those with bronchiectasis and COPD, suggesting an increased cardiorespiratory risk (Rached et al., 2015). Previous research has hypothesised that improving respiratory muscle function through IMT may, potentially, increase fatigue resistance and lessen sympathetic outflow (Ferreira et al., 2013). Therefore, if IMT has the potential to improve heart rate variability (HRV), it may improve lung function in those with CF and bronchiectasis, or vice-versa.

Previous research has shown equivocal results regarding the potential utility of IMT in both CF and bronchiectasis. Specifically, improvements in respiratory muscle strength and HRQoL have been reported in CF (Asher, Pardy, Coates, Thomas, &

Macklem, 1982; Bieli, Summermatter, Boutellier, & Moeller, 2017; De Jong, Van Aalderen, Kraan, Ko Ter, & Van Der Schans, 2001) and bronchiectasis (Liaw et al., 2011; Newall, Stockley, & Hill, 2005; Ozalp et al., 2019). Furthermore, improvements in vital capacity have been reported in CF (Sawyer & Clanton, 1993) and improvements in endurance and exercise capacity have recently been found in bronchiectasis (Ozalp et al., 2019). Nonetheless, Bieli and colleagues (2017) recently concluded that regular respiratory muscle endurance training was not supported in children with CF, with a recent Cochrane review also highlighting that the effect of IMT in CF is inconclusive due to insufficient evidence (Hilton & Solis-Moya, 2018). However, it is pertinent to note that, despite lung function decline on those with CF being manifest from early adolescence (Welsh, Robertson, & Ranganathan, 2014), there has been an almost exclusive focus on the effect of IMT in middle-aged populations with CF, with little known regarding its impact in youth. Indeed, there are significant physiological and age-related differences that may affect the plasticity and response to IMT, therefore, the current findings in adults with CF are unlikely to applicable to youth (Shei, Dekerlegand, Mackintosh, Lowman, & McNarry, 2019).

In bronchiectasis, it has been reported that the beneficial effects of IMT are limited to improvements in inspiratory and expiratory muscle strength (Liaw et al., 2011), or conversely, that IMT adds no additional advantage to those obtained through PR (Newall, Stockley, et al., 2005). The conflicting findings regarding the effectiveness of IMT, and inter-disease variability, are likely to be attributable to inter-study differences in the type of inspiratory muscle training (strength or endurance) and the intensity, duration and frequency of training. Furthermore, the equivocal findings regarding the effectiveness of IMT are also likely to be attributable to a lack of control of workload (Smith, Cook, Guyatt, Madhaven, & Oxman, 1991) or the volume at which training is applied (Hart et al., 2001), a failure to maintain overload on the inspiratory muscles throughout (Chatham, Baldwin, Griffiths, Summers, & Enright, 1999) and a lack of reporting of adherence or participant's perceptions. Inspiratory muscles are morphologically and functionally skeletal muscles and therefore adopting general training theory, inspiratory muscle gains should be achieved at 80-90% of maximal inspiratory pressure (MIP) whilst strength and/or endurance gains would be anticipated to be elicited at 60-80% of MIP, which is comparable to high-intensity training regimes in systemic exercise (Kraemer et al., 2002). When these physiological

training principles are applied to IMT, increases in lung volume, strength, total lung capacity and exercise capacity have been found in adults with CF (Enright, 2001), however whether this applicable to children with CF or those with bronchiectasis remains to be elucidated. More empirical research is required to ascertain whether IMT is a plausible intervention for those with a chronic respiratory condition.

1.1 General Aim

The overarching aim of this thesis was to investigate non-pharmacological strategies to enhance health and well-being in those with chronic respiratory conditions. Specifically, the aim was to determine whether the effectiveness of conventional PR was dependent on respiratory condition and to determine the acceptability and effectiveness of inspiratory muscle training as an alternative treatment method in those with a chronic respiratory condition. The specific aims of the experimental chapters (Chapters 4 to 8) are outlined in Table 1.1.

Table 1.1 Experimental study aims

	Aims
Chapter 4	To investigate the effectiveness and feasibility of PR in respiratory diseases other than COPD.
Chapter 5	To investigate the physiological and psychological effect of a pilot IMT intervention on HRV and respiratory function in children with CF.
Chapter 6	To elicit the perceptions and experiences of children, adolescents, and their multi-disciplinary team on their experiences of an IMT intervention.
Chapter 7	To investigate the physiological and psychological effects of an 8-week high-intensity IMT intervention in children with cystic fibrosis.
Chapter 8	To determine the physiological and psychological effects of a high-intensity IMT intervention on adults with non-CF bronchiectasis.

Chapter 2

Literature Review

2.1 Introduction to Obstructive Pulmonary Diseases

The anatomical and functional development of the respiratory system is susceptible to harmful infection, inflammation and trauma, as well as genetic disorders (Merkus et al., 2004). The potential resultant structural and/or functional damage to the lungs and airways is dependent on several factors, such as the timing, severity, duration of the damage, the host response and subsequent repair process and the effects of initial and chronic treatments (Merkus et al. 2004). Obstructive disease of the airways often result in weakness of the respiratory muscles, the advancement of which can result in respiratory muscle failure, which is ultimately fatal (Laghi & Tobin, 2003).

2.1.1 Pathophysiology of Non-Cystic Fibrosis Bronchiectasis

Mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene drive the earliest pathogenic events in epithelial cells that ultimately lead to the emergence of bronchiectasis (Schafer et al., 2015). Bronchiectasis is a major chronic pulmonary disease defined by infection, inflammation and the presence of chronic dilation of the bronchial wall (Chandrasekaran, Aogáin, Chalmers, Elborn, & Chotirmall, 2018). It is characterised by mild to moderate airflow obstruction (King, Holdsworth, Freezer, Villanueva, & Holmes, 2006) that usually worsens over time (de Vries, Chang, & Marchant, 2018; Wurzel et al., 2014). Clinical features include shortness of breath, cough, chronic daily sputum production and recurrent respiratory infection leading to increased morbidity and deterioration of quality of life (QoL; Keistinen, Säynäjäkangas, Tuuponen, & Kivelä, 1997; Lonni et al., 2015). Bronchiectasis has a wide range of causes and comorbidities, including, but not limited to, previous severe respiratory infection, impairment of ciliary clearance, allergic bronchopulmonary aspergillosis, and primary or secondary immunodeficiency (Lonni et al., 2015). Bronchiectasis can be found in a variety of pulmonary diseases, both genetically caused and acquired, such as severe pulmonary infections and CF, as well as being a feature of chronic obstructive pulmonary diseases, severe asthma or primary immunodeficiencies (Chalmer et al., 2015; Sidhu et al., 2014; McShane et al., 2013).

In children with CF, structural damage in the lungs associated with bronchiectasis has been evidenced in those as young as 10 weeks of age (Mott et al., 2012; Sly et al., 2009; Stick et al., 2009; Davis et al., 2007). In 50-70% of children with CF aged 3-5 years, CT defined bronchiectasis is evident (Mott et al., 2012; Stick et al., 2009; Wainwright et al., 2011). Despite receiving the best current respiratory therapy, bronchiectasis persists and progresses in approximately 75% of young children (Mott et al., 2012). The cause is unknown in half of all cases of bronchiectasis worldwide. Therefore, idiopathic cases together with other known aetiologies such as post-infectious and allergic hypersensitivity, fall under the category of non-CF bronchiectasis (Boyton & Altmann, 2016).

The most widely known model for the pathophysiology leading to bronchiectasis is termed “the vicious cycle hypothesis” (Cole, 1986). This model suggests that in, a genetically predisposed individual, an environmental insult stimulates a robust inflammatory response to pulmonary infection or damage, leading to subsequent structural damage that results in impaired muco-ciliary clearance (King, 2009). This subsequently leads to more infections and a cycle of progressive inflammation causing lung damage (Figure 2.1; Cole, 1986; King, 2009).

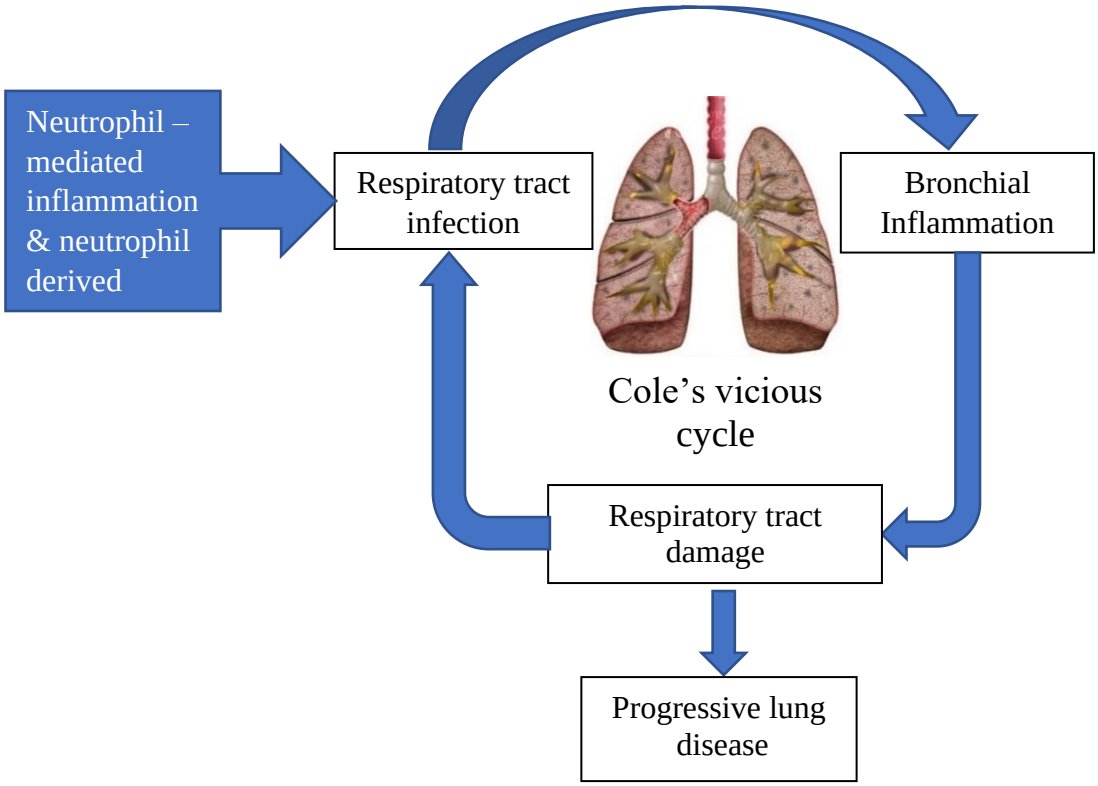


Figure 2.1 Cycle of infection and inflammation in bronchiectasis. Based on the "vicious cycle hypothesis" described by Cole (1986).

Those with bronchiectasis present with respiratory muscle weakness (Liaw et al., 2011; Moran, Piper, Elborn, & Bradley, 2010; Newall, Stockley, & Hill, 2005), the underlying cause of which is unknown. It has been postulated that the cause of loss in strength is primary and hyperinflation-related functional weakness (O'Shea, Taylor, & Paratz, 2004). Inspiratory muscle weakness could lead to discordance between muscle loading and capacity, resulting in decreased exercise tolerance, hypoventilation, dyspnoea, and, ultimately, respiratory failure (Ozalp et al., 2019). A decrease in expiratory muscle strength diminishes the effectiveness of coughing and decreases the removal of airway secretions (Moran et al., 2010; Troosters, Gosselink, & Decramer, 2005). Subsequent airway obstruction and air trapping may be responsible for reduced diffusion capacity (Loubeyre et al., 1996), which has been attributed to a reduction in forced expiratory volume in one second (FEV_1; Roberts et al., 2000).

Previous studies have found that women have an increased predisposition to developing bronchiectasis, but that the rate of lung damage progresses at the same rate in both sexes (Quint et al., 2016; Pasteur et al., 2000). Since 2004, the incidence of bronchiectasis in women has increased from 21.24 per 100,000 person-years to 35.17 per 100,000 person-years in 2013, and from 18.19 to 26.92 per 100,000 person-years in men, in the UK alone (Quint et al., 2016). As the incidence of bronchiectasis increases (Seitz, Olivier, Adjemian, Holland, & Prevots, 2012; Weycker, Edelsberg, Oster, & Tino, 2005), hospital admissions (Ringshausen et al., 2013) and mortality (Roberts & Hubbard, 2010) continues to rise.

2.1.2 Pathophysiology of Cystic Fibrosis

Cystic Fibrosis (CF) is the most common autosomal recessive disease in Caucasian populations (Donaldson & Boucher, 2007). In 1985, the genetic defect responsible for CF was localised to the long arm of chromosome 7; the gene was named *cystic fibrosis transmembrane conductance regulator* (CFTR) and was subsequently identified by full length sequencing in 1989 (Kerem et al., 1989; Riordan et al., 1989; Rommens et al., 1989). To date, more than 2,023 mutations have been identified in the CFTR mutation database (http://www.genet.sickkids.on.ca), however, the majority of these mutations are rare and their pathomechanisms remain poorly understood. The most common mutation worldwide is the ΔF508 mutation, caused by the depletion of

phenylalanine in position ΔF508 (Ratjen, 2009). Within the UK, 89.5% of people with CF have the ΔF508 mutation; 4,789 (49.1%) and 3,882 (40.4%) of which are homozygous and heterozygous, retrospectively (Jeffery, Charman, Cosgriff, & Carr, 2017).

CFTR codes for a protein by the same name that belongs to a family of adenosine triphosphate (ATP) binding cassette proteins (Filbrun, Lahiri, & Ren, 2016) and is found in the membranes of cells that line the passageways of the lungs, liver, pancreas, intestines, reproductive tract and skin. CFTR's primary role is the regulation of ion transport across cell membranes in mucosal surfaces (Donaldson & Boucher, 2007). Given CFTR's role as a key regulator of salt and water transport across multiple epithelia, abnormalities in its function result in the alteration of the ion transport necessary for the appropriate function of the epithelial structures (Griesenbach, Pytel, & Alton, 2015). This alteration results in less chloride secretion out of, and less water transport in to, the epithelial surface layer, due to ion transport creating an osmotic gradient (Boucher, 2007). CF mutations are influenced by modifier genes (Collaco & Cutting, 2008; Cutting, 2010), environmental factors (Kopp et al., 2015) and the socioeconomic status of patients (Barr, Britton, Smyth, & Fogarty, 2011; Schechter, Shelton, Margolis, & FitzSimmons, 2001; Veit et al., 2016). CFTR mutations can be grouped into six distinct classes, dependent on their functional consequences on the CFTR within the cell

- Class I mutations cause changes in the synthesis of CFTR by affecting the CFTR transcription.
- Class II mutations involves those that affect the processing of CFTR.
- Class III affects the regulation of CFTR, specifically the binding of ATP to the nucleotide binding domains (NBDs) which are required to activate CFTR. Mutations that affect CFTR interaction with ATP have been shown to alter this binding function (Drumm et al. 1991; Anderson & Welsh 1992).
- Class IV mutations alter chloride conduction properties of CFTR, resulting in changes to the CFTR protein structure that forms the pore of the channel. This 'misshaped' CFTR pore can restrict the movement of chloride ions (Cl^-)through the channel, known as a 'conductance' defect (Tabcharani et al., 1993).

- Class V mutations result in extremely reduced amounts of normal CFTR protein that can be synthesised, resulting in less protein at cell surface, and is associated with a milder form of CF.
- Class VI mutations destabilise the channel in post- endoplasmic reticulum compartments and/or plasma membrane (PM), resulting in accelerated PM and reduced apical PM expression (Silvis et al., 2003).

The frequency of CFTR mutation classes varies considerably. De Boeck and colleagues (2014) found that 80% of those with CF in European countries had at least one class II mutation containing ΔF508. At least 16.4% of those with CF have at least one class I mutation, and 2.9%, 3.3% and 3.0% for class III, IV and V, respectively (De Boeck, Zolin, Cuppens, Olesen, & Viviani, 2014). Furthermore, genotypes which result in partial functioning CFTR (classes IV, V) are usually associated with a milder phenotype and, subsequently, later diagnosis (Kerem & Kerem, 1996). Over the past 10 years, modulators of CFTR protein function have progressively transformed the outcome and quality of life of those with CF (Elborn, 2016). There are a number of modulators dependent on an individual's genotype mutation: (i) ivacaftor for individuals with sequence variants associated with class III mutation; (ii) combination therapies in individuals homozygous for ΔF508 such as lumacaftor/ivacaftor or tezacaftor/ivacaftor; and (iii) a triple combination therapy (tezacaftor/ivacaftor and elexacaftor), which has been shown to be a highly effective modulator treatment for individuals with at least one ΔF508 mutation and more robust compared to tezacaftor/ivacaftor alone. These modulators have shown improvements in quality of life, reduced pulmonary exacerbations and variable improvement FEV_1 in those with CF (Elborn, 2020). These drugs have revolutionised the treatment of CF, which is likely to evolve over the next decade as modulator treatment is more widely implemented.

Lung cilia are bathed in airway surface liquid, the depth and composition of which is regulated by the CFTR. Airway surface liquid possesses a mucus component that traps inhaled particles, and, therefore, mucus clearance is an essential component of the lung's innate defence system against disease. The rate of mucociliary clearance is dependent on the rate of ciliary beating (Matsui, Davis, Tarran, & Boucher, 2000), as well as the hydration state of airway surface liquid/mucus (Kilburn, 1968; Puchelle, de Bentzmann, & Zahm, 1995; Spring, 1999). Mucus hydration is dependent on the

volume of liquid present on the airway surface, which is modified by active ion transport (Spring, 1999).

In CF, the volume of airway surface liquid is depleted, resulting in the cilia being less efficient at moving particles and mucus (Boucher 2007). Specifically, abnormalities in ion transport, including a reduction in chloride secretion and increased sodium absorption, coupled with low airway surface liquid, results in abnormally viscous mucus secreted by the submucosal glands and epithelial cells (Cutting & Zeitlin, 2012). In healthy people, the submucosal glands produce mucus in the form of strands, which initiate the movement of large particles, facilitating their removal from the airways (Fischer et al., 2019). However, in those with CF, the insufficient airway luminal liquid prevents the release of the mucus strands from the glands, leading to tethering of mucus to the gland ducts (Cantin, Hartl, Konstan, & Chmiel, 2015; Hoegger et al., 2014; Figure 2.2). The subsequent mucus build-up provides a rich environment for bacterial infections leading to chronic and persistent bronchopulmonary infections such as *Pseudomonas aeruginosa (P.aeruginosa)*, *Staphylococcus aureus*, and *Burkholderia complex*. These infections lead to chronic airway and systemic inflammation, destruction of tissue and respiratory insufficiency (Boucher 2002; Boucher 2007).

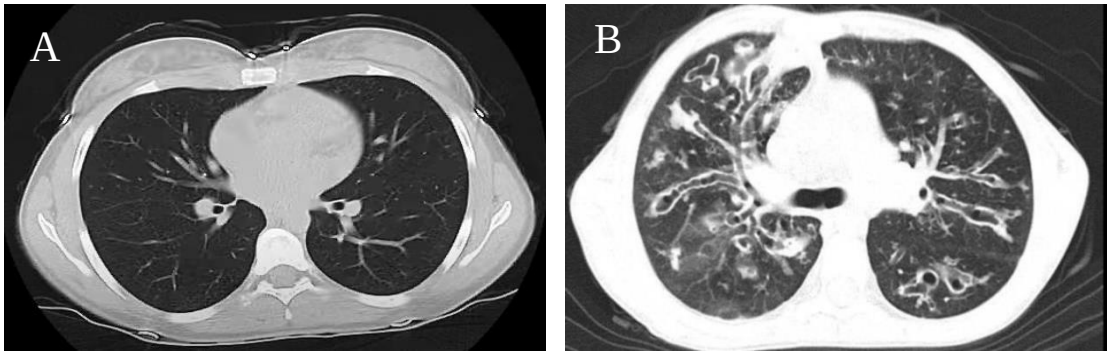


Figure 2.2 Chest computed tomography showing individuals with A) healthy lungs and B) cystic fibrosis lungs, showing peribronchial thickening and mosaic attenuation due to small airway disease.

A decline in lung function due to recurrent vicious cycles of lung infection, inflammation and obstruction, remains the main cause of mortality and morbidity in

those with CF, (Dinwiddie, 2000). Indeed, even before symptom onset in CF, pulmonary inflammation and infection are often present, although what manifests first is still unclear (Khan et al. 1995; Balough et al. 1995; Armstrong et al. 1997; Stoltz et al. 2015). As CF progresses, lung function deteriorates (Holford, 2013), as reflected by changes in forced expiratory volume in one second (FEV_1), which has been suggested to be predictive of mortality in CF (Sanders & Goss, 2013). A recent systematic review found that the relationship between the decline in FEV_1%predicted and age was not static or directly proportional, but a non-linear dynamic and time-varying relationship. Specifically, the highest, and most stable, lung function was evident between 5-10 years of age, with the steepest decline in FEV_1%predicted from 11 to 15 years of age, with a continued, albeit less rapid, subsequent decline up to 30 years of age (Harun, Wainwright, Klein, & Hennig, 2016). In those > 30 years of age, FEV_1%predicted was shown to be relatively stable (Harun et al., 2016).

Lung function remains the single most important predictor of survival in CF, with those exhibiting an FEV_1 of <30% predicted reportedly having 50% increased risk of mortality (Kerem, Reisman, Corey, Canny, & Levison, 1992). However, more recent research utilising UK CF registry data found that 50% of individuals with an FEV_1 below 30% predicted lived > 5.3 years, a 4.1 year increase from 1990 (Elborn, Shale, & Britton, 1991; George et al., 2011). This discrepancy could be attributed to improved pharmacological treatments, the comprehensive multidisciplinary CF care now part of the treatment routine or the eradication of *P.aeruginsosa* (Stephenson et al., 2015). It is also pertinent to note that reduced exercise capacity has been shown to predict both mortality and an increased risk for hospitalisation, independent of lung function (Pérez et al. 2014; Pianosi et al. 2005; Nixon et al. 1992). Therefore, these interstudy discrepancies may also reflect the growing recognition of the importance of physical activity (PA) and exercise promotion in the treatment strategies of those with CF.

Interestingly, sex may influence disease progression and prognosis in those with CF, with females suggested to demonstrate a higher mortality rate than their male counterparts (Corey & Farewell, 1996; Marshall et al., 2005; Morgan et al., 1999; Sweezey & Ratjen, 2014). Demko et al. (1995) demonstrated that females with CF acquired chronic *P.aeurginosa* at an earlier age (median of 9.5 years) in comparison to males (median of 11.2 years) and had a more rapid decline in lung function after

P.aeruginosa colonisation. Moreover, females have shown a more rapid decline in FEV_1%predicted during adulthood in comparison to males (Harun et al. 2016). In youth, girls with CF have a lower peak capacity than boys with CF at the same age (Orenstein & Nixon, 1991), which may be of relevance as aerobic capacity is an important predictor of survival in this population (Nixon et al., 1992). Sex differences have also been reported in body composition in those with CF. Specifically, females have a higher risk of an abnormal BMI (Harness-Brumley et al., 2014), with impaired nutritional status evident in CF girls aged 8 years, compared to CF boys whose BMI remain close to the WHO normative reference values up to the age of 10 years (Boëlle et al., 2012). Moreover, the effect of a low lean body mass appears to differ according to sex, with deleterious consequences only evident in females when they were below the 50^{th} percentile, whereas, in males, any decline in lean body mass is reported to be associated with worse pulmonary function (Sheikh et al., 2014). However, several reports have refuted the continued presence of a gender gap in CF outcomes, suggesting that improved airway clearance therapies have narrowed the gender bias (Harun et al., 2016; Sanders et al., 2014), yet a recent study found that male sex was associated with better survival at diagnosis, but only in ΔF508 non-homozygotes (Keogh et al., 2018). If a gender gap is evident, it has been postulated that this may be predominately related to a differential effect of sex hormones on inflammation and nutritional status in CF (Sweeney & Ratjen, 2014). Indeed, oestrogen has been implicated as a hormone that decreases airway surface liquid on the bronchial epithelial cells, thereby enhancing mucus viscosity (Harness-Brumley et al., 2014; Nick et al., 2010). Furthermore, oestrogen has been shown to promote *P.aeruginosa* from a nonmucoid to mucoid form that is more pathogenic and drug resistant (Assael, 2002; Verma, Bush, & Buchdahl, 2005). Further research is needed to further understand the interrelationships between sex, disease severity, aerobic fitness, and lung function.

Forty years ago, CF was almost exclusively a paediatric disease but now more paediatric patients are surviving to adulthood with the life expectancy having increased from <5 years of age in 1972 to 47 years in 2017 (Stephenson, Stanojevic, Sykes, & Burgel, 2017). With this ever-increasing adult population, the individual psychological and physiological burden of living with a chronic illness has led to increases in CF-related comorbidities, such as pulmonary disease, renal disease,

metabolic bone disease, CF-related diabetes, cancers, drug allergies and toxic effects, and complications associated with lung transplantation (Elborn, 2016; Plant, Goss, Plant, & Bell, 2013; Ronan, Elborn, & Plant, 2017). Therefore, interventions that could help combat these comorbidities and improve overall health are paramount.

2.1.3 Pharmacological and Non-Pharmacological Interventions for those with Obstructive Pulmonary Disease

Respiratory diseases are leading causes of death and disability in the world (Forum of International Respiratory Societies [FIRS], 2012), with an estimated 1 billion people suffering from either acute or chronic respiratory conditions (Wang et al., 2016). Medical advancements have increased the length and QoL in those suffering from respiratory disease, however, changing lifestyles, manifestations of disease, new types of infections and changing environments have created new challenges (FIRS, 2012).

Medical treatment for respiratory diseases often incorporates a comprehensive approach aiming to reduce symptoms, improve QoL and prevent exacerbations, which are associated with worsening outcomes. Some standard pharmacological treatments for respiratory disease include: (i) airway clearance techniques involving either a physical or mechanical means to manipulate airflow to aid in the mobilisation of secretions and facilitate evacuation by coughing, helping to prevent further inflammation and infection (Volsko, 2013); and (ii) bronchodilators, which are short- or long-acting beta-2 agonists that aim to relax the smooth muscle of the airway, allowing better airflow for a period, however consistent use of beta-2 agonists for extended periods reduces their efficacy due to the downregulation of the beta-2 receptor in the airways (Kim & Story, 2016); and (iii) inhaled Corticosteroids which are often used in combination with long-acting beta-2-agonists to reduce the risk of exacerbation and improve lung function and health status (Tashkin & Strange, 2018). For respiratory disease, treatment is individualised and based on the availability of existing drugs, disease severity, patient preferences, drug interactions, and comorbidities (Fernandes et al., 2017).

Medical advancements have brought considerable costs that have threatened the financial health of many nations (FIRS, 2012). Specifically, the total cost of respiratory disease in the European Union exceeds €380 billion (Gibson et al., 2013). Therefore, non-pharmacological management must be utilised to reduce

pharmacological costs. Indeed, non-pharmacological therapy has been shown to provide symptomatic improvements and better QoL in those with chronic respiratory conditions (Safka & McIvor, 2015). There is a vast range of non-pharmacological treatment methods for those with chronic respiratory conditions. Popular non-pharmacological treatment options include: (i) oxygen therapy, which is a widely used treatment method for patients with advanced respiratory disease and is used for the relief of symptoms and prolongation of survival (Gibson et al., 2013); (ii) smoking cessation to halt the progression of lung function decline and has been shown to have a mortality benefit, however, the rates of success of current smokers maintaining a smoke-free lifestyle remains low (Safka & McIvor, 2015); (iii) physiotherapy is the most popular non-pharmacological treatment of respiratory diseases. It is particularly helpful as an aid for clearing bronchial secretions. There are a variety of physiotherapy techniques used including postural drainage and forced expiration, which can be completed regularly at home (Gibson et al., 2013); (iv) pulmonary rehabilitation (PR) that focuses on exercise capacity, muscular strength, nutrition, education and psychological health has been shown to be successful in a range of respiratory disease (Gibson et al., 2013). Given the multi-faceted nature of PR it often requires input from occupational therapists, physiotherapists, dietitians, physicians, specialist respiratory nurses and smoking cessation counsellors (Hill, Vogiatzis, & Burtin, 2013). However, more research is required in order to evaluate the benefits of PR in respiratory diseases other than COPD while understanding the optimal schedule and the maintenance of benefits on a long-term basis (Gibson et al., 2013).

2.2 Physical Activity and Exercise for Cystic Fibrosis and Non-Cystic Fibrosis Bronchiectasis

PA is defined as any bodily movement produced by the skeletal muscles, resulting in a substantial increase in energy expenditure above resting, while exercise is defined as regular participation to improve physical performance, cardiovascular function or muscle strength, or any combination thereof (Caspersen, Powell, & Christenson, 1985). There are several challenges to exercise prescription and PA promotion in patients with chronic respiratory conditions, due in part to the heterogeneity of exertional symptoms and the high prevalence of comorbidities in patients (Crisafulli et al., 2008). Despite these challenges, PA and exercise in chronic respiratory

conditions has been shown to decrease dynamic hyperinflation and exertional dyspnoea, improve exercise tolerance, enhance quality of life, reduce disease exacerbations and augment patients' ability to perform tasks of daily living (Burr, Davidson, Shephard, & Eves, 2012; Eves & Davidson, 2011).

Both PA and exercise have been shown to positively impact health and well-being in those with CF. Specifically, increasing PA and exercise result in higher exercise capacity, and consequently longer survival (Nixon et al., 1992), an improved sense of well-being (Orenstein, Nixon, Ross, & Kaplan, 1989) and greater education/employment capabilities (Frangolias, Holloway, Vedal, & Wilcox, 2003) in both children and adults with CF. Additionally, higher levels of habitual PA amongst CF individuals are associated with a slower rate of decline in lung function (Wilkes et al. 2007) and bone mineral density (Wilkes et al. 2008).

Although exercise and PA are currently recommended as part of the standard CF care (Boas 1997; Bradley & Moran 2008; Shoemaker et al. 2008; Rand & Prasad 2012; Wheatley et al. 2011; Cerny 2013; LeBlanc & Lands 2014), there is little guidance on the optimal type or dose required to achieve beneficial outcomes, with PA promotion in CF clinics limited to informal discussion and generic PA advice (Swisher et al., 2015; Shelley et al., 2018). Current guidelines recommend that healthy children and young people aged 5-17 years should accumulate at least 60 minutes of moderate-vigorous physical activity (MVPA) daily, the majority of which should be aerobic (World Health Organisation, 2019). For adults aged 18-64 years, 150 minutes of moderate physical activity (MPA), or at least 75 minutes of vigorous physical activity (VPA) throughout the week, is recommended (World Health Organisation, 2019). For young children with CF who have little disease-related limitations to their PA, the guidelines recommended by WHO for their healthy peers are deemed appropriate, though patients will need individually tailored PA and exercise prescriptions that are frequently re-evaluated as the disease progresses (UK CF Trust, 2020).

A significant proportion of those with bronchiectasis have shown marked decreases in their exercise tolerance and PA levels (Burtin and Hebestreit, 2015; Pehlivan et al., 2019). Additionally, the bronchiectasis population have demonstrated largely inactive lifestyles, with few meeting the recommended PA guidelines (Bradley et al., 2015).

While the benefits of a PR, exercise and PA has been well documented in other respiratory diseases such as COPD, there is limited studies investigating how these effect bronchiectasis (José et al., 2017; Ong, Lee, Hill, Holland, & Denehy, 2011). Improvements in exercise capacity and HRQoL have been reported following PR in bronchiectasis (Ong et al., 2011; Mandal et al., 2012; Lee et al., 2014, 2017; Patel et al., 2019). Indeed, one study showed maintained improvements in physiological and psychological health at a 12-month follow-up (Ong et al., 2011), however, contrastingly another study found improvements weren't maintained at a 6-month follow-up (Lee et al., 2014). A major limitation of PR in bronchiectasis is the lack of long-term follow-up to determine whether improvements were maintained (Metersky & ZuWallack, 2019a). Further studies are needed to assess the impact of PA and exercise on bronchiectasis in both short- and long-term outcomes and whether a PR program is best for this population.

2.2.1 Physical Activity for Children and Adolescents with Cystic Fibrosis

There is little consensus regarding the PA in children with CF. Some have reported that, compared to their healthy peers, children with CF aged 6-17 years old engage in lower volumes of habitual PA (Aznar et al., 2014; Nixon, Orenstein, & Kelsey, 2001). Indeed, Aznar et al. (2014) reported that as little as 2.1% of children with CF meet the government guidelines of at least 60 minutes of MVPA every day. Nonetheless, the same children demonstrated higher levels of total and light PA. Conversely, other research has found no significant differences in PA between CF children and their healthy peers (Jantzen et al., 2016; Mackintosh, Ridgers, Evans, & McNarry, 2018; Selvadurai et al., 2004). These variations could be attributed to methodological inconsistencies such as a failure to account for maturity, disease severity or the relative intensity of PA, thereby limiting inter study comparisons. Specifically, it could be argued that the relative intensity for children and adolescents with CF could be greater, than in their healthy counterparts (Mackintosh et al., 2018). Therefore, "light" intensity PA for healthy population may actually be moderate intensity for those with CF and subsequently of more benefit to their health (Mackintosh et al., 2018). Such differences in the energy expenditure associated with absolute accelerometery intensities can only be resolved through the development of disease-specific cut-points (Bianchim et al., 2020). These issues associated with the appropriate interpretation of

the intensity and volume of PA are likely to be further exacerbated by the reliance on 15 second epochs in previous studies (Aznar et al., 2014; Jantzen et al., 2016). Given the sporadic nature of children's PA (Bailey et al., 1995), with high-intensity bouts suggested to typically last only 3 seconds and 95% to last less than 15 seconds (Bailey et al., 1995; Baquet, Stratton, Van Praagh, & Berthoin, 2007), using such long epochs may have potentially miscategorised VPA as MPA. Finally, questionnaire-based studies (Selvadurai et al., 2004) raise concerns regarding validity in chronic conditions, such as CF, due to their susceptibility to several forms of bias (Jantzen et al., 2016; Ruf et al., 2012).

A study in CF found that self-reported PA levels peaks at the age of 10 years (Collaco et al., 2014), with lower levels of PA levels not subsequently reversed with increasing age (Cox et al., 2016). Furthermore, in accordance with healthy populations, the PA of girls with CF declines to a greater extent than their male counterparts following the onset of puberty (Wilkes et al., 2007). Indeed, Schneiderman-Walker and colleagues (2005) found that lower PA levels in girls with CF aged 7-17 years were associated with a steeper decline in FEV_1 over a 2-year period, while higher levels of habitual PA were associated with a slower rate of decline, irrespective of sex (Schneiderman et al., 2014). It is important, however, important to note the relatively high FEV_1 of the participants within Schneiderman and colleague's (2014) study, which may confound the generalisability of the findings to the wider CF population. Collaco and colleagues (2014) emphasised the importance of developing PA habits at a young age, as when the disease progresses in severity, it in itself becomes a direct cause hypoactivity (Williams & Stevens, 2013). Indeed, being as active as possible in early childhood is essential, especially in youth with CF, as the ability to engage in activities of daily living, improved body image and self-esteem as well as perceptions of wellness, acceptance and resilience are secondary QoL related outcomes associated with PA (Enright, Chatham, Ionescu, Unnithan, & Shale, 2004; Moola, Faulkner, & Schneiderman, 2012; Selvadurai et al., 2002; Stanghelle, Hjeltnes, Bangstad, & Michalsen, 1988). However, a self-selection bias whereby those with milder disease are most likely to take part in exercise and PA research is a fundamental limitation of the majority of CF-related studies.

Whilst the PA levels of those with CF remain to be conclusively elucidated, numerous factors that could influence PA levels in the CF population could be attributed to the treatment burden. Those with CF are required to attend regular clinic appointments, comply with drug therapy and physiotherapy sessions, and may miss school due to pulmonary exacerbations and/or increased illness (Williams & Stevens, 2013). Therefore, the burden of treatments and lung disease may reduce the opportunity for those with CF to be active on a regular basis (Williams & Stevens, 2013). Furthermore, parental overprotection, child fears, lack of understanding of the disease by teachers, self- or peer-imposed social isolation (Shields, Synnot, & Barr, 2012), as well as the perception of "no time to play" (Moola et al., 2012), could also contribute potential inactivity in children with CF.

A commonly cited barrier to PA in those with CF are CF-specific concerns, such as coughing and poor perceptions of body image (Withers, 2012). Studies of adolescents have shown that adolescent girls have greater public self-consciousness compared to boys (Rankin, Lane, Gibbons, & Gerrard, 2004) and experience more strains and poorer treatment adherence (Patterson, Wall, Berge, & Milla, 2009). Adolescent girls have a greater need to fit in with their peers, reporting embarrassment with activities that are disdained by their peers (Allgood-Merten, Lewinsohn, & Hops, 1990; Christian & D'Auria, 1997; Rankin et al., 2004). Indeed, adolescent's behaviours are increasingly influenced by significant others; social support from healthy peers could promote their QoL, adaptive psychological adjustments, and in some cases, greater treatment adherence (Helms, Dellon, & Prinstein, 2015). Specifically, social support has been shown to be protective for psychological well-being in youth with CF (Graetz, Shute, & Sawyer, 2000), with family support in particular being associated with greater treatment adherence (Collins, O'Loughlin, & Henry, 1998; Patterson, 1985), as well as better health outcomes (Patterson, Budd, Goetz, & Warwick, 1993). Future research is needed to determine how peer relationships influence health and behaviour over time and the possible mediators and moderators of these effects in CF (Helms et al., 2015).

It is imperative to ascertain the interests and abilities of children and adolescents with CF in order to ensure long-term adherence to a physically active lifestyle (Hebestreit et al. 2010). A recent study by Shelley et al (2018) found that PA monitoring is a

potential clinical tool for promoting physical PA in young people with CF, whilst allowing an individualised approach to activity prescription. Indeed, one study has shown that free-choice in PA is correlated with maximal aerobic capacity (Hebestreit et al., 2006), suggesting that the mode of PA may not be as influential as choosing activities in which the adolescent will agree to engage in. Furthermore, better treatment adherence in youth with CF has been attributed to family support (Collins et al., 1998; Patterson, 1985), resulting in better physical health outcomes (Patterson et al., 1993).

2.2.2 Physical Activity for Non-Cystic Fibrosis Bronchiectasis

Despite the strong evidence that adherence to PA guidelines is associated with health benefits and reduced mortality in chronic disease populations (Arne et al., 2009; O'Donovan et al., 2010), studies investigating the impact of PA on bronchiectasis are scarce (Bradley et al., 2015; Wilson et al., 2016). In other respiratory conditions such as COPD and CF, PA has been strongly related to mortality and lung health (Schneiderman et al., 2014; Waschki et al., 2011). Previous research has found that those with bronchiectasis have reduced PA and exhibit significantly lower walking distances (Cakmak et al., 2016; José et al., 2018) and fitness measured through intermittent shuttle walk test (ISWT) distance (704 ± 204.30 m vs 909 ± 200.58 m, $p = 0.016$) compared to healthy controls (Cakmak et al., 2016). Significant correlations have been observed between PA and FVC, FEV_1, ISWT and dyspnea in bronchiectasis (José et al., 2018). Furthermore, pulmonary function, dyspnea, ISWT and long-term oxygen therapy were also identified as independent factors associated with PA (José et al., 2018). Bradley et al. (2015) used accelerometers in 55 bronchiectasis participants and found that only 11% of patients met the PA guidelines. Average daily time spent being sedentary was 634 ± 77 minutes, with time spent in LPA and MVPA being 207 ± 63 and 25 ± 20 minutes, respectively (Bradley et al., 2015). However, the utilisation of pedometers in José et al. (2018) and Cakmak et al. (2016), and the omission of comparing week and weekend day step count data, limits the accuracy of the PA levels presented. A recent study found that low PA levels and high sedentary time at baeseline were associated with a higher risk of hospitalisation as a result of bronchiectasis exacerbation (Alcaraz-Serrano et al., 2020). Alcaraz-Serrano et al. (2020) concluded that these findings needed to be validated in future studies but recommended that PA and sedentary behaviour should be incorporated into disease

severity scores. However, no other studies have considered the impact of Bronchiectasis and its range of clinical characteristics (disease severity, exercise capacity, HRQoL and symptoms) on sedentary behaviour and PA, thus their importance remains to be elucidated (Bradley et al., 2015). Indeed, more research is needed within this population to identify the need for PA interventions and how to tailor these to this population.

2.2.3 Exercise for Children and Adolescents with Cystic Fibrosis

Aerobic exercise, defined as any activity that uses large muscle groups, can be maintained continuously, and is rhythmical in nature (Wahid et al., 2016), is the recommended form of exercise by most CF centres as it is the most studied mode of exercise within this population (Hebestreit et al., 2015). The maintenance, or improvement, of pulmonary function and aerobic capacity, thereby slowing down the annual rate of decline in FEV_1 and $\dot{V}O_{2peak}$, are vitally important given that they are both strong predictors of survival (Hebestreit et al., 2019; Nixon, Orenstein, Kelsey, & Doershuk, 1992; Pianosi, LeBlanc, & Almudevar, 2005). Furthermore, in a large cohort of adolescent CF patients, an acceleration of lung function decline was found in early adulthood (Vandenbranden et al., 2012). This decline was attributable to adolescents who exhibited early-stage lung disease ($FEV_1 \geq 70\%$). This finding is consistent with previous research, whereby a higher baseline lung function was a risk factor for FEV_1 decline in children and adolescents with CF (Konstan et al., 2007). Therefore, it is intuitive that any intervention that can positively impact these health outcomes would potentially enhance patient prognosis. Nonetheless, it is still unknown whether exercise training can improve survival in this population (Williams & Stevens, 2013). However, it is noteworthy that several mechanisms such as pulmonary, cardiac and peripheral skeletal muscle dysfunction, contribute to the reported limitation in exercise capacity in those with CF (Saynor et al., 2020; Aljamed & Lands, 2012). Ventilatory dysfunction in CF may contribute to exercise intolerance due to deleterious changes in lung function, dead space ventilation, respiratory muscle function, ventilatory reserve, and ventilatory control (Shei et al., 2019). Furthermore, muscle abnormalities including muscle weakness, mitochondrial dysfunction and altered muscle metabolism could also contribute to exercise intolerance (Gruet et al., 2016; Werkman et al., 2016; Gruet et al., 2017). Whilst the mechanisms of exercise

intolerance in CF is often complex and interdependent (Huzelbos et al., 2015; Jiang et al., 206; Gruet et al., 2017), it has been postulated that age-related progressions in disease severity may be integral to the decrements annually observed (Shei et al., 2019). Despite this, several studies have demonstrated that those with CF can tolerate aerobic exercise and improve aerobic capacity (Radke et al., 2017).

In children and adolescents with CF, a significant psychosocial barrier is parental overprotection (Moola, Faulkner, Kirsh, & Schneiderman, 2011). Termed the "vulnerable child syndrome," parents with children with a chronic illness may worry excessively about their child's health and their capacity to undertake exercise (Wilkes et al., 2009). Indeed, parents of children with CF expressed concerns about their child's participation in vigorous play or sports (Nixon et al., 2001). Parents are critical to health-related behaviour change by either facilitating or hindering their child's engagement (Golan, 2006). Processes such as role modelling and observational learning mean children adopt their parents practices and their beliefs and attitudes, therefore strongly influencing youth's PA and exercise (Moola et al., 2011). To enhance PA and exercise, processes such as dialogue about exercise in the home, availability of exercise equipment and access to facilities, are vital. Furthermore, interventions that involve parents are more applicable to the nuances of participants' local environments and more likely to have benefits for all family members (Moola et al., 2011; Nader et al., 1989). Minimising the perceived barriers to exercise in CF, emphasising how exercise can modulate the disease process, and optimising motivators, are likely to influence the success of any program (Abu-Hasan, Armstrong, Andersen, Weinberger, & Nixon, 2010; Prasad & Cerny, 2002).

During the last decade, the importance of exercise as an essential element in the treatment of CF has grown. Thus, exercise has been incorporated into many treatment regimens, with exercise capacity used as an outcome variable in many intervention studies (Schmidt et al., 2011). Additionally, it has been stated that aerobic capacity correlates with QoL measures, and changes in aerobic capacity are associated with changes in the QoL (Hebestreit et al., 2006). However, QoL remains an under-utilised assessment tool regarding the impact of PA and exercise in CF. In children, Selvadurai et al (2002) reported significant improvements in QoL at a one-month follow-up of an aerobic exercise programme. However, no significant improvements in QoL were

reported in the resistance or control group (Selvadurai et al., 2002). Specifically, improvements in QoL were only reported where $\dot{V}O_{2peak}$ significantly increased (Selvadurai et al, 2002). This is consistent with previous research that found that QoL correlated more strongly with changes in aerobic fitness than changes in pulmonary function (Orenstein et al., 1989). These improvements in QoL may be related to the suggested influence of physical exercise training on anxiety, depression and feelings of well-being in CF (Hebestreit et al., 2014).

Overall, there is a lack of research determining the psychological benefits of PA and exercise within youth with CF. As the complexity of treatment evolves with the ageing CF population, QoL could be negatively impacted due to the increased burden (Gee et al., 2005). With research emphasising the importance of cardiopulmonary exercise testing in not only providing important clinical information regarding the impact of disease, but the impact of the disease on patients QoL (Williams & Stevens, 2013), it is important that future exercise and PA interventions utilise psychological parameters to understand the full impact that PA and exercise can have on the well-being and QoL in CF patients.

2.2.4 Exercise for Non- Cystic Fibrosis Bronchiectasis

Exercise is important for those with bronchiectasis and is a critical component of PR (Spruit et al., 2013). The rationale for PR and exercise training within the bronchiectasis population is based on evidence that muscle weakness and physical inactivity may play a role in disease progression and therefore impact HRQoL, frequency of infectious exacerbations and the ability to mobilise secretions (Burtin & Hebestreit, 2015). Minimising inflammation and infection, addressing structural lung damage and optimising airway clearance are paramount for managing bronchiectasis (Polverino et al., 2017). Therefore, current guidelines recommend PR for those with bronchiectasis with the aim of improving exercise tolerance and HRQoL within this population (Pasteur, Bilton, Hill, & British Thoracic Society Bronchiectasis non-CF Guideline Group, 2010).

A recent systematic review incorporating four trials with 164 bronchiectasis patients concluded that 8 weeks of supervised PR and exercise training initiated short-term

improvements in exercise capacity and HRQoL, with the maintenance of these improvements being challenging (Lee et al., 2017). High-intensity exercise training incorporated into a PR programme was effective in improving ISWT distance and endurance capacity (Newall, Stockley and Hill, 2005), whilst a standard eight-week supervised PR programme showed improvements in ISWT and 6MWT distances, though these were not sustained at 6 or 12 months (Lee et al., 2014). Furthermore, the eight-week PR programme did not impact cough-related QoL, mood or the frequency of acute exacerbations compared to the control group (Lee et al., 2014). However, the reduced exacerbation frequency should be interpreted with caution due to the reduced proportion of patients who attended the 12-month follow-up. A cohort of 108 bronchiectasis participants showed that males, baseline FEV_1/FVC >70% and greater than two exacerbations in the previous year, were independent predictors of PR efficacy in terms of improvement in 6MWD (Zanini et al., 2015).

Although the evidence suggests that PR and exercise training is beneficial for those with bronchiectasis, numerous questions remain to be addressed (O'Neill, O'Donnell, & Bradley, 2019). Specifically, the timing of referral in relation to the stage of disease that patients may experience the most benefits remains to be elucidated. Furthermore, many patients with bronchiectasis are older adults and frail with orthopaedic risks (Bellelli et al., 2016), therefore exercise training within this population could be associated with risks of cardiac comorbidities, exercise-induced hypoxemia and haemoptysis (Burtin & Hebestreit, 2015). Overall, further research is required to investigate the effects of both short-and long-term exercise, at varying intensities, to determine the impact on the physiological and psychological health of those with bronchiectasis.

The clinical profile associated with bronchiectasis results in increased anxiety, depression, reduced HRQoL and impaired exercise tolerance (Martínez-García et al., 2005b; Olveira et al., 2013). Indeed, sputum production, breathlessness and exacerbations have been found to be the key determinants of QoL in bronchiectasis, with *P.aeruginosa* and nontuberculous mycobacteria having the highest burden on (Polverino et al., 2018). A recent study including 8,389 bronchiectasis patients (58% female) found that women living with the condition are significantly more affected in physical, emotional and social functioning aspects of their lives than their male

counterparts (Finch et al., 2017). This has implications for tailoring care and suggests further research is warranted to determine the sex-specific impact of bronchiectasis.

It has been found that patients with bronchiectasis who experience frequent exacerbations, experienced more hospitalisation, higher symptom burden and poorer QoL (Visser et al., 2019). As mortality rates and burden increases in adults with bronchiectasis (Roberts & Hubbard, 2010), more high-quality research in key areas is needed (Welsh, Evans, Fowler, & Spencer, 2015). Conflicting evidence and limited longitudinal research in bronchiectasis means the effect of PR interventions, and indeed PA's impact on HRQoL remains to be elucidated. Therefore, further research is imperative given that general well-being, mental health and the overall impact of disease on their activities of daily living will affect compliance to medical therapy and, ultimately, morbidity and mortality (de Bruyne, Eg, & Thavagnanam, 2017; Quittner et al., 2014).

2.2.5 Medicalisation of Physical Activity and Exercise

"Prescribed exercise" draws PA into the medical paradigm and shifts the focus of exercise culture to a clinical context. The medicalisation of sport is the process whereby 'a problem is defined in medical terms, defined using medical language, understood through the adoption of a medical framework, or "treated" with a medical intervention' (Conrad, 1992; p211). However, the majority of evidence-based practice in the health sector fails to consider the patient perspective (Rand, Dunn, Slade, Upadhyaya, & Sheehan, 2019). Furthermore, the need for new supplementary methods to evaluate treatment results and health status, aside from basing the evaluation of an intervention's and/or treatment's effectiveness against an objective biomedical goal, draws in patients' own opinions of their general well-being (Mainz, Kristensen, & Bartels, 2015). It is therefore important to ensure that evidence-based sports medicine such as "prescribed exercise" integrates three key aspects: (i) research-based knowledge; (ii) clinical expertise; and (iii) patient values (Hallinan & Jackson, 2008). When structured PA, thereby exercise, is implemented in a treatment regimen, there is a possibility that the desire for PA is replaced by the focus on clinical health and illness. Furthermore, when the patient's own motivation is not the driving force, and when PA is prescribed and orientated towards medical parameters, the participant can

become distanced from their own treatment (Hallinan & Jackson, 2008). It is therefore essential that both short-and long-term perspectives are obtained from patients and considered in the form of feelings, thoughts and values about exercise in relation to their own lifestyle. Motivating people to take responsibility for their own health as well as a 'responsibility-giving' process (Hallinan & Jackson 2008), could potentially result in a more sustainable and well-adhered intervention and/or treatment regimen.

2.2 Respiratory Muscle Training

An alternative method to traditional exercise interventions and/or pulmonary rehabilitation in those with a chronic respiratory condition is respiratory muscle training (RMT). RMT was first investigated in the late 1960s and research in both clinical and athletic populations has rapidly expanded over the last 30 years. Specifically, Delhez et al. (1966) conducted the first RMT programme in a clinical population, concluding that increases in inspiratory muscle strength may reduce the potential for the respiratory muscles to limit ventilatory work. Further research observed that five weeks of RMT, using repeated static inspiratory manoeuvres, improved mean inspiratory pressure (MIP) by 55% (Leith & Bradley, 1976). Additionally, Leith and Bradley (1976) found that volitional hyperpnoea training at rest improved maximal sustainable ventilatory capacity by 18%, thereby demonstrating that known strength-training principles can be applied to the respiratory muscles. The home-based, time-efficient nature of respiratory muscle training makes it an attractive alternate to hospital or community-based interventions. Furthermore, advancements in RMT devices mean clinicians and researchers can monitor adherence, effort and health remotely, reducing burden on health care practitioners and patients alike.

2.3.1 Training the Respiratory Muscles

Respiratory muscles are morphologically and functionally similar to skeletal muscles and therefore respond to training stimuli in the same manner, with improvements in strength and endurance reported following training (Romer & Polkey, 2008). These key principles to elicit training adaptations in skeletal muscles are well recognised, with suggestions that similar principles may be relevant to RMT, (i.e. overload, specificity and reversibility; Faulkner, 1985). Indeed, RMT utilises restricted airflow

breathing exercises to increase the mechanical load on the external intercostal muscles and diaphragm. The increased load engendered by RMT provides a stimulus to elicit a hypertrophic response (Enright et al., 2004).

Training methods for the respiratory muscles can be divided into resistive, and endurance, training (McConnell, 2013). Resistance training is where the muscles are subjected to an external load and can be split into three further categories: (i) inspiratory flow resistive loading; (ii) inspiratory threshold loading; and (iii) expiratory threshold loading. Inspiratory flow resistive loading requires inspiration via a variable diameter orifice whereby, for a given flow, the smaller the orifice, the greater the resistive load (Figure 2.3). Flow-resistive loading specifically targets the inspiratory muscles, in which the effect on the inspiratory muscle force-velocity curve is solely dependent on flow rate and the amount of resistance. Inspiratory threshold loading requires individuals to produce a negative pressure sufficient to overcome a threshold load, thereby initiating inspiration (Figure 2.4). This results in the inspiratory muscles primarily performing an isometric contraction until the threshold valve opens to allow inspiratory flow, after which the contraction becomes isotonic (Dixit & Prakash, 2014).

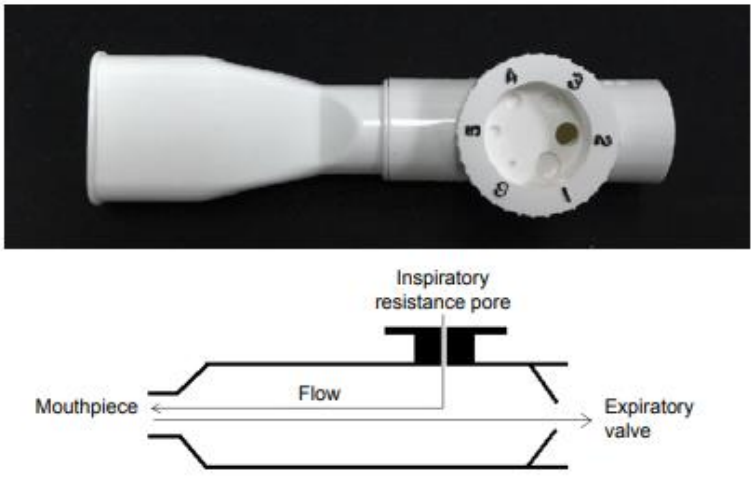


Figure 2.3 Respiratory resistance device (PFLEX; Respironics Inc; Pittsburgh, PA, USA). Adapted from Wu et al., (2017).

Finally, expiratory pressure threshold loading requires individuals to produce an expiratory pressure sufficient to overcome a positive pressure load, and thereby initiate expiration. The ventilatory response to expiratory loading is hypothesised to depend

on the compensatory reflexes and the impedance of the respiratory systems (Kimoff, Cheong, Cosio, Guerraty, & Levy, 1990; Milic-Emili & Zin, 2011). Indeed, a typical acute response includes slowing of expiratory flow and lengthening of expiratory time, such that breathing frequency and minute ventilation decrease (Milic-Emili & Bishop, 1979). Endurance training, specifically voluntary isocapnic hypernoea training, requires participants to maintain high target levels of ventilation for up to 30 minutes. To prevent hypocapnia (a state of reduced carbon dioxide in the blood), participants re-breathe through a dead space. Training sessions are usually completed at ~60-90% of maximum voluntary ventilation (MVV), three to five times per week (McConnell, 2013).

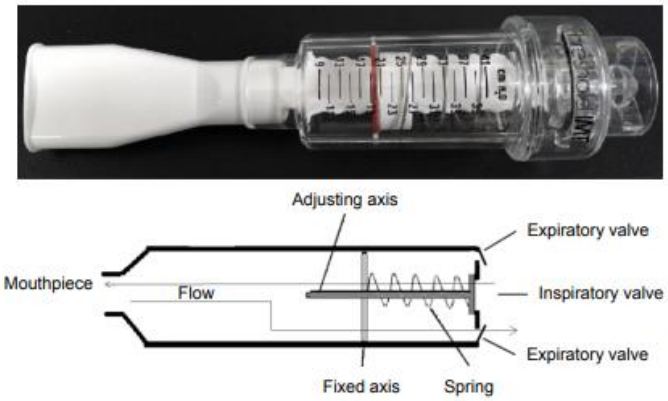


Figure 2.4 Respiratory threshold loading device (Threshold Inspiration Muscle Training; Respironics Inc; Pittsburgh, PA, USA). Adapted from Wu et al., (2017).

Neural adaptations have been shown to occur over the first four weeks of a strength training intervention (Brown et al., 2017; Ramsay et al., 1990), with both adults and children exhibiting a learned response (Larson et al., 1993) and increased frequency, and improved co-ordination, of neuromuscular firing (Astrand & Rodahl, 1986; Ozmun, Mikesky, & Surburg, 1994). Any improvements beyond four weeks are considered to be morphological adaptations (Folland & Williams, 2007), which incorporate increases in the oxidative capacity, the capillary bed of the muscle and muscle fibre hypertrophy (Komi & Hakkinen, 1991). Indeed, research has suggested that, akin to skeletal muscles, inspiratory muscles can adapt according to the stress placed on them (Boutellier, Büchel, Kundert, & Spengler, 1992). A recent review (Shei, 2018) on RMT highlighted that seven key effects of RMT. Specifically, RMT: (i) decreases the inspiratory muscle motor drive while preserving pressure generation

(Huang, Martin, & Davenport, 2003); (ii) promotes hypertrophy of the diaphragm and increases the proportion of type I fibres and size of type II fibres in the external intercostal muscles (Downey et al., 2007; Enright, Unnithan, Heward, Withnall, & Davies, 2006); (iii) attenuates the respiratory muscle metaboreflex (Witt, Guenette, Rupert, McKenzie, & Sheel, 2007); (iv) decreases the rating of perceived breathlessness or rate of perceived exertion (McConnell, 2009; Sheel, 2002); (v) improves respiratory muscle economy (Turner et al., 2012); (vi) reduces the work of breathing (Held & Pendergast, 2014); and (vii) improves respiratory muscle endurance (Sales et al., 2016). It is plausible that these mechanisms are linked, however, how these factors interact and their subsequent impact on exercise performance is, at present, not well understood (Shei, 2018).

2.3.2 Respiratory Muscle Training in Healthy Populations

Inspiratory muscle fatigue has been suggested to compromise exercise performance in healthy individuals (Mador & Acevedo, 1991; Verges, Boutellier, & Spengler, 2008), possible due to impaired blood flow to the working muscles via the respiratory muscle metaboreflex, resulting in the acceleration of fatigue development in these muscles (Wüthrich, Notter, & Spengler, 2013). It is hypothesised that during exhaustive endurance exercise the changes in locomotor muscle blood flow have an important effect on O_2 transport to the working locomotor muscles and, subsequently, on their fatigability (Scano, Grazzini, Stendardi, & Gigliotti, 2006). RMT has been shown to reduce the development of respiratory muscle fatigue (Romer & McConnell 2003; Verges et al. 2008) and blood lactate concentration during exercise (Brown, Sharpe, & Johnson, 2008). This is due to increased uptake and metabolism of lactate by the trained respiratory muscles (Spengler et al. 1999; Romer & McConnell 2003; McConnell & Sharpe 2005; Brown et al. 2008) and sympathetic activation by reducing sympathetic, and increasing parasympathetic, modulation (Ferreira et al., 2013; McConnell & Lomax, 2006; Witt et al., 2007). A recent systematic review of RMT in healthy participants included a detailed analysis of 46 original RMT studies (Illi, Held, Frank, & Spengler, 2012). Specifically, Illi et al. (2012) found that respiratory muscle performance improved to a similar extent irrespective of fitness levels, with no effect of fitness with regards to improvements in MIP, MEP or respiratory muscle endurance.

Furthermore, inspiratory and expiratory strength training did not differ in their effect on improving exercise performance (Illi et al., 2012).

In healthy populations, a minimum training intensity with an overload of 20-40% of peak power has been recommended (Chatham et al., 1999). However, whilst a load of 20-40% would increase power, it is postulated that it may be below the recommended optional intensity, which is consistent with strength and endurance training (Faulkner, 1985). To gain strength, training theory suggests intensities of 80-100% of maximum voluntary contraction, with a strength-endurance set ranging between 60 to 80%, and endurance at approximately 60% of peak (Newton & Karmer 1994). To ensure changes in load, constant maximal strength of contraction is needed to guarantee true overload is consistently applied through a training intervention (Dirix, Knuttgen, Tittel, International Olympic Committee., & International Federation of Sports Medicine., 1991). Incremental loading involving decreased rest periods between muscle contractions, thereby resulting in an increase in the efficiency of the aerobic response to loading by training in the pre-fatigued state, could be defined as overloading resulting in a high-density training programme (Acre, 1994). To be able to exhibit a training effect, frequency, duration and intensity of RMT must be carefully considered. Pardy and Rochester (1992) found a significant positive relationship between the percentage increase in MIP and relative magnitude of the IMT load. Therefore, it could be postulated that relative to an individual's inspiratory muscle strength, the higher the load the greater the increase in strength achieved (Ernesto Crisafulli, Costi, Fabbri, & Clini, 2007).

2.3.3 Respiratory Muscle Training in Clinical Populations

Impairment in respiratory muscle function can significantly interfere with performance of daily activities in those living with a respiratory disorder (Charususin et al., 2018). Inspiratory muscles are used to generate airflow. Specifically, when inspiratory muscles contract, the changes in intrathoracic pressure allow air to enter lungs; conversely, when they relax air exits the respiratory system. However, if additional effort is required, the alveolar to atmosphere pressure gradient is altered and ventilatory demand increased (Gea, Casadevall, Pascual, Orozco-Levi, & Barreiro, 2012). A muscle may not be defined as 'weak' in absolute terms, however, if the

demands that are placed on it are excessive then it is rendered 'weak' functionally. For example, in pulmonary fibrosis patients, respiratory muscle strength may be considered normal, but if the intrinsic inspiratory load is elevated this results in functional weakness that then manifests as reduced inspiratory muscle endurance (Hart et al., 2002). The majority of RMT research has been completed in those with COPD. Patients with COPD often exhibit respiratory muscle weakness and reduced muscle endurance, due to chronic mechanical loading of the inspiratory and expiratory muscles (Orozco-Levi, 2003). RMT has been shown to improve inspiratory muscle strength, endurance, exercise capacity, dyspnoea and QoL in those with COPD (Geddes, O'Brien, Reid, Brooks, & Crowe, 2008; Gosselink et al., 2011; Shoemaker et al., 2008). Although RMT has the potential to enhance respiratory muscles, its clinical use for those with respiratory conditions remains largely inconclusive.

2.3.3.1 Bronchiectasis

High levels of fatigue and dyspnoea are common features of bronchiectasis (Ozalp et al., 2012; Inal-Ince et al., 2014; de Carmargo et al., 2018), the causes of which are often multifactorial. However, the key contributors to dyspnoea include altered respiratory mechanics and insufficient gas exchange (Ozalp et al., 2012). Previous research has identified an expiratory flow limitation in people with moderate-to-severe bronchiectasis due to increased dynamic hyperinflation (Koulouris et al., 2003; Ozalp et al., 2012).

Given that non-CF bronchiectasis has commonality in pathology with COPD, and RMT shows significant benefits to those with COPD (Geddes et al., 2008; Gosselink et al., 2011; Shoemaker et al., 2008), RMT could be a potential treatment strategy to improve both physiological and psychological health for those with non-CF bronchiectasis. Three studies have investigated IMT in bronchiectasis (Liaw et al., 2011; Newall et al., 2005; Ozalp et al., 2019), with equivocal results. Specifically, Newall et al. (2005) found that adding an eight-week moderate-intensity (MIP 30-60%) IMT intervention 15 minutes, two times a day, to an exercise training programme (PR-IMT) produced significant improvements in respiratory muscle strength, exercise capacity and health status, which was maintained three months after training cessation (Newall, Stockley and Hill, 2005). This is in contrast to the sham

IMT group, whose increase in exercise performance was not maintained, suggesting an additive effect of IMT in the PR-IMT group (Newall, Stockley and Hill, 2005). Contrastingly, a sole IMT intervention (30% MIP increasing by 2cmH_2O each week) for 30-minutes daily, five days a week for eight weeks found increases in both inspiratory (39%) and expiratory respiratory muscle strength (44%), but had no significant effect on respiratory function, QoL or walking capacity (Liaw et al., 2011a). Most recently, a high-intensity programme involving IMT three days a week for eight weeks at 30% MIP and an exercise to rest ratio of 2:1, found both MIP and MEP increased by 43.53% and 11.67%, respectively (Ozalp et al. 2019). Additionally, Ozalp et al. (2019) found IMT increased exercise capacity, respiratory muscle endurance and reduced dyspnoea in patients with non-CF bronchiectasis. However, it is important to acknowledge the near-normal lung function (Newall et al. 2005; Ozalp et al. 2019) and relatively young age of participants in studies to date (Liaw et al. 2011; Ozalp et al. 2019), making IMTs applicability in those suffering from more severe symptoms difficult to ascertain. Bronchiectasis is associated with rising hospitalisation rates, resulting in growing healthcare utilisation (Seitz et al., 2010, 2012) and economic burden (Joish, Spilsbury-Cantalupo, Operschall, Luong, & Boklage, 2013; Ringshausen et al., 2013). Considering the economic and physical burden, increased dyspnoea and reduced exercise tolerance of tidal expiratory flow limitation in those with bronchiectasis (Koulouris, Retsou, Kosmas, Dimakou, Malagari, Mantzikopoulos, Koutsoukou, Milic-Emili, & Jordanoglou, 2003), there is an urgent need for cost-effective interventions irrespective of disease severity, to allow the identification of those who would benefit the most from IMT.

2.3.3.2 Cystic Fibrosis

Due to airway obstruction, respiratory muscles in those with CF are subject to an increased load (Reilly et al., 2011). Hyperinflation, because of gas trapping puts those with CF on the upper, flattened portion of the pressure-volume curve, causing an increase in the elastic work of breathing and causing the development of intrinsic positive end expiratory pressure (Reilly et al., 2011). Therefore, an imposing load is needed to overcome each breath due to increased airway resistance (Hart et al., 2002). Furthermore, a reduction in inspiratory muscle length and altered geometry on account of hyperinflation reduces the ability of the inspiratory muscles to generate negative

pressure (Polkey et al., 1996). This imbalance between ventilatory load and capacity of the respiratory muscles in those with CF is exemplified by inefficient breathing patterns (Hart et al., 2011) and exercise intolerance (Almajed & Lands., 2012).

Preventing deterioration in pulmonary function has led to a substantial increase in life expectancy for those living with CF. As respiratory dysfunction is the major cause of morbidity in CF and associated with approximately 80 to 95% mortality (Lyczak, Cannon, & Pier, 2002), interventions that not only improve pulmonary function but associated health outcomes, would be extremely beneficial. Research regarding the impact of IMT in CF is scarce, with the limited number of studies adopting different training protocols and outcome measures, thereby limiting interstudy comparisons.

The optimal duration and length of IMT to elicit beneficial improvements in health in CF remains unknown. It is hypothesised in normal strength training programmes that the optimal frequency of training is three times a week, with maintenance achieved by continued training one or two times per week (Fleck, 1994; Wernbom, Augustsson, & Thomee, 2007). However, there is little consensus within the literature, with considerable inter study variations in the frequency, intensity and duration of IMT interventions. It is therefore perhaps unsurprising that the outcomes vary between studies. Specifically, while de Jong et al. (2001) found improvements in respiratory muscle endurance following a five times a week IMT protocol at 20-40% MIP for 20 minutes, others have reported improvements in strength, but not endurance, following daily IMT for 30 minutes at 60% MIP for 10 weeks (Clanton, 1993) or twice daily for 15 minutes at 60% MIP (Asher et al, 1982). Low-intensity training has been shown to result in improvements in inspiratory muscle endurance, with inspiratory muscle strength targeted by high-intensity training (Celli, 1995; Reid & Samrai, 1995). This may explain the influence observed by de Jong et al. (2001) on inspiratory muscle endurance, although it is worth noting that a 30% maximal capacity IMT programme conducted two times a day for six weeks also reported improvements in respiratory muscle endurance, with additional improvements in FVC and P_{IMAX} (Amelina et al., 2006). Furthermore, Enright et al. (2004) conducted a high-intensity inspiratory muscle-strength-training programme three times a week for eight weeks (80% MIP), which elicited improvements in MIP (19%), respiratory muscle endurance, lung function and psychological status. The improvements elicited in both endurance and

strength in Amelina et al. (2006) and Enright et al. (2004) could be attributed to the frequency of training, with shorter and less fatiguing sessions, leading to higher average training intensities, thereby eliciting neural adaptations and, consequently, increased strength gains (Andersen et al., 2012).

In children, 50-60% MIP once a day for 10 weeks elicited improvements in inspiratory muscle strength, vital capacity, total lung capacity and exercise tolerance (Sawyer & Clanton 1993). An eight-week, two times a day for 15 minutes IMT programme combined with a 'whole strength' training programme improved $\dot{V}O_{2peak,}$ inspiratory and whole-body strength (Santana-Sosa et al., 2014). However, the specific influence of IMT is not possible to differentiate as there were no participants who solely completed the IMT programme. Furthermore, the failure to demonstrate improved exercise tolerance could be attributed to the scheduling of IMT sessions after aerobic training (Santana-Sosa et al., 2013), which could mean respiratory muscles may not have recovered sufficiently to gain the maximal benefit of IMT. Whilst an IMT protocol for children conducted twice per day, on five days across the week, for eight weeks, improved respiratory muscle endurance, the intensity was unknown and there were no changes in exercise endurance, lung function, QoL or CF clinical score (Biele et al., 2017). This could be attributed to the age difference, with CF adults tending to have more advanced lung disease than the young population in. Furthermore, Sartori et al. (2008) conducted the intervention over 12 weeks, in contrast to the eight weeks utilised in Biele et al. (2017) study, highlighting the importance of attributing the appropriate training length for specific outcomes. Finally, exercise performance could have been limited by factors other than, or in addition to, ventilatory performance. RMT may only be minimally affected, if at all, by airway obstruction, thereby inducing dynamic hyperinflation and/or breathing reserve resulting in limited exercise tolerance (Bieli et al., 2017; Williams et al., 2014).

Adherence to therapies in the CF population are often attributed to time constraints and burden of care (Bregnballe, Schiøtz, Boisen, Pressler, & Thastum, 2011; George et al., 2010). RMT protocols can be quite physically demanding which could results in non-compliance in CF participants. Table 2.1 summarises the literature involving respiratory muscle training in CF. For CF adults, complex daily medications, airway clearance routines, nutritional monitoring, PA, physiotherapy and clinical visits are

part of their daily routine (Flume et al., 2007; Yankaskas, Marshall, Sufian, Simon, & Rodman, 2004). The resultant treatment burden coupled with balancing family, work, education and other responsibilities, pose continuous challenges in this population. Indeed, adherence to antibiotic treatment is highest (80-95%), nebulized medications and pancreatic enzymes is moderate (65-80%), and vitamin therapy, dietary changes, exercise and physiotherapy is lowest (40-55%; Kettler et al., 2002). Therefore, in an era of increasing number of additive therapies in CF, determining the effects of RMT in this population is imperative due to its time-efficient nature and the possibility it could replace more time-consuming treatments. Indeed, in clinical populations, long-term adherence to therapeutic exercise regimens may be influenced by patient attributes and environmental factors (Buckworth & Dishman, 1999; Franklin, 2000; Schneider, 1995). Therefore, understanding what type of RMT intervention children and adults with CF would be willing to participant in, and the factors that influence their adherence to an intervention, has become increasingly important. Such understanding can potentially provide better adherence to interventions and improvements in health outcomes and QoL, as well as guiding the development of future interventions (Kettler et al., 2002).

As long-term survival in CF has increased significantly in the past 25 years, patient-related outcomes and HRQoL are regarded with equal importance to medically beneficial therapies (Royce & Carl, 2011). However, only three RMT studies have included HRQoL as an outcome measure (Bieli et al., 2017; Chatham et al., 1997; Enright et al., 2004). The chronic respiratory disease questionnaire (CRQD) is the most commonly used disease specific measurement tool, which evaluates four domains considered important to individuals with chronic airflow obstruction: dyspnoea, mastery, fatigue and emotion (Chauvin, Rupley, Meyers, Johnson, & Eason, 2008). Utilising the CRQD, Chatham et al. (1997) reported significant improvements ($p < 0.01$) between groups in two parameters of mastery and emotion when working at 80% of maximal effort; however, Enright et al. (2004) found no significant differences in CRQD scores between groups working at 20% of maximal effort. Nonetheless, Enright et al. (2004) found that anxiety and depression scores decreased in the 80% IMT group, with no changes in the 20% or control group. It could be postulated that higher-intensity IMT could result in greater reductions in anxiety, depression and QoL, however more IMT studies need to investigate the

effects of differing intensities of IMT on psychological factors. Furthermore, Biele et al. (2017) found no differences in HRQoL between treatment groups using the cystic fibrosis questionnaire (CFQ). When adopting the CF clinical score (CFCS), which indicates overall symptom severity, no significant difference was reported between groups at baseline or post-intervention (Biele et al., 2017). Given that the CF population in Biele et al. (2017) were 9-18 years old, their condition and lung function were likely more stable, the CFCS and CFQ may not be sensitive enough to observe small treatment effects. Indeed, the CFCS was developed for patients experiencing pulmonary exacerbation, thereby limiting its usefulness in stable CF participants (Kanga, Kuhn, Craigmyle, Haverstock, & Church, 1999). However, there is currently no alternative scoring system in CF for short-term changes in symptoms. HRQoL is an essential measure that is needed to prioritise the various therapeutic interventions that are available for those with CF, not only to provide longevity, but meaningful QoL (Royce & Carl, 2011). Furthermore, the external validity of the studies reported may also be limited by the under-use of assessing dyspnoea and exercise capacity. These measures are important to consider for further interventions as previous research in healthy individuals have found after RMT individuals' perceptions of breathlessness and maximal capacity has improved (el-Manshawi, Killian, Summers, & Jones, 1986; Romer, McConnell, & Jones, 2002), which could be extremely beneficial in the CF population. Alternatively, akin to most interventions, RMT seems to have responders and non-responders (Guenette et al., 2006) and, therefore, an effect may not be observed in all participants and could be better prescribed on a patient-by-patient basis.

Table 2.1 Respiratory muscle training protocols in cystic fibrosis participants.

Author	Mode	Age (years)	Sample Size	Intensity	Frequency	Duration	Length	Outcome
Asher et al. (1982)	Flow	9-24	11	60% MIP	15 mins	2 x per day	4 weeks	↑ IMS, IME. Little effect on exercise performance
Sawyer & Clanton (1993)	Threshold	TG 11.46 ± 2.45 CG 9.76 ± 2.57	n=10 TG n=10 CG	50-60% MIP	30 mins	1 x per day	10 weeks	↑ IMS, VC, TLC and exercise tolerance
Chatham et al. (1997)	Flow	UNKNOWN	n=9 TG	80% MIP	UNKNOWN	UNKNOWN	8 weeks	↑ sputum clearance, RMF, mastery and emotion
de Jong et al. (2001)	Threshold	Group mean 19 ± 5.5	n=9 TG n= 8 CG	40% MIP	20 mins	5 x per week	6 weeks	↑ IME No changes in IMS, pulmonary function, exercise capacity,

								dyspnoea or fatigue
Enright et al. (2004)	Flow	Group mean 22 ± 4.2	n=9 TG1 n=9 TG2 n=10 CG	80% MIP	6 sets of 6 reps	3 x per week	8 weeks	↑ $P_{IMAX,}$ S_{PIMAX}, TR, VC, TLC, PWC ↓ anxiety and depression
Amelina et al. (2006)	Threshold	UNKNOWN	n=10 TG n=10 CG	30% MIP	10-15 mins	2 x per day	6 weeks	↑ FVC, $P_{IMAX,}$ RME No improvement in exercise capacity
Sartori et al. (2008)	Isocapanic hypernoea	21.36 ± 6.6	n=24	UNKNOWN	30 mins	4 sessions over 3 months	12 weeks	↑ lung function, perception of physical fitness ↓ in need for intravenous antibiotic

								Good adherence
Ozaydin et al. (2010)		13.18 ± 2.65	n=14 TG n=14 CG	30 – 80% MIV	20 mins	5 x per week	8 weeks	Abstract only
Santana-Sosa at al. (2013)	Threshold	9-12	n=10 TG n= 10 CG	Week 1-2: 40% baseline MIP Weeks 3-4: 50% baseline MIP Weeks 5-8: 40% of 'new' MIP	15 mins	2 x per day	8 weeks	Sig. benefits in VO_{2peak}, inspiratory and 'whole body' muscle strength. PI_{max} and 5RM leg-press muscle strength maintained after de-training Positive trend in QoL
Giacomodonato et al. (2015)	Normocapnic hypernoea	21-40	n=10	70% MVV	15 mins	1 x per day	8 weeks	Abstract Only

Bieli et al. (2017)	Isocapnic hypernoea	9-18	n=22	UNKNOWN	10-15 mins	2x per day 5 days a week	8 weeks	↑ RME No changes in exercise endurance, lung function, QoL, CF clinical score

MIP: mean inspiratory pressure, MVV: maximum voluntary ventilation, mins: minute, TG: treatment group, CG: control group, IMS: inspiratory muscle strength, IME: inspiratory muscle endurance, VC: vital capacity, TLC: total lung capacity, FVC: forced vital capacity RMF: respiratory muscle function, P_{IMAX}: inspiratory muscle strength, SP_{IMAX}: sustained inspiratory muscle strength, TR: diaphragm thickening ratio, PWC: physical work capacity, 5RM: five rep max, QoL: quality of life.

2.5 Summary

The maintenance of respiratory muscle strength and endurance, and its subsequent effects on lung function, are of vital importance for those with CF and bronchiectasis. Indeed, PA and exercise have been shown to be essential prescriptions in the management of health and well-being in those with CF and bronchiectasis. However, RMT, and specifically IMT, is a cost-effective and time-efficient treatment strategy, which has the potential to positively impact both physiological and psychological health in CF and bronchiectasis. Nonetheless, interpretation of research to date is hampered by differing study protocols, designs, lack of psychosocial outcomes and specific (i.e., children) population-based interventions. Further research is therefore warranted to understand the true extent of the impact of IMT on various health outcomes in those with CF and bronchiectasis. It is also essential to gather the views and opinions of participants across the lifespan and disease severity, as well as of the multidisciplinary team, to understand the key barriers and facilitators to adherence, thereby enabling individually tailored strategies and ultimately aiding adherence to future interventions.

Chapter 3

General Methods

3.1 Ethical Approval

Ethical approval for all studies was granted by the North West – Liverpool Central Research Ethics Committee, REC reference 16/NW/0764. Local NHS Research and Development Committees at each individual hospital site also approved all experimental procedures.

3.2 Infection Control and Patient Safety during Exercise

In accordance with standard clinical practice, segregation was ensured during any visits relating to the research study at outpatient clinics. All equipment was sterilised following each use using appropriate bactericidal wipes; data collection rooms were cleaned and ventilated following each patient. PrO2 devices were also coded to ensure that any device was not given to another CF or bronchiectasis participant.

All participants were closely monitored for any significant development of symptoms, such as severe discomfort, shortness of breath or abnormally high heart rate during exercise testing and the recovery period. Oxygen saturation (SpO_2) was measured during functional exercise capacity field tests as per The British Thoracic Society guidelines (Hardinge et al., 2015). Medical personnel were aware when testing was taking place and were available in the surrounding area in case of any adverse symptoms during or following exercise. If participants did experience any severe or persistent symptoms during testing, a respiratory physician would have provided a medical examination and determined the participant's ability to continue in the study.

3.3 Anthropometrics

Body mass (Seca 220; Hamburg, Germany) and stature (Seca 220; Hamburg, Germany) were measured to the nearest 0.01 kg and 0.01 m, respectively and body mass index was calculated (Equation 3.1). Waist and hip circumference were measured to the nearest 0.01 m at the narrowest point between the bottom of the ribs

and iliac crest, and widest point around the hips, respectively, using anthropometric tape (Seca Ltd., Birmingham, UK). Participants were required to remove their footwear and wear minimal clothing.

$$BMI = \frac{body\ mass\ index\ (kg)}{stature\ (m^2)}$$

Equation 3.1

3.4 Lung and Respiratory Function Measurements

Bronchiectasis and CF are characterised by chronic airflow limitation; therefore, spirometry remains essential to diagnose and assess the severity of the respiratory disease. Specifically, spirometry provides measures of forced vital capacity (FVC), forced expiratory volume in 1s (FEV_1), FEV_1/FVC and peak expiratory flow (PEF). FEV_1/FVC ratio is the gold standard to identify airway limitation, with severity assessed by FEV_1 (Vestbo et al., 2013). In CF and bronchiectasis, FEV_1 decline has been consistently associated with morbidity and mortality, as well as greater risk of pulmonary exacerbations, hospitalisations and colonisation of *Pseudomonas aeruginosa* (Guan et al., 2016; Kosorok et al., 2001; Onen et al., 2007; Sanders et al., 2014). Furthermore, PEF has been identified as an important predictive value for determining acute exacerbations, hospitalisations and the risk of death in those with chronic respiratory disease (Iglesia et al., 2005). Spirometry indices, specifically FEV_1, have been shown to be an important primary endpoint in clinical trials to assess the efficacy of new therapies (Mayer-Hamblett, Ramsey, & Kronmal, 2007; VanDevanter & Konstan, 2012).

FVC, FEV_1, FEV_1/FVC and PEF were assessed using a portable spirometer (Micro1, MicroRPM, Numed, Sheffield, UK), which is validated in children (>6 years; Jat, 2013) and adults (Miller et al., 2005). Participants were directed to breathe in as deeply as possible, place their lips tightly around a 'single-use' antibacterial mouthpiece and blow out as hard and as fast as possible into the mouthpiece until no air is left to exhale. Instructions for children included prompts such as "sucking on a straw" for deep inspiration and "blowing out birthday candles" for a forceful expiration (Jat, 2013). Spirometry is an invaluable screening test of general respiratory health, which allows the monitoring and assessment of therapeutic interventions, as well as how disease

course affects lung function (Miller et al., 2005). As such, spirometry is an extremely beneficial tool in clinical research. The interclass correlation coefficients (ICCs) for FEV_1, FVC, FEV_1/FVC and PEF are 0.99 (CI; 0.97, 0.99), 0.98 (0.96, 0.99), 0.86 (0.66, 0.94), 0.98 (0.96, 0.99), respectively, demonstrating excellent repeatability within this thesis.

The development of symptoms and functional limitations associated with respiratory disease are highly associated with the respiratory muscles (Moran, Piper, Elborn, & Bradley, 2010). Inspiratory muscle weakness can potentially lead to a disparity between muscle load and capacity, consequently producing higher levels of dyspnoea, reduced exercise capacity and the promotion and development of hyperventilation and respiratory failure (Gibson, 1995; Moxham, 1991; Troosters et al., 2005). Conversely, a reduction in expiratory muscle strength can adversely impact the efficiency of coughing, thereby affecting removal of secretions from the airways (Arora & Gal, 1981; Troosters et al., 2005). Previous research has shown significant reductions in respiratory muscle strength during exacerbations in CF (Naon, Hack, Shelton, Gotthoffer, & Gozal, 1993), with a reduction in respiratory muscle strength shown to contribute to respiratory problems in spontaneous breathing in bronchiectasis (BTS/ACPRC, 2009). Consequently, the assessment of both maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) and sustained maximal inspiratory pressure (SMIP) are useful to monitor changes in disease over time and to determine the impact of interventions (Moran, Piper, Elborn, & Bradley, 2010).

MIP and MEP were assessed using a portable electronic respiratory pressure meter, with a 2 mm leak to prevent glottal closure (MicroRPM, Carefusion 232 Ltd, Hampshire, UK), reported to be are valid in individuals older than 6 years (Laveneziana et al., 2019).To measure MIP, participants were asked to seal their lips firmly around the ‘single-use’ antibacterial mouthpiece. They were then instructed to exhale slowly, until they felt they had no air left in their lungs (to residual volume), and then inhale maximally for more than one second against the resistance of the gauge (ATS/ERS, 2002). To determine MEP, participants were required to inhale as much as possible and then exhale maximally for more than one second against the resistance of the gauge (ATS/ERS, 2002). Furthermore, MIP and MEP allow a simple assessment of respiratory muscle strength in a clinical setting (ATS/ERS, 2002) and

have been found to be suitable to evaluate changes within participants (Laveneziana et al., 2019). Measurements of both MIP and MEP had an excellent test-retest reliability in this thesis of ICC = 0.90 (0.77, 0.96) and 0.93 (0.84, 0.97), respectively.

The PrO2Fit (Design Net, Smithfield, USA; Figure 3.2) requires participants to inspire through a manometer from residual volume to total lung capacity, whilst sustaining that breathe for as long as possible (Formiga et al., 2018). Due to the nature of this test, the PrO2Fit can provide measures of MIP, sustained maximal inspiratory pressure (SMIP) and inspiratory duration (ID). Both SMIP and ID reflect pressure-generating and endurance capacity from residual volume to total lung capacity (Cahalin & Arena, 2015). SMIP and ID are emerging measure across several populations (Cahalin et al., 2016; Formiga, Campos, & Cahalin, 2018), correlating with a number of physiological measures, including pulmonary function, functional exercise capacity, breathlessness and health-related quality of life measures (Chatham, Baldwin, Griffiths, Summers, & Enright, 1999; Gething, Williams, & Davies, 2004; Mickleborough, Nicholas, Lindley, Chatham, & Ionescu, 2010).

For all lung function measurements, a minimum of three clinically 'acceptable' manoeuvres were performed, with a minimum rest period of 30 seconds between each attempt to minimise respiratory fatigue. The best of three consistent exhalations was recorded and values were deemed acceptable if the reported values did not exceed the next greatest by 10% or 10 cm H_20. Strong verbal encouragement was given throughout all assessments and they were performed in line with recommendations by the British Thoracic Society (BTS, 1994) and the American Thoracic Society/European Respiratory Society (2002).

3.5 Measures of Functional Exercise Capacity

The gold standard of exercise testing is cardiopulmonary exercise testing (CPET), however it is costly, needs highly specialised equipment and technical expertise to supervise and interpret (Urquhart, 2011). Field tests are low-cost, requiring minimal equipment and act as a surrogate of measuring exercise capacity. However, field walking tests are often volitional and submaximal, lacking precise measure outcomes (Urquhart, 2011). Despite this, both the six-minute walk test (6MWT) and intermittent shuttle walk test (ISWT) have been shown to be valid and reliable measures of

functional exercise capacity that are responsive to change in chronic respiratory diseases (Holland, Spruit, & Singh, 2015). Additionally, field tests can be used as predictors of survival and hospital re-admission (Singh et al., 2014).

Participants were required to wear comfortable clothing and appropriate walking shoes and to have refrained from vigorous exercise within two hours of the test commencement. All subsequent testing visits occurred, where possible, at the same time of day to minimise intra-day variability, associated with bronchodilator use (Um, Yoo, Young, Sung, & Shim, 2007). Ambulatory oxygen testing was supplied to participants if their haemoglobin saturation (SpO_2) decreased by more than 4%, or fell below 90%. Ambulatory oxygen was then provided if it was shown to be beneficial as per The British Thoracic Society home oxygen guidelines (Hardinge et al., 2015). Those participants who already used ambulatory oxygen were reassessed to ensure it remained adequate. At rest, and immediately following test cessation, measures of SpO_2, heart rate, dyspnoea, fatigue and blood pressure were taken.

3.5.1 Six-Minute Walk Test

The 6MWT is a practical self-paced test of walking capacity. Participants are required to walk as far as possible in six minutes along a 10 metre corridor (ATS/ERS, 2002). Participants were permitted to slow down their pace, and to stop and rest if necessary. Patients were verbally encouraged using standard phrases as per the ERS/ATS Technical Standard (Holland et al., 2014). The main outcome measured is walk distance (6MWD) in metres, that is strongly related to measures of peak exercise performance and moderately related to PA in daily life (Singh et al., 2014). A change in 6MWD of 30 metres or more is considered to be clinically important (Holland, Spruit, & Singh, 2015).

3.5.2 Intermittent Shuttle Walk Test

The ISWT is an externally paced maximal exercise test, controlled with pre-recorded series of beeps, where the speed of walking increases with each level (Noonan & Dean, 2000; Singh, Morgan, Scott, Walters, & Hardman, 1992; Thomson et al., 2015). A course of 10 metres in length, with two markers inset of 0.5 metres from either end

was utilised. Participants were required to walk around the cones to avoid abrupt changes in direction (Singh et al., 1992). The test was terminated when the participant could no longer continue or keep with the required pace. The test was terminated when either: (i) the patient indicated that they were unable to continue; (ii) the operator determined the participant was not fit to continue; or (iii) the operator assessed the patient was unable to sustain the speed and cover the distance prior to the beep sounding, defined as the participant being more than 0.5 metre away from the come when the beep sounds on a second successive 10 metre length (Singh et al., 1992; Thomson et al., 2015). The maximal duration of the test was 20 minutes. The number of lengths walked in metres was calculated with lower ISWT distance associated with poor survival and risk of hospitalisation in those with chronic respiratory diseases (Emtner, Arnardottir, Hallin, Lindberg, & Janson, 2007; Williams et al., 2012).

3.6 Cardiopulmonary Exercise Testing with Supramaximal Verification

CPET provides a global assessment of the integrative exercise responses, involving the pulmonary, cardiovascular and skeletal muscle systems (Weisman et al., 2003). CPETs are a relatively non-invasive, dynamic physiological overview of both submaximal and peak exercise responses, providing relevant information for clinical decision making for assessing the effectiveness of intervention strategies (Weisman et al., 2003). Although a large range of measures can be ascertained from CPET, obtaining the maximal oxygen consumption ($\dot{V}O_{2max}$) is of particular importance in clinical populations as it defines the limitations of the cardiopulmonary system (Balady et al., 2010). Indeed, $\dot{V}O_{2max}$ represents the highest physiologically attainable value, whereas $\dot{V}O_2$peak is defined as the highest value attained during exercise and represents a participant's exercise tolerance (Day, Rossiter, Coats, Skasick, & Whipp, 2003). $\dot{V}O_{2max}$ is defined by the Fick equation, as the product of cardiac output and arteriovenous oxygen difference ([C (a - v) O_2]; Equation 2) and is recognised as the gold standard for cardiorespiratory fitness and the best index of aerobic capacity (Weisman et al., 2003).

$$VO_{2max} = (HR \times SV) \times [C\,(a-v)O_2]$$

Equation 3.2

Exercise testing is an valuable investigative tool for the clinical management in those with a chronic respiratory condition (ERS, 1997; Roca & BJ, 1997; Weisman et al., 2003). Indeed, $\dot{V}O_{2max}$ is an indicator of prognosis (Nixon et al., 1992; Pianosi et al., 2005), quality of life (de Jong et al., 1997; Verhage et al., 2010) and risk of hospitalisation for exacerbations (Pérez et al., 2014) in chronic respiratory conditions.

Participants were asked to refrain from eating at least two hours before testing and to avoid strenuous exercise for at least 24 hours prior to the CPET (ERS Task Force, 1997). Following familiarisation, exercise was performed on a cycle ergometer (ViaSprint 150P; ViaSys Healthcare, Hoechberg, Germany). A cycle ergometer was chosen as it is less prone to introduce movement or noise artefacts into measurements and the work rate can be easily quantified (Weisman et al., 2003). Cycle ergometry has therefore been identified as the preferable mode of exercise in respiratory conditions. After a three-minute warm-up (10 W), participants completed an incremental ramp test with work rate determined based on information regarding the individual's PA, clinical status and familiarity with cycling (Radtke et al., 2019). Consequently, resistance was increased at a predetermined rate ranging from 10 to $25W^{\cdot -1}$, ensuring a test duration of ~ 8-12-min (Saynor, Barker, Oades, & Williams, 2013a, 2013b). Ramp protocols on cycle ergometers have been shown to represent a higher correlation between oxygen consumption ($\dot{V}O_2$) and workload compared to step, thereby reducing the error in predictive metabolic cost in individual workloads (Myers et al., 1991). Participants were required to maintain a cadence of ~70-80 revolutions per minute (rpm) until volitional exhaustion, defined as a drop-in cadence of >10 rpm for five consecutive seconds, despite strong verbal encouragement. Peak workload (W_{peak}) was recorded upon exhaustion. Following completion of the CPET, a five-minute warm-down (10 W) followed by a 10-minute seated recovery was undertaken (Saynor et al., 2013a, 2013b). Supramaximal verification (S_{max}) of maximum rate of oxygen consumption ($\dot{V}O_{2max}$) was then performed, whereby a three-minute baseline (10 W) preceded a 'step transition' to a constant work rate equivalent to 110% of peak power output (Saynor et al., 2013a, 2013b). This work rate was

maintained until voluntary exhaustion. A five-minute active recovery at 10 W was utilised following test cessation. Cardiopulmonary exercise testing with supramaximal verification has been shown to be a safe and valid measure of $\dot{V}O_{2max}$ in children, adolescents and adults who span the spectrum of CF disease severity (Causer et al., 2018) and the European Respiratory Society (ERS) supports its usage in other chronic lung diseases (Radtke et al., 2019).

Breath-by-breath pulmonary gas-exchange data were collected continuously during the incremental exercise tests (MetaMax 3B, Cortex Medical, Germany). Participants wore a facemask and breathed through an impeller turbine assemble (Jaeger Triple V, Hoechberg, Germany). The inspired and expired gas volumes were continuously sampled at 100 Hz. The $\dot{V}O_{2max}$ was taken at the highest moving average measured over 15 seconds prior to exhaustion. The gas exchange threshold (GET) was determined as the $\dot{V}O_{2max}$ at which there was a non-linear increase in carbon dioxide production ($\dot{V}CO_2$) relative to $\dot{V}O_{2max}$ and an increase in minute ventilation ($\dot{V}E$)/ $\dot{V}O_{2max}$ without an increase in $\dot{V}_E/\dot{V}CO_2$. The intraindividual day-to-day variation in measuring $\dot{V}O_{2max}$ is variable in itself, with previous research finding children and adults with no known cardiopulmonary pathology or impairment showing an ~4-6% (Jones, 1988; Shephard, 1984), or no variation (De Mendonça & Pereira, 2008; Garrard & Emmons, 1986). However, day-to-day variation is thought to be higher than those with pulmonary disease with a variation between 6% and 10% reported in those with COPD (Brown, Fischer, Stansbury, & Light, 1985; Noonan & Dean, 2000). Indeed, children with CF, a 9% intra-participant coefficient of variation has been reported (Saynor et al., 2013b), though to the author's knowledge no indices are available for intraindividual variation in bronchiectasis. Variation could be attributed to biological aspects, equipment measurement error or patient motivations (Schaun, 2017). Despite this, the MetaMax 3B has been shown to reliable and valid method of pulmonary gas analysis (Polese et al., 2015; Macfarlane & Wong, 2012), with an excellent test-retest reliability within this thesis (ICC = 0.99 (0.97, 1.0)).

Subjective ratings of perceived exertion (RPE) were recorded every minute during the CPET (Borg and Dahlstrom, 1962; Borg, 1998; Borg and Linderholm, 2009). The Borg scale has been shown to be valid and reliable method of recording exhaustion in children (Roemmich et al. 2006; Marinov et al. 2007), adults (Shariat et al., 2018;

Shinya Yamauchi, 2013) and during $\dot{V}O_{2max}$ testing (Eston, Faulkner, Mason, & Parfitt, 2006; Eston, Lamb, Parfitt, & King, 2005).

3.7 Handgrip Strength Test

There are four key hand dynamometer instruments: strain, mechanical, pneumatic and hydraulic. Whilst strain dynamometers are expensive and can be heavy, mechanical instruments have limited reproducibility in grip force measurements due to calibration problems and pneumatic devices can be influenced by the hand size of the participant due to its dependency on surface area over which the force is applied (Roberts et al., 2011). In contrast, hydraulic handgrip dynamometers are portable, economic and have a large amount of normative data available in both healthy and obstructive lung disease, making it the most suitable instrument for the interventions utilised within this thesis (Roberts et al., 2011).

Handgrip strength (HGS) is a validated measures of peripheral muscle function, which has been shown to be correlated with lung function in those with CF (M. P. Smith et al., 2018; Wells et al., 2014) and a strong determinant of exercise capacity in those with chronic lung disease (Rik Gosselink, Troosters, & Decramer, 1996). In bronchiectasis HGS was independently associated with the six-minute walk test distance (Ozalp et al., 2012) Handgrip strength was measured using a hand dynamometer (Takei 5401, Tokyo, Japan), with the grip distance altered to suit each individual participant to ensure fingers and palm were completely clasped around the handle. The Takei 5401 dynamometer has been shown to have good validity and reliability, and higher precision than other dynamometers, with systematic bias of 0.49 kg and reliability analyses of 0.02 kg (España-romero, 2010; Cadenas-Sanchez et al. 2016). Participants were asked to stand upright with the arm naturally extended straight, pointing to the floor, and squeeze as hard as they could. A total of four measurements were taken (two from each hand), alternating hands each time and the best value from each hand was recorded in kilograms. The best value from each hand was recorded in kilograms. Of importance, hand dominance was recorded given that research has found a 10% difference in strength between dominant and non-dominant hands (Hepping, Ploegmakers, Geertzen, Bulstra, & Stevens, 2015). Verbal encouragement was given throughout the test. The same hand dynamometer was used

throughout the study to ensure reliability (ICC = 0.92, (0.82,0.97)) and to minimise systematic error.

3.8 Inspiratory Muscle Training Protocol

The PrO2Fit (Design Net, Smithfield, USA; Figure 3.1) is a flow resistive device, requiring participants to breathe through a 2mm leak, present to prevent glottal closure. The PrO2 fit has several psychologically and physiologically appealing characteristics such as live biofeedback, monitoring of adherence remotely, auditory and visual support via an app, increasing work-to-rest ratio, as well as being home-based and being easy to alter the IMT parameters. Due to the specific PrO2 software being able to correct and adjust airflow, and therefore inspiratory muscle power, a very accurate workload is provided (Chatham et al. 2009; Enright & Unnithan 2011; Enright et al. 2004; Ionescu et al. 1998). This correction and adjustment results in a constant workload being imposed on the inspiratory muscles and therefore is equivalent to the inspiratory force throughout all inspirations (Cahalin et al., 2013). Thus, the PRO2fit provides a workload that is isokinetic-like, yielding consistent work throughout all inspiration (Cahalin et al., 2013). Compared to other forms of IMT testing or training, the diagnostic and rehabilitation attributes of isokinetic work in the peripheral muscles has been observed to be superior (Chatham, 2000; Chatham, Baldwin, Griffiths, Summers, & Enright, 1999; Chatham et al., 1994)**.** The reliability and validity of measurements from PrO2Fit have only been reported in patients COPD with an ICC of 0.99 (0.95-1.0; Formiga, Roach, et al., 2018).

Figure 3.1. A PrO2Fit inspiratory muscle training device.

Training was performed three times a week, with at least 24 hours separating training sessions, over eight weeks. In adults and children, neural adaptations have been found to occur in the first four weeks of a strength training intervention (Brown et al., 2017; Ramsay et al., 1990), with any improvements beyond four weeks considered morphological (Folland & Williams, 2007). Indeed, previous IMT studies have found eight weeks to be sufficient in producing significant physiological and psychological adaptation in bronchiectasis (Liaw et al., 2011; Newall, Stockley, et al., 2005; Ozalp et al., 2019) and CF (Chatham et al., 1997; Enright et al., 2004; Santana-Sosa et al., 2014). Furthermore, a similar IMT protocol produced significant improvements in MIP, SMIP, vital capacity, total lung capacity, physical work capacity and diaphragm thickness, as well as reductions in anxiety and depression scores (Enright et al., 2004). To improve the respective components of strength, strength endurance and endurance intensities of 80-100%, 60-80% and approximately 60% of maximum voluntary contraction are required (Newton & Karmer, 1994). A significant positive relationship between percentage increase in MIP and relative magnitude of IMT load (Rochester, 1991), suggests that the higher the load, the greater the relative inspiratory muscle strength increase (Ernesto Crisafulli et al., 2007). Therefore, the three SMIP measurements were recorded at the start of each training session and the highest sustainable profile was selected automatically and redrawn by the computer as a training template equating to 80% of the maximum pressure profile (Figure 3.2). This ensures that a true, real-time 80% target is provided for that day, facilitating an individualised and progressive nature of training (Cahalin & Ross, 2015).

Inspiratory training manoeuvres were repeated using a regime of six repetitions across six levels. During each set of inspirations, the rest time between repetitions was progressively reduced from 60 seconds to 45, 30, 15, 10 and finally 5 seconds. If at any point the participant failed to achieve a least 80% of the computer-generated template, the test would terminate. All training sessions were uploaded automatically to the cloud allowing monitoring sessions and encouraging adherence.

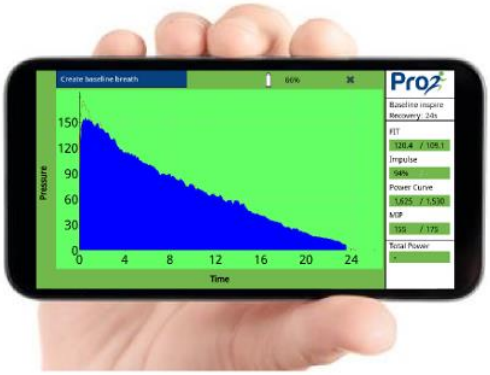


Figure 3.2 PrO2Fit app showing example training template equal to 80% of an individual's maximum pressure profile.

Participants were given full training on the PrO2Fit device and guided on how to set up and navigate the app to complete a training session. Training was also given to ensure participants were completing an appropriate inspiratory manoeuvre. To begin with, participants were coached without the device to 'empty' their lungs slowly and with control and then inspire by 'sucking' in the air hard and fast. When they were comfortable with this procedure, they were then given the PrO2Fit device to practice undergoing a SMIP manoeuvre with the app. Participants were encouraged to practice and ask any questions until they were comfortable with the training regime.

3.9 Physical Activity Levels

PA is defined as any bodily movement generated by the contraction of skeletal muscles that raises energy expenditure above resting metabolic rate, and is characterised by a modality, frequency, intensity, duration and context of practice (Caspersen et al., 1985). Sedentary behaviour is defined as any waking behaviour characterised by an energy expenditure ≤ 1.5 metabolic equivalents (METs), while in a seated, reclined or lying posture (Sedetary Behaviour Research Network, 2012; Tremblay et al., 2017). The validity and reliability of self-reported questionnaire-derived physical activity levels have been questioned as they are susceptible to bias and subsequently over- or under-estimate PA and sedentary time (Jantzen et al., 2016; Ruf et al., 2012). Direct measures, such as accelerometery, can provide accurate information regarding the

quantity, intensity and pattern of PA and have been shown to be well tolerated in clinical populations (Bassett, John, & Bassett, 2010).

Participants wore an ActiSleep+ (ActiGraph LLC, Pensacola, FL) accelerometer for seven consecutive days (Aznar et al., 2014; Mackintosh, Ridgers, Evans, & McNarry, 2018; Watz, Waschki, Meyer, & Magnussen, 2009), on their right mid-axillary line at the level of the iliac crest, which assesses acceleration in the vertical, antero-posterior and mediolateral axes. A high sampling frequency of 100Hz was chosen to prevent the loss of vigorous data processing that occurs at lower frequencies (e.g. default 30Hz; Deenik, 2019). Hip placement of the ActiSleep+ was chosen due to its optimal close location to the centre of mass, therefore reflecting movement of the whole body (Rosenberger et al., 2013; Westerterp, 1999). Furthermore, better classification of activities into sedentary and light and moderate-to-vigorous PA have been reported from hip placement (Rosenberger et al., 2013). Additionally, a self-report log accompanied the monitors to record if and why the ActiSleep+ was removed (i.e water-based activities) and a PA log (type, duration), allowing for cross examination of the data (ActiGraph, 2012). ActiSleep+ has been shown to be valid and reliable for PA measures in healthy paediatric (Kinder et al., 2012) and adult populations (Aadland & Ylvisåker, 2015; Cellini, Buman, Mcdevitt, Ricker, & Mednick, 2013), as well as those with CF (Ruf et al., 2012) and bronchiectasis (O'Neill et al., 2017).

Data was downloaded and analysed using ActiLife Software 6 (ActiGraph v6.10.4; Pensacola, FL). One second epochs with sustained periods of at least 20 minutes at zero counts were considered non-wear time to ensure accurate assessment of PA intensity (Catellier et al., 2005). To be included for analyses, participants were required to have worn the ActiSleep+ for $\geq$ 9 hours$\cdot$day^{-1}, for at least three days (Mattocks et al., 2008), including one weekend day (Aadland, Andersen, Anderssen, & Kvalheim, 2013), which has been previously used in clinical populations (Ryan et al., 2015). PA is suggested to differ between weekdays and weekend days in children with CF (Aznar et al., 2014; Mackintosh, Ridgers, Evans, & McNarry, 2018) and in adults with chronic respiratory condition (Watz et al., 2009). It is, therefore, pertinent to analyse the type of day separately to gain further insight into PA levels in chronic respiratory populations. Currently, there is a lack of developed and validated age- and

population-specific cut-points for CF and bronchiectasis populations (Mackintosh, Ridgers, Evans, & McNarry, 2018; O'Neill et al., 2017). Cut point selection may be specifically relevant in chronic respiratory conditions, whose relative intensity of a given count rate could be argued to be higher than their healthy peers (Mackintosh et al., 2018).

For children, Evenson et al. (2008) cut-points have been shown to be a valid and reliable measurement of activity intensity (sedentary: <100 counts·min^{-1}, light: 100-2,295 counts·min^{-1}, moderate- to- vigorous 2,296-4,011 counts·min^{-1} and vigorous: physical activity >4,012 counts·min^{-1}) in children and adolescents (Trost et al., 2011). In adults, Troiano et al. (2014) cut-points were used to determine activity spent at different intensity categories (sedentary: <99 counts·min^{-1}, light: 100-2,019 counts·min^{-1}, moderate- to- vigorous 2,020-5,998 counts·min^{-1}, vigorous PA: >5,999 counts·min^{-1}). Moderate and vigorous PA were summed to obtain moderate-to-vigorous physical activity (MVPA) for all ages.

3.10 Questionnaires

3.10.1 Cystic Fibrosis Questionnaire

All participants completed the age-appropriate version of the cystic fibrosis questionnaire–revised (CFQ-R; Modi & Quittner, 2003; Quittner et al., 2000), a disease-specific health-related quality of life (HRQoL) questionnaire designed to measure the physical, social and emotional impact of CF on participants. The CFQ-R was the first disease-specific patient reported outcome for CF patients and has demonstrated reliability, interval validity and clinical sensitivity (Gee, Abbott, Conway, Etherington, & Webb, 2000; Quittner, Buu, Messer, Modi, & Watrous, 2005; Quittner et al., 2012). Furthermore, a strong convergence between the CFQ-R scales and key health outcomes has been reported (Quittner et al. 2012). Quality of life dimensions, disease-related symptoms and overall health perceptions are assessed on Likert-type scales and scores are standardised on each scale ranging from 0 to 100. The CFQ-R child version consists of 35 items grouped into eight dimensions and the adolescent/adult version consists of 50 items grouped into 12 domains. Specific subscales include physical functioning, role functioning, energy/fatigue, psychological, emotional and social functioning, eating disturbances, body image,

respiratory symptoms, digestive symptoms, weight disturbance, treatment burden and subjective health perceptions. Higher scores on the subscales indicate a better HRQoL.

3.10.2 Self-Determination Theory

Self-determination theory (SDT) posits three universal psychological needs (autonomy, competence, and relatedness), suggesting that all three must be met to ensure ongoing satisfaction for people to maintain optimal performance and well-being. Needs satisfaction is a questionnaire used to assess the degree to which people feel satisfaction regarding their three key needs (Deci & Ryan, 2000). SDT is the only theory of motivation and behaviours which emphasises the importance and assessment of autonomous self-regulation (Levesque et al., 2006). Autonomous or self-determined functioning are differentiated by SDT as types of behavioural regulation. There are four different types of behavioural regulation: i) introjection, which refers to taking in an activity but not accepting it as one's own; ii) identification, which refers to accepting the value of an activity as personally important; iii) integrated, which refers to integrating that identification with other aspects of one's self and; iv) extrinsic, which refers to the external influence behind one's choices (Ryan & Deci, 2000). The treatment self-regulation questionnaire assesses participants' perceptions as to the degree in which they perceive an intervention provides autonomy support (Williams, Rodin, Ryan, Grolnick, & Deci, 1998). Within SDT, competence is assumed to be one of the three fundamental psychological needs, therefore a person's feelings of perceptions of competence towards an activity is theorised to be important as it facilitates people's goal attainment, while providing a sense of need satisfaction from engaging in an activity at which they feel effective (Ryan & Deci, 1985). Therefore, employing a self-determination theory grounding (Ryan & Deci, 1985), all participants completed psychological measures of self-regulation, needs satisfaction and perceived competence in relation to IMT. These measures were taken at baseline and following initial evaluation tests were appropriate. All measures are validated for use with clinical populations and modifications of items to the specific context, as done in this thesis, are permitted (Ng et al., 2012; Williams, Ryan, & Deci, 1985).

3.11 Interviews

There are three fundamental types of research interviews: structured, semi-structured and unstructured. Structured interviews consist of a list of predetermined questions, with little to no variation and no scope for follow-up questions to answers that warrant further elaboration. They only allow limited participant responses and therefore are of little use when looking for in-depth discussion (Gill, Stewart, Treasure, & Chadwick, 2008). In contrast, unstructured interviews are performed with little or no organised questions and do not reflect any preconceived ideas or theories (Legard et al., 2003) and therefore are at risk of interviewer bias (Saks & Allsop 2013). Semi-structured interviews are composed of several key questions that help define the areas to be explored and allows the interviewer or interviewee to diverge in order to pursue an idea or respond in more detail (Britten, 1999). The flexibility of this approach makes it advantageous in an intervention setting, allowing discovery and elaboration of information that is important to the participant that may not have been thought of by the research team (Gill et al., 2008). Interviews were conducted with individuals to allow comparison of responses between healthy and clinical populations, while also looking for consensus opinions among individuals with differing levels of health and ability (Carter & Wheeler, 2019)

Children and adults were required to complete one, face-to-face, individual semi-structured interview with follow-up questions. All questions were open-ended allowing interviewees the opportunity to explore their experiences and to expand on their thoughts, feelings and ventures in undertaking an IMT program (Dicicco-Bloom & Crabtree, 2006; Given, 2008). Clarification and/or elaboration was sought when required and themes were pursued as they arose. The language was adapted to ensure full understanding from younger children. Interviews were recorded and transcribed verbatim for analyses, which was completed manually.

Thesis Map

Traditional PR is a supervised program that incorporates exercise training, health education, and breathing techniques for those with lung conditions or problems. However, PRs applicability and effectiveness in other respiratory diseases other than COPD remains to be elucidated.

Determination of Pulmonary Rehabilitation Efficacy in those with Respiratory Disease	
Aims	**Findings**
To determine the effectiveness of PR in various respiratory disease and investigate the influence of sex, and socioeconomic status and their interaction on adherence	

Chapter 4

Determination of Pulmonary Rehabilitation Efficacy in those with Respiratory Disease

McCreery, J.L., Mackintosh, K.A., Duckers, J., Lines, T., Chamberlain, J., Jones, M., McNarry, M.A. (2019). P21 Influence of attendance rate on pulmonary rehabilitation in those with respiratory disease. *Thorax*, 74: A100.

4.1 Introduction

Pulmonary rehabilitation (PR), first defined by the American College of Chest Physicians Committee in 1974, is a comprehensive multi-faceted intervention tailored to individual needs. Specifically, PR includes education, behaviour change and exercise training components, all of which are intended to improve physical and psychological health (Spruit et al., 2013). In chronic obstructive pulmonary disease (COPD), PR has been shown to relieve dyspnoea and fatigue and improve health-related quality of life (HRQoL). Moreover, PR has been shown to significantly improve exercise capacity in those with COPD, while enhancing the sense of control that individuals have over their condition (McCarthy, 2015). Indeed, given the strength of evidence, the Cochrane Airways Editorial stated that no further research is required regarding the benefits of PR in those with COPD (McCarthy, 2015). However, the applicability of PR to other respiratory conditions, and the factors that influence its effectiveness, largely remains unresolved.

Evidence suggests that PR is feasible, safe and possibly effective for those with a variety of respiratory diseases (Rochester, Fairburn, & Crouch, 2014). Specifically, PR has been associated with improvements in HRQoL, exercise capacity, clinical symptoms and/or exacerbations in both restrictive lung diseases (Naji et al., 2006), including idiopathic pulmonary fibrosis (Jastrzębski et al., 2006), and obstructive lung diseases, such as bronchiectasis (Lee et al., 2017; Patel et al., 2019) and asthma (Schultz et al., 2017). However, many of these studies are characterised by small participant numbers due to poor participant uptake and a large dropout rate (Steiner et al., 2017), with suggestions that the high treatment burdens associated with some of these respiratory diseases may preclude such patients from adhering to a regular combined exercise and education programme (Metersky & ZuWallack, 2019). Steiner et al. (2017) suggested that socioeconomic status (SES) may also be a key contributor. It is also pertinent to note that even in studies that have reported beneficial effects of

PR, the magnitude of these effects is generally considerably smaller than those elicited in those with COPD. It therefore appears that PR may not be transferable from COPD, potentially due to the composition of the PR programme being unsuitable for the specific, and highly varied, aetiologies of different chronic respiratory diseases (Holland, Wadell, & Spruit, 2013). However, considerable inter-study heterogeneities in the specific composition of the PR programme precludes the determination of whether the inter-condition differences in effectiveness are due to these methodological variations, adherence or disease-specific factors.

Biological sex is a potent determinant of disease aetiology and progressions; in comparison to their male counterparts, females with COPD have been shown to have significantly higher degrees of dyspnoea, lower disease-related HRQoL, poorer exercise performance and function, and poorer psychological status (De Torres et al., 2005; Martinez et al., 2007; Watson et al., 2004). However, despite such differences, PR guidelines do not vary by sex. This may be because little is known regarding whether there is a sex-specific response to PR, whereby males and females respond to a different extent or in a different manner (Robles, Brooks, Goldstein, Salbach, & Mathur, 2014). Nonetheless, research has suggested that women elicit significantly greater improvements in dyspnoea, and functional health status in response to PR, whereas men have engendered greater increases in exercise capacity (de Torres, Casanova, de Garcini, Jaime, & Celli, 2007; de Torres et al., 2006; Watson et al., 2004).

Overall, the benefit of PR in respiratory diseases beyond COPD remains equivocal. Therefore, the primary aim of the present study was to ascertain the relative effectiveness of a standardised PR programme according to respiratory disease. The secondary aim was to determine the influence of sex and SES, and their interaction with adherence, on effectiveness.

4.2 Methods

A retrospective analysis was conducted on all patients enrolled at a university outpatient PR programme in South Wales between 2011 and 2019. A total of 1,284 participants who had a primary respiratory diagnosis: (COPD (n= 878), asthma (n= 39), interstitial lung disease (ILD; n= 211), COPD/Asthma (n=79) and bronchiectasis (n= 77)) were included in the current analyses. Patients were referred to PR if they

met the eligibility and exclusion criteria outlined by The British Thoracic Society (Bolton, Bevan-Smith, Blakey & et al., 2013). Values of forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) were measured using spirometry in line with the European Respiratory Society Taskforce guidelines (Miller et al., 2005). Predicted values for pulmonary function were determined according to Cotes et al. (2009). Anthropometric measures of height (m), body mass (kg), and BMI ($kg \cdot m^2$) were taken. The program content and delivery remained consistent over the period included within this study. All patients with a primary diagnosis of respiratory disease, who were referred to the PR programme, irrespective of whether they had secondary concomitant conditions, were included in this study. Given that some patients participated in the PR programme more than once over the specified period, only data from the initial engagement were included.

4.2.1 Pulmonary Rehabilitation Programme

The outpatient PR programme was multidisciplinary, including input from occupational therapists, physiotherapists, dietitians, physicians, specialist respiratory nurses and a smoking cessation counsellor. Patients were requested to attend the rehabilitation unit three days per week, for six weeks. Each session lasted approximately two hours and consisted of educational activities, exercise, and mental well-being sessions. Educational activities, which were delivered for approximately 40 minutes at the start of each session, focused primarily on patients' understanding of their pulmonary pathophysiology, behavioural change and anxiety management and how to integrate rehabilitation into their daily lives. Further discussions were aimed at the mechanisms of breathlessness and how to identify and cope with breathless episodes, as well as methods of chest clearance, the type and use of pulmonary medicines and the importance of exercise and nutritional status.

Beyond education, an individually prescribed 30-minute exercise training programme consisted of upper- and lower-body exercises. An upper-body, mixed-apparatus circuit consisting of weights or elastic resistance bands, was used, with patients completing as many repetitions in a two minute period as possible on each apparatus. Step-ups, treadmill and self-paced cycle exercise were used for the lower-body. Specifically, patients were required to walk for as long as possible on the treadmill at 80% of their maximum walking speed, derived from the shuttle walk test (Singh, Morgan, Scott,

Walters, & Hardman, 1992), rating their breathlessness on a modified Borg scale (Borg, 1998). Once the patient was comfortable, increases in either speed or incline on the treadmill and resistance on the bike, were continued until the target of three-to-five out of ten on the Borg Scale was achieved. During the initial exercise test, if patient's haemoglobin oxygen saturation (SpO_2) decreased by more than 4% or fell below 90%, they were offered ambulatory oxygen testing. If shown to be beneficial, ambulatory oxygen was subsequently provided and used as per The British Thoracic Society home oxygen guidelines (Hardinge, Annadale, Bourne, & et al, 2015). If patients already used ambulatory oxygen, they were reassessed to ensure it remained adequate and titrated if indicated. The final component of the PR programme involved stress management and relaxation to promote the patients' mastery and control over their illness. Throughout the PR programme, individuals were encouraged to set goals and focus on specific needs in activities of daily living or specific physiotherapy advice. Additionally, patients were offered dietary advice, with those with a body mass $< 20\ kg \cdot m^{-2}$ advised on formal supplementation and those $> 25\ kg \cdot m^{-2}$ on weight loss techniques.

4.2.2 Clinical Outcomes

The primary anthropometric outcome was considered free fat mass (FFM; kg) assessed using Tanita bio-impedance scales (Tanita TBF-300MA). Depending on patient ability, the intermittent shuttle walk test (ISWT) or the six minute walk test (6MWT) were used, to estimate cardiorespiratory fitness levels. The ISWT is a progressive 10 metre walking test with audio cues indicating change of speed and progression to the next level (Singh et al., 1992; Noonan & Dean, 2000). The test was terminated when patients were unable to cover the distance in time for the beep, or if they exhibited breathlessness, reached 85% of their maximum heart rate or there were any obvious signs or symptoms of distress. For the 6MWT, the distance covered, along a 10 metre corridor , in six minutes was used to asses performance capacity (ATS/ERS, 2002). Patients were able to rest within the six minutes if necessary. Finally, handgrip strength was measured using a hand dynamometer (Takei 5401, Tokyo, Japan), with grip distance altered to suit each individual patient. Patients were instructed to stand upright with the arm straight down by their side pointing to the floor and squeeze as hard as they could. Two repetitions were performed on each hand and a combined

overall average was calculated from both right- and left-hand results (Jeong et al., 2017; Roberts et al., 2011).

To determine the impact of the patient's condition on their overall health, daily life and perceived well-being, the St George's Respiratory Questionnaire (SGRQ) was used (Jones, Quirk, Baveystock, & Littlejohns, 1992). The SGRQ has three components focusing on symptoms (frequency and severity), activities (that cause or are limited by breathlessness) and impact (social functioning, psychological disturbances resulting from airway disease). The SGRQ yields a total score out of 100, with higher scores indicative of more severe limitations. Internal consistency reliability, assessed with Cronbach's alpha (Cronbach, 1951), was 0.85 for the overall SGRQ scale and 0.81, 0.78 and 0.80 for symptoms, activity and impact subscales, respectively. The Hospital Anxiety and Depression Scale (HADS) was used to assess the symptom severity of anxiety disorders and depression (Snaith, 2003). The HADS, a valid and reliable measure (Snaith, 2003), is a 14-item questionnaire on a scale of 0 (no anxiety/depression) to 21 (maximum anxiety/depression); scores greater than eight indicate clinically relevant anxiety and depression. Cronbach's reliability coefficient was 0.82 and 0.74 for HADS anxiety and depression, respectively.

4.2.3 Index of Multiple Deprivation

The Welsh Index of Multiple deprivation (WIMD; www.wimd.gov.wales), a measure of relative deprivation for areas in Wales was used to assess SES. The WIMD incorporates eight separate domains and weights of deprivation (income [22%], employment [22%], health [15%], education [14%], access to services [10%], community safety [5%], physical environment [5%] and housing [7%]). The overall index is constructed from a weighted sum of the deprivation score for each domain. The weighted score reflects the importance of the domain as an aspect of deprivation, and the quality of the indicators available for that domain. WIMD ranks all areas in Wales from 1 (most deprived) to 1,909 (least deprived). Patient postcodes were used to obtain deprivation data pertaining to the area in which the patient lived at the time of their enrolment on the PR programme.

4.2.4 Statistical Analysis

A general linear model with univariate analysis was used to determine the relationship of the differing respiratory groups between variables at baseline. To account for the

repeated and correlated nature of data, linear mixed-effects models were used to determine the influence of, and interaction between, respiratory disease percentage attendance, overall deprivation score, sex, and walk test distance in each respiratory disease compared to COPD. All condition combinations were entered into one model, with a covariate (SGRQ activity domain) added to subsequent adjusted models to determine their effect. Statistical analyses were performed using statistical package STATA.13 (StataCorp 2001. Statistical Software: College Station, TX: Stata Corporation). All data are presented as means ± SD and statistical significance was accepted when $p \leq 0.05$.

4.3 Results

There were significant differences in age, FEV_1%predicted, FVC, FFM, BMI and SES between respiratory groups at baseline ($p < 0.001$; Table 4.1). COPD patients had the lowest FEV_1% predicted (47.0 ± 20.0) and highest FVC (2.5 ± 3.9 l), with those with COPD/Asthma having the highest BMI (30.8 ± 5.6 $kg \cdot m^2$). Those with ILD had the highest FEV_1% predicted (79.6 ± 20.6), and FFM (52.7 ± 9.9 kg), while bronchiectasis patients had the lowest FVC (2.0 ± 0.5l), FFM (45.1 ± 7.8 kg) and BMI (25.9 ± 5.0 $kg \cdot m^2$). SES was highest in the bronchiectasis group (1,136.0 ± 650.6) and lowest in asthma (782.1 ± 588.5; Table 4.1).

Table 4.1. Baseline characteristics according to respiratory disease.

	Total n = 1,268	**COPD n = 881**	**Asthma n = 39**	**Bronchiectasis n = 77**	**ILD n = 192**	**COPD/Asthma n = 78**	**Between Group Differences *p-values***
Age	68.2 ± 9.7	67.5 ± 9.5	70.0 ± 10.1	69.8 ± 10.8	72.1 ± 9.8	64.4 ± 9.7	0.000*
Sex Male	680	456	13	18	113	27	
Sex Female	663	422	26	59	98	52	
Height (m)	1.7 ± 0.9	1.6 ± 9.5	1.7 ± 0.1	1.6 ± 0.1	1.7 ± 0.1	1.6 ± 0.3	0.899
FFM (kg)	50.0 ± 11.0	49.6 ± 10.7	48.8 ± 9.4	44.8 ± 6.8	52.9 ± 10.1	51.7 ± 11.4	0.000*
BMI (kg·m^2)	28.0 ± 6.8	28.0 ± 6.6	29.1 ± 5.6	25.9 ± 5.0	28.4 ± 5.7	31.2 ± 5.6	0.000*
FEV_1 (l)	1.51 ± 0.6	1.5 ± 2.2	1.23 ± 0.5	1.3 ± 0.4	1.9 ± 0.5	1.3 ± 0.5	0.940
FEV_1 %pred	54.9 ± 21.2	48.1 ± 0.1	54.6 ± 18.0	61.9 ± 23.5	79.6 ± 20.6	56.4 ± 20.2	0.000*
FVC (l)	4.5 ± 0.9	2.6 ± 6.9	2.4 ± 0.9	2.0 ± 0.5	2.4 ± 0.7	2.4 ± 0.7	0.154*
FVC %pred	76.8 ± 22.4	76.0 ± 20.2	71.1 ± 18.1	79.3 ± 20.8	78.3 ± 21.5	81.3 ± 21.7	0.168
SES	899.4 ±654.9	810.8 ± 637.4	782.1 ± 588.5	1,136.0 ± 650.6	870.2 ± 609.1	1,126.7 ± 679.8	0.000*

*COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease; BMI, body mass index; FFM, free fat mass; FEV_1, forced vital capacity in 1 second; FEV_1%pred, forced vital capacity in 1 second percentage predicted; FVC, forced vital capacity; FVC%pred, forced vital capacity percentage predicted; SES, socioeconomic status.*p <0.05.*

Table 4.2. Changes pre-and post -pulmonary rehabilitation in physiological and psychological measurements across differing respiratory diseases.

	Total n = 1,284	**COPD n = 878**	**Asthma n = 39**	**Bronchiectasis n = 77**	**ILD n = 211**	**COPD/Asthma n = 79**
			SGRQ			
Symptom	57.4 ± 22.7*	57.4 ± 23.0*	68.3 ± 17.7*	58.0 ± 18.0	51.3 ± 21.6	61.6 ± 21.5
Activity	77.7±15.5*	79.3 ± 16.3*	85.5 ± 11.3	67.3 ± 17.4*	75.1 ± 16.9	77.9 ± 18.4*
Impact	37.7 ±16.2*	37.6 ± 16.7*	36.1 ± 17.0*	32.6 ± 14.6*	35.7 ± 15.3*	36.5 ± 16.3*
Total	52.5 ± 14.0*	53.4 ± 14.9*	54.4 ± 11.6*	47.3 ± 13.3*	50.1 ± 13.6*	53.3 ± 15.3*
			HADS			
Anxiety	6.3 ± 3.8*	6.4 ± 4.0*	7.2 ± 4.1	6.1 ± 4.0*	5.0 ± 3.3*	7.2 ± 4.3*
Depression	4.3 ±3.4*	4.5 ± 3.4*	4.5 ± 3.4*	3.6 ± 3.0*	3.8 ± 2.9*	4.3 ± 3.5*
			Strength			
HGS	26.2 ±9.4*	25.7 ± 8.9*	26.3 ± 8.3	21.5 ± 6.9	27.6 ± 9.6	25.7 ± 9.9
			Exercise Capacity			
6MWT (m)	221.3 ± 79.3* (n = 356)	220.5 ± 80.6* (n = 282)	246.7 ± 77.6 (n = 10)	243.6 ± 91.3* (n = 16)	237.3 ± 84.3* (n = 26)	192.4 ± 59.3 (n = 16)
ISWT (m)	212.7 ± 95.8* (n = 650)	213 ± 87.5* (n = 456)	181 ± 62.3* (n = 23)	231.7 ± 91.6* (n = 42)	223.5 ± 104.3* (n = 78)	224.9 110.3* (n = 38)

*COPD, chronic obstructive pulmonay disease; ILD, interstitial lung disease; HADS, hospital anxiety and depression scale; SGRQ, St Georges Respiratory Questionnaire; HGS, handgrip strength; 6MWT, six-minute walk test; ISWT, intermittent shuttle walk test. *p<0.05.*

Irrespective of condition, there were significant sex differences at baseline, with females having a higher BMI (28.3 ± 6.9 kg·m^2; p = 0.017), and higher anxiety levels (9.6 ± 4.7; p< 0.001), in comparison to males (27.3 ± 5.9 kg·m^2 and 8.1 ± 4.6, respectively). In contrast, males had significantly higher FFM (57.8 ± 9.8 kg; p<0.001), HGS (31.5 ± 8.1kg; p< 0.001) and walking distance (161.9 ± 81.0 m; p <0.001), in comparison to females (42.5 ± 6.5 kg, 18.9 ± 5.2 kg, 144.6 ± 74.9 m, respectively). Post PR, a number of these differences were ameliorated, but significant differences still occurred between sexes, with females still demonstrating a higher BMI (28.5± 5.6 kg·m^2; p = 0.03) and higher anxiety levels (6.9 ± 3.9; p <0.001), compared to their male counterparts (27.5 ± 6.0 kg·m^2 and 5.7 ± 3.9, respectively). Males continued to have significantly higher HGS (32.4 ± 7.6 kg; p <0.001), FFM (57.5 ± 9.6 kg; p <0.001) and walking distance (226.5 ± 93.0 m; p <0.001) in comparison to females (19.8 ± 5.6 kg, 42.6 ± 6.5 kg, 204.1 ± 86.0 m, respectively; Table 4.3). Those with a low SES exhibited significantly higher levels of anxiety, SGRQ total score and dyspnoea at baseline and post PR (p<0.05).

Table 4.3. Pre- and post-pulmonary rehabilitation in physiological and psychological outcome measurements between and withing females and males, irrespective of disease.

	PRE		POST	
Parameters	**Male**	**Female**	**Male**	**Female**
		Anthropometrics		
FFM (k)	27.4 ± 6.9	28.5 ± 6.9*	27.4 ± 5.9	28.5 ± 6.9*
BMI (kg·m$^{2)}$	57.5 ± 9.6	42.8 ± 6.4*	57.3 ± 9.6	42.7 ± 6.2*
		SGRQ		
Symptom	65.0 ± 20.9	66.3 ± 21.1	57.3 ± 22.3	58.7 ± 22.6
Activity	83.8 ± 15.6	84.9 ± 14.8	76.6 ± 17.2	79.0 ± 16.8
Impact	47.7 ± 17.6	50.0 ± 18.4	37.3 ± 16.7	36.6 ± 16.4
Total	61.4 ± 14.9	63.3 ± 15.3	52.4 ± 15.0	53.1 ± 14.8
HADS		***HADS***		
Anxiety	7.8 ± 4.5	9.4 ± 4.6*	5.8 ± 3.9	6.9 ± 3.9*
Depression	7.4 ± 3.9	7.7 ± 3.7	4.6 ± 3.5	4.2 ± 3.2
		Strength		
HGS	31.7 ± 7.8	18.8 ± 5.1*	32.3 ± 7.7	19.8 ± 5.5*
		Exercise Capacity		
6MWT (m)	182.2 ± 76.5	155.4 ± 69.8*	235.5 ± 82.3	210.2 ± 73.7*
ISWT (m)	153.7 ± 79.5	142.6 ± 201.7*	221.1 ± 97.1	201.7 ± 93.2*

*SGRQ, St George's Respiratory Questionnaire; HADS, hospital and anxiety scale; FFS, free fat mass; BMI, body mass index; HGS, handgrip strength; 6MWT, six-minute walk test; ISWT, intermittent shuttle walk test. Between group differences *p <0.05.*

There was a significant interaction between attendance and exercise capacity ($p < 0.001$), irrespective of disease. When compared to COPD, PR was shown to be effective across all disease types in both physiological and psychological parameters (Table 4.4). There was a significant improvement in exercise capacity following PR, irrespective of disease. Males had a significantly higher exercise capacity at both baseline and post PR.

Overall, there was 70.5% average adherence (number of sessions completed) across the programme, with COPD (84%), asthma (85%) and bronchiectasis (75%), having the highest adherence rates, and fibrotic lung disease (54%) the lowest. All participants, irrespective of disease, were categorised into four groups: did not attend ($n = 133$), low adherence (<33% sessions; $n = 130$), moderate adherence (33-66% sessions; $n = 134$) and high adherence (>66% sessions; $n = 950$). SES had a significant impact on attendance, with those in a lower SES exhibiting poorer attendance ($p = 0.026$).

Table 4.4 Linear mixed models with random effects looking at chronic respiratory conditions compared to chronic obstructive pulmonary disease and the impact of sex, time, attendance and deprivation to a pulmonary rehabilitation programme.

Coefficients	Estimate	SE	z	95% Confidence Intervals		*p-value*
Asthma	-5.64	25.85	-0.22	-56.31	45.03	0.270
ILD	14.26	14.29	1.00	-13.75	42.27	0.318
COPD/Asthma	4.53	16.80	0.27	-28.39	37.45	0.787
Bronchiectasis	26.45	14.24	1.86	-1.47	54.36	0.063
Male	26.31	7.07	3.72	12.45	40.45	0.000*
Time	58.84	3.99	14.76	51.02	66.65	0.000*
Attendance	41.89	2.09	20.05	37.80	46.00	0.000*
SES	0.01	0.004	2.15	0.001	0.02	0.026*

*COPD, chronic obstructive pulmonay disease; ILD, interstitial lung disease; SES, socioeconomic status; SE, standard error. *p<0.05.*

4.4 Discussion

The aim of this retrospective study was to ascertain the relative effectiveness of PR to enhance physiological and psychological health according to respiratory disease. Overall, in comparison to COPD, patients were similarly able to adhere to, and benefit from, a six-week PR programme, irrespective of the specific respiratory disease. However, SES was found to have a significant impact on attendance to PR.

The United Kingdom (UK) has a higher morbidity and mortality associated with respiratory disease compared to other western countries (Chung et al., 2002; Salciccioli et al., 2018). It is therefore paramount to identify effective treatment strategies that can address this problem, with one potential strategy being PR. The effectiveness of PR has been well documented (McCarthy, 2015), however, relatively little is known about the utility and feasibility of PR in other respiratory diseases. In contrast to previous studies, which appear to suggest a lower magnitude of effect in other respiratory diseases, the current results found a similar degree of improvement, irrespective of disease. Specifically, whilst functional capacity and HRQoL have been reported to be improved by PR in various respiratory conditions, including asthma (Conemans et al., 2018), bronchiectasis (Metersky and ZuWallack, 2019) and in those with pulmonary fibrosis (Gomes-Neto et al., 2018), there has been little consistency in the PR programmes implemented, limiting comparisons and interpretations. Moreover, such inter-study discrepancies, may reflect the specific physiological and psychological effects of each condition, or indeed the requirement for a tailored education component. Future research is therefore warranted to determine whether PR needs to be tailored to disease-specific needs. Specifically, the optimal duration, frequency and intensity of PR has yet to been identified, with current guidelines recommending a programme of three times a week for eight weeks to gain beneficial improvements. However, the current study elicited training effects in a six-week program, irrespective of disease. Poor uptake and adherence remain a significant challenge to rehabilitation and there is a need for robust, well designed, trials to explore the overall effectiveness of PR, as well as exploring exacerbations post PR (Candemir, Kaymaz, & Ergun, 2017). Furthermore, improvements in exercise capacity and HRQoL from PR have been shown to diminish over time, therefore sustaining these enhancements is fundamental to ensure long-term well-being in those with a respiratory disease (Lee & Holland, 2014).

Accessibility to PR services for patients in the UK is variable, with over 37% of patients waiting more than three months (Steiner et al., 2015). However, despite what these waiting list suggests, the rate of attendance to PR is reported to be approximately 50%, with 40% of those assessed for PR failing to enrol on or complete treatment (Garrod et al., 2006; Fischer et al., 2009; Keating, Lee and Holland, 2011; Steiner et al., 2015). Conversely, adherence to the PR reported within this retrospective study was substantially higher, with 70.5% of patients reporting high attendance, defined as >66% of sessions completed. Key reasons cited for poor compliance to large-scale PR programmes include a lack of resources, geographical distance from treatment centres and the time of scheduled classes (Steiner et al., 2015). Furthermore, working patients have been shown to be particularly disadvantaged as classes are often delivered during the traditional working day (Steiner et al., 2015; Bourne et al., 2017). Indeed, one of the reasons for the high adherence in our patient group could be their geographical closeness to the hospital, with the average travel time being 18 minutes. Qualitative studies have found that barriers to adherence in PR for those with COPD, include a lack of perceived benefit by patients, convenient transport, personal determination and physical health (Keating, Lee and Holland, 2011; Oates et al., 2017). Conversely, Guo and Bruce (2014) and Oates et al (2018) found that building patient confidence through motivational and supportive staff, access, evidence of tangible results and recognising and adjusting issues of readiness were all facilitators to participation in PR for those with COPD. However, whether these barriers and facilitators are also applicable to those undertaking PR with other respiratory diseases remains to be elucidated.

Health disparities are common in those with respiratory disease, with lower socioeconomic groups up to 14 times more likely to have a respiratory disease (Pleasants, Riley, & Mannino, 2016; Sahni, Talwar, Khanijo, & Talwar, 2017; Schraufnagel et al., 2013). Furthermore, the prevalence and impact (e.g., risk of hospitalisations) of COPD is inversely associated with SES in many countries (Prescott, Lange, & Vestbo, 1999), including the UK (Gershon, Dolmage, Stephenson, & Jackson, 2012). Similarly, asthma severity and frequency of hospitalisations are negatively related to SES (Sahni et al., 2017). In accord with a recent study (Steiner et al., 2017), the present study found that those living in a more socially deprived area had poorer attendance to the PR program. It was also noted that, at baseline, those with a lower SES had higher anxiety levels, well-being (SGRQ total score) and dyspnea.

Symptoms of anxiety have been shown to manifest in a variety of ways, including dyspnea, with patients with COPD describing their understanding of dyspnea as an experience related to anxiety and emotional functioning (Tselebis et al., 2016). A systematic review concluded that PR is beneficial in reducing anxiety, by providing active distraction from worrying thought patterns, increasing self-efficacy, and providing a meaningful mastery experience, with regular social content and support (Coventry & Hind, 2007; Tselebis et al., 2016). Educating patients on breathing control exercises during PR teaches them to recognize and control their dyspnea, increasing confidence, control and autonomy (Lorig et al., 1999). Indeed, in line with previous research (Wadell et al., 2013), improvements in anxiety post PR in the current study were shown to significantly correlate with improvements in overall health, daily life and perceived well-being (SGRQ total score). However, anxiety may manifest in physical symptoms during the course of a PR program, and it is therefore essential that patients are treated on an individual basis (Tselebis et al., 2016). The paradox that currently exists in PR is that those most likely to benefit, are least likely to adhere or participate (Fischer et al., 2007; Robertson, 2010). Therefore, understanding the impact of an individual's SES on adherence is paramount to improving outcomes for those with respiratory conditions. It is, however, important to note that SES in the current study (e.g., WIMD) was calculated based on home postcode at the time of PR enrolment, which is a reflection of the whole local area within which there is likely to be considerable variation in individual levels of deprivation.

There is a growing body of evidence that suggests that alternative strategies to conventional PR needs to be considered for lower SES patients to improve overall adherence. Specifically, the British Thoracic Society guidelines highlight the need for fundamental research on the optimal structure of PR and to improve accessibility (Bolton et al., 2013). Home-based PR could be an effective strategy in those with lower SES. Indeed, a recent study in 459 COPD patients found that a once-weekly, home-based PR for eight weeks was effective, regardless of SES (Grosbois et al., 2019). Furthermore, research found no significant differences when comparing the effects of online and conventional PR programmes on all outcomes measured following a six-week intervention (Bourne et al., 2017). However, it is important to acknowledge that this was a single-centre study and the applicability across different

providers and regions remains to be determined. Future multi-centered studies are therefore warranted. Whilst home-based PR may facilitate greater PR programmes in the UK, methods to offer remote supervision, provide home-based exercise equipment, as well as patient selection, need careful consideration (Bolton et al., 2013).

Congruent with previous research (Haggerty, Stockdale-Woolley, & ZuWallack, 1999; Verrill, Barton, Beasley, & Lippard, 2005), the current study found that females had poorer fitness, irrespective of disease or time-point, in comparison to their male counterparts. Reduced walking capacity, as a proxy measure for fitness, may imply progressive deterioration and thereby increase prevalence of morbidity and mortality (Awotidebe et al., 2017). Salciccioli et al. (2018) found that mortality trends for men in the UK are similar to EU15+ countries, yet women in the UK have a significantly greater mortality with respect to obstructive respiratory disease. Furthermore, the current results showed sex differences post PR in handgrip strength and anxiety, but no difference in depression or overall health, daily life and perceived well-being (SRGQ total score). However, a systematic review (Robles et al., 2014) reported that some studies showed no gender differences in PR, concluding that sex-related responses to PR remains unclear. Such contradictory evidence could be attributed to differing PR programs, settings and outcome assessments. Therefore, the impact of sex-related differences on the efficacy of PR remains to be fully elucidated; further research is therefore needed to ascertain such outcomes and the underlying needs associated with sex and respiratory diseases. Such research is warranted to enable the modification of traditional training methods to align with specific patient needs.

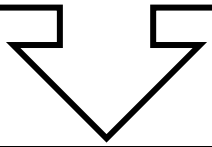
4.5 Conclusion

In conclusion, this retrospective study highlights the applicability of PR to a variety of respiratory disease, while highlighting the clinical importance of participants adhering to, and engaging in, a PR program. Further prospective studies are warranted to investigate sex differences and predictors of adherence for PR programmes.

Thesis Map

Determination of Pulmonary Rehabilitation Efficacy in those with Respiratory Disease	
Aims	**Findings**
To determine the effectiveness of PR in various respiratory disease and investigate the influence of sex, and socioeconomic status and their interaction on adherence	Pulmonary rehabilitation (PR) is applicable to a variety of respiratory diseases. Sex differences occur at baseline and post-PR. Low socioeconomic status has a negative effect on adherence.

To investigate the feasibility of alternate Pulmonary Rehabilitation strategies in those with a chronic respiratory condition, a short, home-based inspiratory muscle training intervention was undertaken. Children with Cystic Fibrosis and their multidisciplinary team were asked their thoughts and feelings on undertaking inspiratory muscle training and their thoughts for future interventions.



Assessing the Perceptions of a POWERBreath Inspiratory Muscle Training Intervention in Children with Cystic Fibrosis and their Multidisciplinary Team	
Aims	**Findings**
Ascertain the views and opinions of inspiratory muscle training from children with CF and their multidisciplinary team	

Chapter 5

Assessing the Perceptions of a POWERBreath Inspiratory Muscle Training Intervention in Children with Cystic Fibrosis and their Multidisciplinary Team

McCreery, J.L., Mackintosh, K.A., Cox, N.S., McNarry, M.A. (2018). Assessing the perceptions of inspiratory muscle training in children with cystic fibrosis and their multidisciplinary team: Mixed-methods study. *JMIR Paediatrics and Parenting*, 1(2).

5.1 Introduction

Cystic Fibrosis (CF) is the most common, inherited, life-shortening condition in the UK (Jeffery et al., 2017). Despite recent advances in pharmacological interventions (Wainwright et al., 2015), the median life expectancy remains around 40 years (Jeffery et al., 2017). Characterised by recurrent respiratory infections, breathlessness, cough, and gastrointestinal complications, CF is a multi-system disease requiring many hours of daily therapy (Sawicki, Sellers, & Robinson, 2009). With no current cure, the development or refinement of treatment strategies that increase or maintain quality of life (QoL), exercise capacity and respiratory function are paramount for the well-being of people with CF.

Inspiratory Muscle Training (IMT), which utilises restricted airflow breathing exercises to increase the mechanical load on the external intercostal muscles and diaphragm, is a subject of research interest. The increased muscular load engendered by IMT provides a stimulus to elicit a hypertrophic response (Enright et al., 2004), similar to that observed in response to strength training in limb muscles (Reid, Geddes, O'Brien, Brooks, & Crowe, 2008). Significant improvements in respiratory muscle endurance (Asher, Pardy, Coates, Thomas, & Macklem, 1982; De Jong et al., 2001), respiratory muscle strength and vital capacity (Sawyer & Clanton, 1993), have been reported in patients with CF who have undertaken IMT, and there is some evidence for a positive effect on lung function and QoL (Enright et al., 2004). Despite the potential benefits of IMT, there is a lack of consensus regarding its routine use in clinical practice due to significant variations in study protocols, small sample sizes

and lack of psychosocial outcome measures (Houston, Mills, & Solis-Moya, 2013; Reid et al., 2008). Specifically, only two studies report psychosocial health as an outcome, reporting that anxiety and depression scores decreased in an IMT group that trained at 80% of their maximal effort (Enright et al., 2004), and a trend towards an improved QoL with a combined IMT, 'whole muscle' training programme (Santana-Sosa et al., 2014). Regardless of potential efficacy, many treatment strategies are limited by participant's perceptions of, and thus adherence to, the intervention. Indeed, a common barrier to adherence cited by many adolescents with CF is the embarrassment of taking their treatments in front of other people (Rand & Prasad, 2012; Selvadurai et al., 2004). This suggests the potential utility of home-based interventions, such as IMT, that may increase adherence to treatments in adolescents with CF. However, no studies are presently available regarding the perceptions, opinions or recommendations of participants, or indeed of a MDT, concerning IMT. Furthermore, the mean age of participants in IMT studies is approximately 18.5 years (Hilton & Solis-Moya, 2018b). With average life expectancy around 45.1 years, the participants in these studies are effectively middle aged and therefore further research in the younger CF population is warranted (Carr, Cosgriff, & Rajabzadeh-Heshejin, 2015). This lack of evidence makes it difficult to establish the overall efficacy of IMT as a therapeutic strategy for adolescents with CF (Houston et al., 2013).

Therefore, the aim of this study was to ascertain the views of children, and their respective CF MDT, in relation to IMT following a four-week training programme.

5.2 Methods

Five children (11-14 years), were included if they met the following criteria: (a) took part in the pilot study of IMT conducted by Swansea University; (b) had a confirmed diagnosis of CF or were a matched control; (c) absence of any additional non-CF illness and/ or disease; and (d) voluntarily participated and provided written informed parental consent and child assent. The MDT participants (two physiotherapists; one respiratory physician) were eligible for inclusion if they provided clinical care for children with CF and had been involved in the same IMT pilot study.

5.2.1 Inspiratory Muscle Training

The IMT intervention consisted of participants undertaking 30 inspirations, twice a day, for 28 consecutive days using a POWERbreath Plus device (POWERbreath Plus LF Level 1, Gaiam Ltd. E & OE, UK). A progressive approach was adopted, whereby participants initially trained at a load of 40% of their baseline PI_{max}, increasing to 50% during weeks three and four (Santana-Sosa et al., 2014a). All procedures and protocols utilised in this study were approved by the local NHS committee (13/LO/1907).

5.2.2 Qualitative Protocol – Interviews

Children and MDT members took part in individual semi-structured interviews with follow-up questions. A semi-structured interview includes a series of pre-determined but open-ended questions, thereby allowing the interviewer to follow topical trajectories in the conversation as well as providing the interviewee freedom to express their views in their own terms (Dicicco-Bloom & Crabtree, 2006; Given, 2008). Children's interview questions were related to their thoughts and opinions of IMT. MDT's interview questions were centred around their opinions of IMT, responses from patients, and IMT reflections and recommendations. All interviews were conducted by one investigator (JM). Sample interview questions are presented in Table 5.1. All interviews were recorded and transcribed verbatim for analysis.

Table 5.1. Example Interview Questions

Interview	Topic	Examples
Children	Inspiratory Muscle Training (IMT)	What did you like and dislike about the training device? What made it easy/difficult to do the training programme?
	Future	How would you react if you were asked to do this training again?
Multi-disciplinary Team (MDT)	Inspiratory Muscle Training (IMT)	What is your opinion of the IMT device? How did the patients respond to the IMT device?
	Future	What do you think about the National Health Service adopting an IMT intervention as a treatment? What recommendations do you have for interventions you would like to see for CF patients?

5.2.3 Data Analysis

All interviews were transcribed verbatim by one author (JM) and analysed thematically (Braun & Clarke, 2014), using a manual approach. One author (JM) read and familiarised the transcripts and an initial list of codes were developed to organise the data to identify and develop themes from them (Fereday & Muir-Cochrane, 2006) A cross-examination of thematic data was undertaken by the research team in reverse,

tracing verbatim quotations back to transcripts to ensure that the developed themes were grounded in the original data (Tobin & Begley, 2004). To ensure methodological rigour, themes and verbatim quotations were then reviewed by three authors to ensure findings were worthy of attention and to offer alternative interpretation of the data (Boddy et al., 2012; Mackintosh, Knowles, Ridgers, & Fairclough, 2011). This process continued until an acceptable consensus had been reached by the group.

5.3 Results

Five children (n=3 boys) and 3 MDT's (two physiotherapists; one respiratory physician) completed the interviews. All interviews were semi-structured and lasted between 30-40 minutes. Example verbatim quotes and frequency counts have been added to provide further context. Four themes emerged from the interviews: (i) acceptability; (ii) facilitators; (iii) barriers and; (iv) recommendations.

5.3.1 Acceptability

Feedback from all participants was very positive regarding acceptability of the intervention. The MDT noted children's enthusiasm and all of the children reported enjoying the IMT intervention:

"I felt really excited [to do IMT] I just wanted to have a go at." [Girl; n = 5]

With patients even suggesting they would like to take part in future interventions:

"I was pretty sad I didn't have to do it again. I'd happily do it again." [Girl; n = 4]

Children reported good participation and adherence to the IMT intervention due to the ease of implementation:

"Like it was easy you just do it [IMT] at home. You don't have to go anywhere specific or special. You could just do it in your bedroom if you wanted." [Girl; n = 2]

And the ease of integration into daily routine;

"I got into it…I feel like I've always don't it. When you get up in the morning, you normally eat your breakfast, get ready for school, do IMT and then quickly leave the house for the bus." [Girl; n = 5]

Most importantly, children expressed enthusiasm and enjoyment:

"I really enjoyed it, I got into it…I feel like I've always done it" [Boy; n = 4]

Furthermore, all children perceived IMT to have a positive effect on their ability when partaking in physical activity (PA):

"For some reason, I don't know how, but they [lungs] almost felt like, almost got stronger. You could just breathe more freely…I could keep running for longer, I didn't have to stop and take deep breaths as much as normal." [Girl; n = 5]

Children also indicated reduced embarrassment associated with completing the treatment at home:

"I like it [using the device at home] cause of not having all the constant questions. I don't like, well, I don't mind answering questions when people do ask [about CF], but like I am not getting caught up in it all the time in school with my friends." [Boy; n = 2]

The CF care team also reported positive feedback from their patients and high adherence:

"They would have all liked to have kept the IMT device and carried on. In fact one of the patients subsequently went out and bought one and uses it as part of their routine." [Female Physiotherapist; n = 3]

Akin to the children's perceptions, CF care team members believe that the IMT training schedule fitted well around children's home and school schedules:

"From a practical point of view I think that fitted well. All feedback seemed to confirm that." [Female Physiotherapist; n = 2].

5.3.2 Facilitators

Unsurprisingly, the MDT highlighted the importance of family, specifically parental influence, with "sporty families" being labelled as easier to motivate to undertake an intervention and exercise:

"If you've a sporty family its easier…Families will support them [children] most of the families were very keen on IMT. You have to get the families on board." [Female Physiotherapist; n = 3]

Not only are family facilitators influential, but peer facilitators are key, especially for children. The MDT highlighting the importance of children with CF being seen as equal to their peers:

"It is very important to both keep them healthy and also to keep them in their peer group, you know at school and during sports activities. They need to be able to keep up with the rest of their class, so it is very, very important…A psychological benefit of being able to keep up with their peer group." [Female Physiotherapist; n = 3]

5.3.3 Barriers

Although it seemed the intervention was well adhered to and enjoyed thoroughly by all participants, barriers were nonetheless highlighted, although predominantly by the MDT rather than the children. The MDT highlighted the following main barriers to implementation of IMT:

5.3.3.1 Cost

The clinical care-team highlighted cost to be a major barrier in implementing IMT within the local National Health Service (NHS) framework:

"Obviously there is a cost implication as there is no money in the NHS for any of these things." [Female Respiratory Physician; n = 3]

Furthermore, there is a reliance on charitable income to fund airway clearance equipment:

"Cost would be a big thing and whether it was a benefit to patients" [Female Respiratory Physician; n = 3]

However, it was accentuated that if IMT proved to be successful the cost should be met:

"If it is proven to be beneficial they [the NHS] are more likely to get it. If it's proven to be beneficial and improve lung function compared to the cost of some of the drugs they [the NHS] might pay for it." [Female Physiotherapist; n = 3]

5.3.3.2 Burden

People with CF have a high treatment burden involving daily physical therapy coupled with medication. Incorporating IMT into an already busy treatment schedule was a concern raised by the MDT:

"It's yet another thing for us to ask them to do, because they do have quite a large treatment burden…so that would be the biggest con, a time thing" [Female Physiotherapist; n = 3]

This concern was also echoed by one of the children:

"It was extra work to do with everything else that I have to do." [Boy; n = 2]

Yet, one of the MDT had a solution whereby an IMT program could be viable within a CF patient's treatment schedule:

"Obviously you don't want it to be too much of a burden. Deciding whether it is better than other parts of their treatment and other part of their Physio and then substitute it [IMT] in could be an option." [Female Respiratory Physician; n = 1]

5.3.3.3 Family

Converse to families being deemed as facilitators, a physiotherapist reflected on previous cases whereby children's divorced parents have had a negative impact on children's participation levels in activities:

"The parents have divorced and the girl lives with mum. The mum has a full-time job and mum didn't push any after school clubs, dad was the one that did it previously. So that created a big barrier." [Female Physiotherapist; n = 1].

5.4.7 Recommendations

Participants were requested to comment on any changes they would make to the device and protocol. The children reported no changes, whereas the care team had numerous suggestions to improve future interventions. One of the main changes the care team suggested was the importance of knowing whether participants were adhering to the intervention:

"I don't know if you can measure compliance, but it would be good if it [IMT] can tell us how much they actually did." [Female Respiratory Physician; n = 1]

To ensure future would adherence to IMT protocols and make the intervention attractive to children it was suggested:

"Young people like to have their smart phones and apps, visual feedback in a piece of electrical equipment, that is probably the way forwards." [Female Respiratory Physician; n = 2]

Implementing a competitive element was also highlighted as important additions in future interventions:

"Feedback so they know how well they are doing. They are quite competitive so if they know the others are doing it, they'll be more motivated." [Female Physiotherapist; n = 2]

Contrastingly, despite reporting that a three-times a day intervention fitted well into a child's routine, the MDT suggested a more time efficient intervention to reduce the burden on patients:

"Three times a day would be a problem, it [IMT] would have to be something regular to get them into a routine." [Female Respiratory Physician; n = 3]

5.5 Discussion

The aim of this study was to ascertain the views of children and the CF care team in relation to an IMT intervention, thereby providing population-specific evidence to inform future interventions. Results indicate that all the children enjoyed the home-based intervention, whilst the CF care team raised concerns regarding cost, and treatment burden. Overall, these results provide important insights regarding future IMT interventions, building upon the limited literature available regarding the opinions of patients, respiratory physicians and physiotherapists.

IMT in CF patients has been reported to improve endurance and strength of the inspiratory-muscles, as well as exercise capacity (Reid et al., 2008). Previous research has shown that increases in exercise capacity are associated with improved psychosocial status in patients with chronic pulmonary disease (Lacasse et al., 2001). Additionally, a recent study found that aerobic fitness was positively associated with health-related quality of life (HRQoL) in patients with CF, underlining the importance of good physical fitness (Hebestreit et al., 2014). Whether greater perceived ability to be physically active has the potential to influence psychosocial health and QoL in patients with CF is unknown.

The perceived improvement in physical ability reported by participants could be due to the good adherence to the IMT programme. This is in contrast to previous reports that adherence to treatment in CF is sub-optimal (Jones, Curley, Wildman, Morton, & Elphick, 2015). This discrepancy could be a result of our participant's MDT, the age

of our participants and the small numbers involved in the study. Adherence levels amongst people with CF tend to decline with increasing age (Arias, Bousoño, & Díaz, 2008). In younger children treatment responsibility often lies with parents or guardians resulting in greater adherence. As adherence was a self-reported by participants in this study, it may have been over-or under-estimated and is subsequently subject to risk of bias (Prince et al., 2008). Key factors that influence adherence include family environment, stigma, embarrassment among peers and relationship with their MDT (Jones et al., 2015). Indeed, the interview findings presented here reflect a MDT that actively encourage patients to make their own choices about treatment decisions and are open to trialling new or novel interventions such as IMT.

With a reduced exercise capacity and low daily PA levels potentially impacting on CF patient's psychological and physiological health, parental and family involvement in PA is extremely important when encouraging children to meet recommended PA and exercise guidelines (Edwardson & Gorely, 2010), which can be translated to IMT interventions. Healthy children with physically active parents are over five times more likely to be active than children whose parents are inactive (Hood et al., 2000), which correlates with reports from the MDT that an active "sporty family" is essential regarding children's participation levels. In addition to this, children's moderate-to-vigorous-physical-activity (MVPA) levels have been shown to correlate with their parent's (Fuemmeler, Anderson, & Mâsse, 2011), with family cohesion and parent-child joint PA predicting higher levels of MVPA (Ornelas, Perreira, & Ayala, 2007). Adversely, divorced parents can have a negative impact on child's PA levels when the main parental facilitator becomes less involved (Dempsey, Kimiecik, & Horn, 1993); this impact of divorced parents was highlighted by the MDT.

In addition to families, peer support is influential in determining activity-related self-esteem and therefore treatment behaviours (Coleman & Sykes, 2017). School-aged children with CF report concerns of appearing "different" than their peers (D'Auria, Christian, & Richardson, 1997), and our participants voiced that they like to keep their condition separate from their friendships at school. This is in accordance with research in which children and adolescents with CF attempted to conceal their disease and symptoms to appear "normal" to their peers (Christian & D'Auria, 1997). As the perspectives of peers are critical to social acceptance it is essential that children with

CF are not defined by their disease but have their own identity. The time-efficient nature of IMT provides the capacity for self-directed therapy that does not detract from time spent with peers, which may increase adherence.

Despite the ease of implementation, good adherence and enjoyment reported by participants, the MDT were more reserved with regards to their enthusiasm for an IMT intervention, with reservations relating to cost and treatment burden. Nevertheless, the team expressed an interest in investigating the potential of a longer-term IMT intervention to provide a clearer evidence-base on the impact on psychological and physiological health in CF patients. The main concern voiced by the care team, as well as the children with CF, was the potential burden it may have on patients in terms of their time and current treatments. Reports that a patient with CF can spend a mean of 108 minutes per day on a wide range of CF therapies, regardless of age or disease severity (Sawicki, Sellers, & Robinson, 2009), highlights the importance of establishing the feasibility of time-efficient therapies, such as IMT. The CF care team also recommended that future IMT interventions incorporated technology, including the ability to monitor adherence objectively to reduce risk of bias, linking to smart phones and providing visual feedback. With smartphone ownership increasing, its usability for future interventions is highlighted by its accessibility, real-time assessment, adherence monitoring, visual feedback and adjustability to the user (Griffiths, Lindenmeyer, Powell, Lowe, & Thorogood, 2006). Increasing patient and MDT engagement in intervention design has the potential to improve health outcomes, better patient care and lower costs (Berwick, Nolan, & Whittington, 2008), and, furthermore, is essential in improving quality of health care and efficacy, which is especially important for the CF population whose treatments are highly prescribed (Johnson, 2011).

5.5 Conclusion

In conclusion, the data revealed consistent themes relating to IMT amongst children with CF and their MDT. This preliminary study has highlighted the ease of incorporating an IMT programme into the lives of CF patients, who reported noticeable perceived improvements to their physical ability after only four-weeks of IMT. These preliminary results suggest that an IMT intervention may be well accepted by young patients with CF. This study has also emphasised the importance of

gathering views and opinions of patients and their care teams to ensure good adherence and enjoyment to future interventions.

Thesis Map

Assessing the Perceptions of a POWERbreathe Inspiratory Muscle Training Intervention in Children with CF and their Multidisciplinary Team	
Aims	**Findings**
Ascertain the views and opinions of inspiratory muscle training from children with CF and their multidisciplinary team	Children enjoyed IMT and reported perceived improvement to their physical ability. The Multidisciplinary team suggested monitoring adherence in future intervention.

Chapter Five showed that a short home-based IMT intervention is feasible and acceptable for children with CF. Those with CF have an impaired gas exchange resulting in an increased sympathetic activation. IMT could potentially decrease respiratory muscle oxygen demand and ventilatory-perfusion mismatch, resulting in decreased respiratory fatigue and increased function capacity. Therefore, Chapter Seven aimed to ascertain whether IMT could improve HRV, lung function and psychological health in children with CF.

Effects of a POWERbreath Inspiratory Muscle Training Intervention on Heart Rate Variability in Children with Cystic Fibrosis: A Pilot Study	
Aims	**Findings**
Investigate the effects of inspiratory muscle training on cardiac autonomic control, lung function and quality of life	

Chapter 6

Effects of a POWERBreathe Inspiratory Muscle Training Intervention on Heart Rate Variability in Children with Cystic Fibrosis: A Pilot Study

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6.1 Introduction

Cystic Fibrosis (CF) is the most common, inherited, life-shortening condition among Caucasians, with an estimated population of 10,469 in the UK alone (Charman, Connon, Cosgriff, Lee, & Carr, 2018). It is a multisystem disease affecting the respiratory, gastrointestinal, reproductive tract and sweat glands (Goetzinger, 2018). In addition to respiratory dysfunction, cardiac damage may also be present in those with CF, with primary symptoms including dyspnoea, tachycardia and tachypnoea (Florêncio et al., 2013). Such symptoms may be attributed to β-2 agonist use, with hypoxemia potentially exacerbating cardiac autonomic dysfunction (Florêncio et al., 2013).

In those with CF, the autonomic nervous system may be influenced by the interaction between cardiac and pulmonary dysfunction (Florêncio et al., 2013). Heart rate variability (HRV) provides an insight to the autonomic nervous system and can provide an early indication of damage to the cardiac system (Vanderlei, Pastre, Hoshi, Carvalho, & Godoy, 2009) and increased risk of cardiac mortality (Taskforce, 1996). However, whether CF is associated with derangements in autonomic nervous system function is equivocal, with some reporting similar sympathovagal function during a six-minute walk test (6MWT: Florêncio et al., 2013), whilst others found higher sympathetic (Resqueti et al., 2012) and/or lower parasympathetic tone in children with CF at rest and during recovery (Florêncio et al., 2013). In adults with CF, further derangements in autonomic functions have been reported that have yet to be demonstrated in children with CF which may reflect age-related modulations and/or the progression of the disease itself (McNarry and Mackintosh, 2016). Alternatively, or additionally, the apparent age-related differences may reflect differences in fitness (Hautala et al. 2010) or the impact of medication (Sammito & Bocklemann, 2016).

Irrespective of the mechanisms for these differences, it is suggested that deleterious adaptations in HRV are associated with an increased risk of cardiovascular complications (Pivatelli et al., 2012). Therefore, improving HRV in those with CF is paramount to their physiological and psychological health.

Inspiratory muscle training (IMT), a breathing exercise that aims to strengthen the respiratory muscles by using a restricted airflow breathing technique to increase the load placed upon the intercostal muscles and diaphragm, has been shown to stimulate a hypertrophic response (Enright et al., 2006). In adults with hypertension and diabetes, IMT has been shown to significantly enhance cardiac autonomic modulation in comparison to unloaded IMT (Ferreira et al., 2013; Kaminski, Schaan, da Silva, Soares, & Lago, 2015). Furthermore, a respiratory muscle feedback and breathing retraining program in adults with CF elicited significant improvements in forced expiratory volume in 1 second (FEV_1) and mean expiratory flow during forced vital capacity (FVC) compared to an age and severity matched control group (Delk, Gevirtz, Hicks, Carden, & Rucker, 1994). In children with CF, IMT increases inspiratory muscle strength (IMS; Santana-Sosa et al. 2014; Sawyer and Clanton 1993), vital capacity, total lung capacity and exercise tolerance (Sawyer and Clanton 1993), as well as respiratory muscle endurance (Bieli et al., 2017). In healthy individuals and those with heart failure, improvements in respiratory muscle function following a 12-week IMT are associated with an enhanced metaboreflex activation threshold, resulting in decreased cardiac sympathetic output at rest (Dall'Ago et al. 2006; HajGhanbari et al. 2013; Witt et al. 2007). However, whether similar beneficial adaptations to automatic nervous system (ANS) control following IMT are observed in those with CF remains to be elucidated.

In addition to potential physiological adaptations, IMT has also been suggested to elicit positive benefits on quality of life (QoL; De Jong et al., 2001), anxiety and depression in CF adults (Enright et al., 2004). Little data is available in children with CF, but a weak correlation between HRV and QoL has been observed in healthy children and adolescents, with suggestions that a stronger correlation would be evident in chronically ill children (Seifert, Calaminus, Wiener, & Cysarz, 2014). Interventions that simultaneously promote improvements in lung function and QoL are highly desirable, especially for those with CF who already face a substantial, time consuming, treatment schedule.

Therefore, the aim of this study was to ascertain the effects of IMT on cardiac autonomic control (HRV), lung function and QoL in children with CF compared to their healthy counterparts.

6.2 Methods

Five CF and five matched control participants aged 10.4 ± 1.2 years (40% boys) were recruited from a CF unit in South Wales, from a local school and through University staff emails, respectively. Participants were recruited on the basis of meeting the following criteria: (i) documented clinical features of CF as well as an abnormal sweat test (sweat sodium and chloride 60 $mmol \cdot l^{-1}$); (ii) absence of any additional known illness/or disease in CF patients or absence of any known illness or disease in healthy controls; and (iii) voluntary participation and consent to comply with the study protocol. Ethical approval was obtained from the Bromley National Health Service Research Ethics Committee (REC reference: 13/LO/1907) and written informed assent and consent were obtained from participants and their parents/guardian, respectively. Participants were required to attend two testing visits in total (baseline and post-intervention), which both took place within a week before the first or after the last IMT session.

Participants were supplied with their own personal POWERbreathe Plus device (POWERbreathe Plus LR Level 1, Gaiam Ltd. E & OE, UK) and undertook a familiarisation session to ensure they were comfortable with the training and device. Participants were encouraged to practice breathing technique and ask any questions until they were comfortable with the regime, which involved 30 breaths twice a day, for 28 consecutive days. The device resistance was determined by the participants baseline strength index. Specifically, the first two weeks of the training programme were performed at 40% of participant's pre-IMT maximal strength index, with the remaining two weeks at 50%.

6.2.1 Anthropometrics

Anthropometrical characteristics were measured according to standard procedures pre- and post-intervention. Specifically, body mass was measured to the nearest 0.01kg (Seca 899 flat scale, Seca, UK), stature and sitting stature were measured to the nearest 0.01m (Seca portable stadiometer, Seca, UK). Waist and hip circumference were measured to the nearest 0.01m using a non-elastic anthropometric tape (Seca Ltd,

Birmingham, UK) at the narrowest point between the bottom of the ribs and the iliac crest and around the widest point of the buttocks (WHO, 2008). Maturity offset was calculated using the equations developed by Moore et al. (2015; Table 6.1).

Table 6.1. Participant characteristics of children Cystic Fibrosis and their healthy peers.

	Total	CF	Healthy Controls
Age (yrs)	10.4 ± 1.2	10.8 ± 1.2	10.0 ± 1.1
Mass (kg)	40.3 ± 7.3	43.9 ± 3.6	36.7 ± 8.2
Stature (m)	1.5 ± 0.1	1.5 ± 0.1	1.5 ± 0.1
BMI ($kg \cdot m^{-2}$)	18.3 ± 2.1	19.6 ± 1.4	16.9 ± 1.8
Maturity Offset (y)	-1.9 ± 1.1	-1.9 ± 0.9	-1.9 ± 1.3
W:H (cm)	0.8 ± 0.1	0.9 ± 0.1	0.8 ± 0.2
Strength index (cmH_20)	51.7 ± 12.4	57.9 ± 1.1	46.8 ± 15.0
Flow rate (l·s)	2.9 ± 0.8	3.4 ± 0.1	2.5 ± 0.9
Volume (l)	1.1 ± 0.6	1.4 ± 0.7	0.9 ± 0.4

Mean ± SD. BMI, body mass index; CF, cystic fibrosis; W:H, waist-hip ratio.

6.2.2 Heart Rate Variability

Participants were required to wear an ActiHeart (Actiheart4, Camntech Ltd, Cambridge, UK) recording at 126 Hz for three consecutive days. The ActiHeart, which has high intra-and inter-instrument reliability and demonstrates good validity (Brage, Brage, Franks, Ekelund, & Wareham, 2005), comprises of two standard ECG electrodes adhered at V1 or V2 positions and approximately 10cm away on the left side at V4 or V5. This specific placement ensures a better signal to noise ratio, free from movement artefacts and with higher ECG amplitudes (Brage et al., 2005). At least two complete 24-hour RR recordings were used to obtain HRV parameters which were subsequently averaged. The analogue signal from the ActiHeart was band-pass filtered (10-35 Hz) and processed by a real time QRS-detection algorithm. The RR data also underwent visual examination in order to verify the accuracy of the data prior to subsequent analysis. When the RR interval(s) was anomalous, the RR data points

were removed from the data set. Indices of HRV were derived from the frequency domain (very low frequency (VLF; 0.017 to 0.04 Hz), low frequency (LF; 0.04 to 0.15 Hz), high frequency (HF; 0.15 to 0.4 Hz) power, (LF:HF ratio) according to the guidelines of the Task Force (1996) and presented as relative values. Prior to the frequency domain analysis procedures RR interval data were re-sampled using a sampling frequency of 2 Hz and then linearly de-trended and windowed in consecutive one-minute segments; the power spectral density of each segment was then calculated using the Welch periodogram method, using short-term Fourier transformation and a 50% overlap between adjacent segments.

6.2.3 Respiratory Strength Measurements

Inspiratory muscle function and capacity were measured using the POWERbreathe K5 (HaB International Ltd, UK). The K5 was programmed with the participant's age, stature, mass and sex, and, following a familiarisation session, three maximal inspiratory efforts were performed. Inspiratory volume (l), flow ($l \cdot s^{-1}$) and strength index (cmH_2O) were recorded and the average calculated across all three tests (Table 6.1).

6.2.4 Cystic Fibrosis Questionnaire

All participants completed the age-appropriate version of the cystic fibrosis questionnaire-revised (CFQ-R; Modi and Quittner, 2003; Quittner et al., 2000), a disease-specific patient reported outcome designed to measure the physical, social and emotional impact of CF on a 4-point Likert, true-false or frequency scale. The CFQ-R child version consists of 35 items grouped into the following categories: (i) physical symptoms (6); (ii) emotional functioning (8); (iii) social functioning (7); (iv) body image (3); (v) eating disturbance (3); (vi) treatment burden (3); (vii) respiratory (4); and viii) digestive symptoms (1). Those participants aged 6-11 years undertook an interviewer-administered version of the CFQ-R, whilst 12-year olds completed the self-report version. Control participants were excluded from treatment specific questions and their overall score was made relative to account for the reduced number of questions completed. Moreover, parent/guardians completed a 44-item CFQ-R questionnaire based on their perceptions of their child's QoL. Raw scores from the CFQ-R Child and Parent/guardian questionnaires were standardised to a 0-100 scale, with a higher score indicative of a higher HRQoL. For the respiratory symptom

domain, the minimal clinically important difference (MCID) was defined as a change of 4.0 points (Quittner et al., 2009).

6.2.5 Statistical Analysis

Between group characteristics and anthropometrics were compared at baseline using an independent t-test. A repeated measures ANOVA was used to analyse lung function and HRV in response to the IMT intervention and their interaction with disease status. The MCIDS were calculated using distribution-based methods. Specifically, changes in HRV and lung function from baseline to follow-up were calculated as 0.5 multiplied by SD of baseline. Scores are shown as the proportion of individuals whose scores exhibited a clinically meaningful increase or decrease, in lung function or HRV of $\geq$ 0.05 SD. Effect size was calculated using the mean change in scores divided by the SD of baseline scores (Copay, Subach, Glassman, Polly, & Schuler, 2007). For interpreting effect sizes, Cohen (1988) has proposed the following benchmarks: 0.2 (small), 0.50 (moderate) and 0.80 (large). A moderate effect size is considered a clinically important effect (Guyatt, 1987). Pearson's correlation coefficients were used to assess the relationship between CFQ-R domains, HRV and lung function, with Cronbach's Alpha used to measure internal consistency within the questionnaires (Cronbach, 1951). Internal consistency was good for CF children (α = 0.83-0.98), CF parents (α = 0.92-0.95), control children (α = 0.72-0.79) and adequate for control parents (α = 0.55-0.59). For the CFQ-R, change scores were calculated to established MCID scores in the paediatric CF population (Modi et al., 2010; Quittner et al., 2009). All data was analysed using a statistical software package (IBM SPSS, Version 25.0) and is presented as mean ± SD. Statistical significance was accepted as $p < 0.05$.

6.3 Results

6.3.1 Lung Function

There was no significant difference in lung function between those with and without CF at baseline. IMT elicited increases in lung function, irrespective of group. Specifically, in those with CF, S.Index and flow rate significantly increased by 18.3% and 18.1%, respectively, whilst in the healthy children, S.Index and flow increased by 31% and 57%, respectively (Table 6.2). In contrast, there was not a significant intervention effect on volume in either group. All CF participants exhibited a large clinically meaningful increase in S.Index (d = 8.0) and flow (d = 9.9), but only 25%

showed a clinically meaningful increase in volume which was associated with a small effect size (d = 0.3). When the absolute magnitude of change was considered, the healthy children demonstrated greater increases in flow rate (1.0 ± 1.0 vs. 0.6 ± 0.3 $l \cdot m^{-1}$; $p<0.05$) and S.Index than those with CF (14.8 ± 11.3 vs 10.5 ± 4.0 $l \cdot m^{-1}$; $p<0.05$).

Table 6.2. Lung function variables pre- and post- the inspiratory muscle training intervention in children with CF and healthy controls.

Lung Function Indices	Baseline	Post	Mean change	% of participants with clinically significant increase (≥0.05)	% of participants with clinically significant decrease (≤0.05)	Effect Size
			Cystic Fibrosis			
S.Index	57.9 ± 1.3	68.4 ± 5.4*	10.5 ± 5.6	100%	0%	8.0
Flow	3.4 ± 0.1	4.0 ± 0.3*	0.6 ± 0.34	100%	0%	9.9
Volume	1.4 ± 0.8	1.6 ± 0.6	0.2 ± 0.4	25%	0%	0.3
			Control			
S.Index	47.8 ± 19.1	62.6 ± 7.9*	15.4 ± 16.7	60%	25%	0.9
Flow	2.5 ± 1.1	3.5 ± 0.4	1.0 ± 0.9	60%	0%	1.0
Volume	0.9 ± 0.5	1.0 ± 0.3	0.2 ± 0.4	40%	20%	0.4

*Mean ± SD. S.Index: Strength index. *p<0.05.*

6.3.2 Heart Rate Variability

At baseline, frequency domain measures were not significantly different between those with CF and their healthy peers. A repeated measures ANOVA with a Greenhouse-Geisser correction determined that frequency domain indices did not differ significantly between time-points. Specifically, while IMT in those with CF was associated with an increase in VLF (1.7%) and HF (1.8%) and a reduction in LF (-1.6%) and LF:HF (-0.15%) post-intervention, these were not statistically significant. However, changes in VLF exhibited a moderate clinically meaningful decrease (d = 0.6), while other HRV parameters exhibited small to trivial clinical effect in CF (Table 6.3). In contrast, in the healthy group, reductions in VLF (-2.7%) and LF:HF (-0.29%)

and an increase in LF (0.7%) and HF (2.1%) were observed post-IMT but were similarly not statistically significant.

Table 6.3. Relative frequency domain indices of HRV pre-and post- the inspiratory muscle training intervention in children with CF and healthy controls.

HRV Indices	Baseline	Post	Mean Change	% of participants with clinically significant increase (≥0.05)	% of participants with clinically significant decrease (≤0.05)	Effect Size
			Cystic Fibrosis			
VLF (%)	20.2 ± 0.8	21.9 ± 5.9	-0.1 ± 1.5	25%	75%	0.6
LF (%)	59.7 ± 3.4	58.1 ± 3.3	1.8 ± 9.5	25%	50%	-0.002
HF (%)	20.2 ± 5.1	22.0 ± 4.0	-1.6 ± 3.9	25%	25%	0.04
LF:HF (%)	3.2 ± 0.8	3.4 ± 0.6	-0.2 ± 10.1	25%	50%	-0.2
			Control			
VLF (%)	18.6 ± 3.0	15.9 ± 1.5	-0.3 ± 0.3	25%	50%	-0.8
LF (%)	59.6 ± 4.8	60.3 ± 1.8	-2.8 ± 4.0	0%	25%	-0.3
HF (%)	21.7 ± 2.6	23.8 ± 2.5	0.7 ± 3.8	75%	25%	1.0
LF:HF (%)	2.9 ± 0.5	2.6 ± 0.3	2.1 ± 1.1	0%	50%	-0.5

Mean ± SD. VLF, very low frequency; LF, low frequency; HF, high frequency; LF:HF, low to high frequency ratio.

6.3.3 Cystic Fibrosis Questionnaire

There was no significant difference in HRQoL over time, irrespective of disease status. However, 62.5% of the population increased their HRQoL post-intervention. At baseline, the CFQ-R respiratory domain demonstrated a weak negative correlation with S.Index (r= -0.29) and flow (r= -0.23) and a weak positive correlation with volume (r= 0.24). After the intervention, the respiratory domain of the CFQ-R showed a strong negative correlation with S.Index (r = -0.85; p = 0.008) and flow (r = - 0.84; p = 0.009). The respiratory symptom domain change score indicated that CF participants perceived clinically meaningful improvements (6.3).

Similar to their children, parent/guardian's perceptions of their child's HRQoL did not differ between time-points. The CF group showed no significant difference in perceived HRQoL between child and parents at baseline (child: 88.9 ± 7.5%; parent: 90.9 ± 7.7%) or post-intervention (child: 89.3 ± 8.8%; parent: 90.7 ± 8.4%).

6.4 Discussion

The main finding of this pilot study was that IMT elicited clinically meaningful improvements in S.Index and flow rate, indicative of improvements in IMS irrespective of health status. Whilst the mechanistic basis of these changes in lung function remains to be elucidated, there were some indications of changes in parasympathetic modulation, although these were not significant and a clinically meaningful decrease in sympathetic modulation. In line with the changes in lung function, IMT elicited a perceived improvement in the respiratory symptom domain in CF participants. Overall, the current study provides preliminary indications that the benefits of IMT should be considered to extend to cardiovascular, as well as respiratory, function, and highlights that further work is warranted to ascertain the potential therapeutic benefits of IMT for children with CF.

The significant improvements in S.Index following the 4-week IMT intervention are congruent with previous research in adults (Asher et al. 1982; De Jong et al. 2001; Enright et al. 2004; Sawyer and Clanton 1993) and children with CF (Asher et al., 1982). Indeed, Asher et al. (1982) found significant improvements in IMS and endurance following a 4-week training programme of 15 mins twice per day, in

children and adults with CF. However, in contrast to the present study, Asher et al. (1982) used a substantially higher training intensity of 80% maximal inspiratory pressure (MIP). Similarly, Sawyer and Clanton (1993) reported improvements in IMS following a protocol involving 60% MIP, 30 mins a day for 10 weeks and de Jong et al. (2001) noted improvements in inspiratory muscle endurance following training at 20-40% MIP for 20 mins, five days a week for 6-weeks. Although the optimal training intensity, duration and frequency clearly remains to be elucidated, research suggests that the specific combination used may influence the specific respiratory parameters effected. Specifically, it appears that low intensity training elicits improvements in inspiratory muscle endurance whilst high-intensity training influences IMS (Reid and Samrai 1995). Interestingly, in accord with whole body strength training regimens, it has been suggested that during the first four weeks IMT predominantly induces neural adaptations (Brown et al., 1997; Ramsay et al., 1990), with any improvements thereafter considered to be largely related to morphological adaptations (Folland & Williams, 2007). Therefore, given the 18% clinically meaningful improvement in S.Index observed in the current study, it could be postulated that 40% MIP is the minimum intensity required to elicit significant benefits in IMS. However, it appears that a longer duration and/or greater resistance may be required to elicit changes in lung volume. Indeed, Enright et al. (2006) found significant improvements in lung volume at 80% MIP resistance, but not 20% MIP; this study extends this finding to suggest that greater than 40% MIP is required. The current findings highlight the importance of tailoring the resistance to the desired outcome, whilst being cognisant that lower resistances are likely to be associated with better long-term adherence and perceptions of feasibility and enjoyment (McCreery, Mackintosh, Cox, & McNarry, 2018).

Inspiratory muscle training engendered clinically meaningful improvements in flow rate in those with CF (18.1%) but not in their healthy counterparts. This may be attributable to the slightly, albeit not significantly, lower values at baseline in those with CF, given that baseline “fitness” is broadly associated with the magnitude of response to training interventions (Rossman et al., 2014). However, this finding may also reflect a better adherence to the IMT protocol in those with CF. Whilst measurement of adherence was beyond the scope of the present study, those with CF have been reported to enjoy and perceive the benefits of IMT for their health

associated with CF (McCreery et al., 2018). An improved flow rate has been associated with greater capacity for gas exchange due to more time available for alveolar emptying (McCaffree, and Gray, 1981), while reduced respiratory comfort has been attributed to decreases in inspiratory flow rate (Manning and Schwartzstein, 1995). Therefore, it could be hypothesised that improving inspiratory flow rate may enhance the efficiency of the respiratory system and feelings of discomfort. Indeed, in chronic obstructive pulmonary disease (COPD), IMT has been shown to enable deeper breaths and higher inspiratory flows, reducing inspiratory effort and dyspnoea scores (Dacha et al., 2017). However, whether this is similarly applicable in those with CF requires further investigation.

This is the first study to investigate the influence of IMT on HRV in CF despite the inextricable associations and interrelations between cardiovascular and respiratory systems (Pinsky, 2005; Yasuma and Jun-ichiro, 2004). At rest, the CF group had a higher LF:HF, suggested to be indicative of a higher sympathetic activity (Bartur et al., 2014) and in accord with previous studies (Florêncio et al. 2013; McNarry and Mackintosh 2016). Although the exact mechanisms underpinning this CF-related adaptation remain inconclusive at this time, such findings could be attributed to alterations in respiratory patterns (Pöyhönen, Syväoja, Hartikainen, Ruokonen, & Taka, 2004), differences in participant age and its interaction with disease progression (McNarry and Mackintosh, 2016), higher work of breathing (Heindl et al., 2001) or, indeed, differences in the levels of catecholamines, between those with and without CF (Zouhal, Jacob, Delamarche, and Gratas-Delamarche, 2008). Whilst the decrease in LF and LF:HF in the CF group following IMT was not significant, the clinically meaningful decrease in VLF could result in a reduction in the sympathetic tone relative to parasympathetic tone (Silva et al., 2013). Previous research has suggested that inspiratory muscle fatigue increases the metaboreflex, which increases peripheral sympathetic activity; improving respiratory muscle function by IMT may therefore increase fatigue resistance and lessen sympathetic outflow (Ferreira et al., 2013). However, this remains speculative given the lack of power associated with this pilot study. Nonetheless, the current results are similar to previous IMT studies in healthy adults that reported 8-weeks IMT, 20 minutes a day at 30% MIP increased S.Index and HF and decreased LF (Ferreira et al., 2013), with others reporting the same protocol was associated with an increased lung volume and QoL (Mello et al., 2012).

However, the studies of Ferreira et al. (2013) and Mello et al. (2012) were of a longer duration and in older populations with cardiothoracic complications which may explain the significant improvements in cardiac function. Previous research has shown that respiratory patterns alter autonomic cardiovascular modulation, especially with respect to HF (Taskforce, 1996), which could explain the increase in parasympathetic modulation observed in the current study. Further studies should seek to determine the acute HRV response during, and following, IMT.

Inspiratory muscle training may improve oxygen supply by augmenting tidal volume, leading to a reduction in chemoreflex activity and, consequently, decreased sympathetic nerve discharge (Bernardi, Porta, Gabutti, Spicuzza, and Sleight, 2001; Rodrigues et al., 2013). According to previous research in healthy adults, inspiratory loads lower than 60% of MIP do not engender diaphragm fatigue as the metaboreflex of the inspiratory muscles is not activated and therefore sympathetic tone is not increased (Callegaro, Ribeiro, Tan, and Taylor, 2011). Reduced lung function is related to sympathetic overactivity in those with bronchiectasis and COPD, suggesting an increased cardiorespiratory risk (Rached et al., 2015). Therefore, if IMT has the potential to improve HRV, it may improve lung function in those with CF, or vice versa.

In accord with some (Bieli et al., 2017), but not all (Enright et al., 2006), previous studies, IMT had no significant impact on QoL. However, it is important to acknowledge that Enright et al. (2006) researched adults who may have had more severe impairments in lung function, and thus QoL, and improvements may therefore be more likely to be evident following IMT given the lower baseline. In children, the CFQ may also lack the sensitivity to reveal small treatment effects in stable patients, but no alternative scoring system for short-term changes in symptoms and clinical findings is currently available (Biele et al. 2017). Alternatively, this discrepancy may be related to the length of the intervention, indicating that longer interventions are needed to induce significant improvements in QoL in children (Hebestreit et al., 2010; Schneiderman-Walker et al., 2000). Despite this, the change in the respiratory domain scores, while not statistically significant, was clinically meaningful post IMT. Furthermore, the respiratory domain, S.index and flow were significantly correlated following IMT. A recent systematic review reported that lung function was

consistently associated with respiratory symptoms within the CFQ-R and should be considered an important outcome measure in CF (Habib et al., 2015). However, there is limited research regarding the relationship between QoL and IMT, with HRQoL remaining an underutilised tool that should be more widely incorporated into future IMT research.

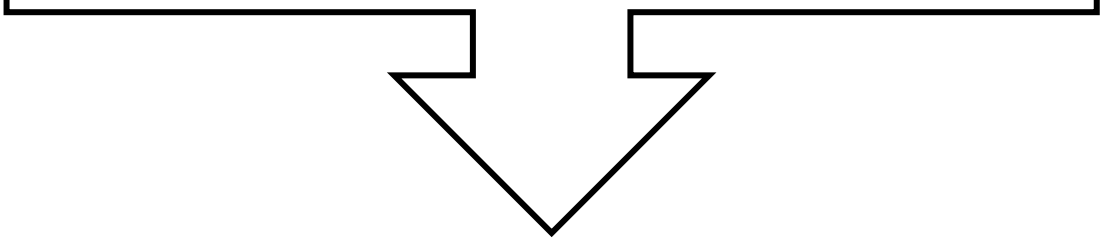
Whilst there are numerous strengths, it is important to consider certain limitations in the interpretation of this study. We acknowledge the controversy that surrounds interpretation of HF, LF and LF:HF (Hayano and Yuda, 2019), however, HRV is a non-invasive tool that provides prognostic insight into global cardiovascular health (Reyes del Paso et al. 2013; Task Force 1996; Wilson et al. 2017). The small sample size limits our statistical power and a larger study is required to ratify our findings. Given the challenges of obtaining large sample sizes of participants with CF (Modi et al., 2010), the application of MCID suggests whilst our results are statistically significant, they were also clinically meaningful, highlighting the potential impact of IMT within the CF population (Beaton, Boers, and Wells, 2002). The short duration of our intervention may also be perceived as a limitation, although it also increases the ecological validity of the findings as it more closely replicates how IMT may be used as an adjunct therapeutic strategy. Indeed, individual responses to exercise training are highly variable and distinguishing patients with- and without-significant, and clinically relevant training responses is a key factor in the identification of effective interventions, ensuring a patient-centred approach. Furthermore, the consideration of intervention fidelity, adherence and the factors that underpin these, which were not assessed in the present study, must be considered in future studies wishing to investigate the potential therapeutic role of IMT in those with CF.

6.5 Conclusion

In conclusion, four weeks of IMT led to clinically significant increases in IMS and in the respiratory symptom domain, while potentially having important influences on the autonomic nervous system in those with CF. Overall, preliminary indications suggest that IMT could be considered to benefit respiratory and cardiovascular function in children with CF.

Effects of a POWERBreathe Inspiratory Muscle Training Intervention on Heart Rate Variability in Children with Cystic Fibrosis: A Pilot Study	
Aims	**Findings**
Investigate the effects of inspiratory muscle training on cardiac autonomic control, lung function and quality of life	Inspiratory muscle training improved inspiratory muscle strength and the respiratory domain of the CFQ-R. A reduction in sympathetic modulation was also seen post inspiratory muscle training.

In combination, Chapters Five and Six highlighted that inspiratory muscle training is feasible and effective in children with CF. Considering the qualitative feedback from the multidisciplinary team, the physiological findings and current literature on inspiratory muscle training, a decision to change the device and training protocol was taken. The Pro2Fit was chosen for its ability to monitor adherence remotely and the live bio-feedback element with interactive app, which was hypothesised to improve training adherence. A training protocol of 80% maximal inspiratory pressure, three times a week for eight weeks, with an eight-week optimal top-up period was implemented.



Effects of an Eight-Week, Pro2Fit Inspiratory Muscle Training Programme on the Physiological and Psychological Health of Children with Cystic Fibrosis	
Aims	**Findings**
Determining the influence of inspiratory muscle training on physiological and psychological health and the efficacy of a 16-week top-up period.	

Chapter 7

The Effects of an Eight-Week PrO2Fit Inspiratory Muscle Training Programme on the Physiological and Psychological Health of Children with Cystic Fibrosis

7.1 Introduction

Cystic Fibrosis (CF) is an autosomal recessive disorder, caused by a genetic mutation in the Cystic Fibrosis Transmembrane Conductance Regulator (*CFTR*) gene (O'Sullivan & Freedman, 2009). The encoded CFTR protein functions as a chloride channel, with mutations in the gene causing abnormalities in chloride transport across epithelial cells on mucosal surfaces (Rowe & Clancy, 2006). Whilst CF is a multi-system disease (Ratjen & Döring, 2003; Rowe, Miller, & Sorscher, 2005), it primarily affects lung function, with the main cause of mortality being respiratory failure (Bhatt, 2013). The progressive decline in respiratory function has been attributed to inflammatory-mediated airflow obstruction but inspiratory muscle weakness may also play a key role (Sovtic, Minic, Markovic-Sovtic, & Trajkovic, 2018). Such inspiratory muscle weakness is potentially exacerbated by higher ventilatory demands, increased airway resistance, and a higher minute ventilation due to ventilation-perfusion mismatch (Pinet et al., 2003). Furthermore, hyperinflation, induced by the airflow obstruction in those with CF, sub-optimally shortens the operating length of the inspiratory muscles, contributing to a mechanical disadvantage (Sharma et al., 2001). Strategies to address inspiratory muscle weakness, which may potentially increase exercise tolerance (Pastré et al., 2014), quality of life (QoL; Zemanick et al., 2010) and even life expectancy (Cohen-Cymberknoh et al., 2011), are therefore of vital importance for those with CF.

One potential strategy to enhance inspiratory muscle strength is inspiratory muscle training (IMT). Specifically, IMT increases the load placed on the intercostal muscles and diaphragm, using a restricted airflow breathing technique to stimulate a hypertrophic response (Enright, Unnithan, Heward, Withnall, & Davies, 2006). IMT has been shown to improve physiological and psychological health in those with respiratory conditions, including an improved inspiratory muscle function (Geddes,

Reid, Crowe, O'Brien, & Brooks, 2005; Gosselink et al., 2011; Hoffman et al., 2019; McConnell, Romer, & Weiner, 2005), a reduction in dysnpoea (Geddes et al., 2005; Gosselink et al., 2011; McConnell et al., 2005), improved exercise tolerance (Geddes et al., 2005; Gosselink et al., 2011; McConnell et al., 2005) and an enhanced QoL (Geddes et al., 2005; Gosselink et al., 2011; Hoffman et al., 2019). However, in CF, a recent Cochrane review and meta-analysis concluded that there was insufficient evidence to conclude whether IMT has a beneficial effect on exercise tolerance and lung function (Hilton & Solis-Moya, 2018). Nonetheless, significant improvements in respiratory muscle strength (Asher, Pardy, Coates, Thomas, & Macklem, 1982; Bieli, Summermatter, Boutellier, & Moeller, 2017; De Jong, Van Aalderen, Kraan, Ko Ter, & Van Der Schans, 2001) and vital capacity (Sawyer & Clanton, 1993) have been reported following IMT in those with CF. However, in accord with the conclusions of Houston et al. (2018), findings should be considered with caution given the lack of methodologically rigorous studies and the range of training techniques and protocols used, which are known to exert divergent effects on the respiratory system (Larribaut et al., 2018), likely contributing to the equivocal findings (Bieli et al., 2017).

To date, there has been an almost exclusive focus on the effect of IMT in middle-aged populations, with little known regarding the utility of IMT in youth with CF. Findings in adults with CF are unlikely to be applicable to youth given the substantially different treatment strategies used in each age group and their consequences for disease progression and experiences (Shei, Dekerlegand, Mackintosh, Lowman, & McNarry, 2019). Indeed, significant physiological and psychosocial age-related differences may affect the plasticity and response to IMT (Shei, Dekerlegand, Mackintosh, Lowman, & McNarry, 2019). Whilst Santana-Sosa et al. (2014) investigated the effects of IMT in young children, it was combined with a whole-body exercise protocol, precluding the identification of the effects of IMT *per se.* More recently, a four-week IMT program was reported to be well-adhered to, and enjoyed by, children with CF (Chapter 5; McCreery, Mackintosh, Cox, & McNarry, 2018), although the short duration prevents conclusions being drawn regarding the efficacy of this intervention. In light of the progressive decline in lung function that manifests from early adolescence (Welsh et al., 2014), the potential role of IMT as an effective tool to delay, or indeed ameliorate, the rate of progression warrants further investigation.

Therefore, the aim of this study was to ascertain the influence of an eight-week, home-based, IMT programme on the physiological and psychological health and wellbeing of youth with CF. Given that sustainability and long-term adherence is paramount to real-world interventions, the secondary aim of this study was to determine the uptake and efficacy of a reduced-volume IMT programme to maintain any beneficial effects over a subsequent eight weeks.

7.2 Methodology

CF participants who were 8-18 years of age, characterised by a diagnosis that had been confirmed by an abnormal sweat chloride test (sweat chloride > 60 $mmol \cdot L^{-1}$ > 100 mg sweat) and were categorised as clinically stable for six months preceding enrolment to the study were recruited from a paediatric CF Clinic in Wales. Ethical approval was granted by the North West – Liverpool Central Research Ethics Committee, (reference 16/NW/0764) and written informed consent and assent were obtained from parents/guardians and participants, respectively. Participants were required to attend two testing visits in total, one at baseline and one post-intervention (week 8). A third visit was required at week 16 for those participants who agreed to the eight-week IMT top-up.

7.2.1 Inspiratory Muscle Intervention

The PrO2Fit (Design Net, Smithfield, USA) is a flow-resistive device, requiring participants to breathe through a 2 mm leak, to prevent glottal pressure. Training was performed three times a week on non-consecutive days, with at least 24 hours separating training sessions, over eight weeks. Three sustained maximal inspiratory pressure (SMIP) measurements were recorded at the start of each training session; the highest sustainable profile was selected automatically and redrawn by the computer as a training template equal to 80% of the maximum pressure profile.

Inspiratory training manoeuvres were repeated using a regime of six repetitions per level (six levels in total) performed at 80% of the SMIP. During each set of inspirations, the rest time between repetitions was progressively reduced from 60 seconds to 45, 30, 15, 10, and, finally, 5 seconds. If at any point the participants failed to achieve at least 80% of the computer-generated template, the test would

automatically terminate. The participants were re-assessed prior to each training session to ensure the work performed during the incremental training on that day was relative to their current maximal effort. All training sessions were uploaded automatically to the cloud allowing monitoring of sessions and encouraging adherence.

7.2.2 Anthropometrics

Body mass (Seca 220; Hamburg, Germany) and stature (Seca portable stadiometer, Seca, UK) were measured to the nearest 0.1 kg and 0.01 m, respectively. Waist and hip girth were measured to the nearest 0.01 m using an anthropometric tape (Seca Ltd., Birmingham, UK); measurements were taken at the narrowest point between the base of the ribs and the iliac crest for waist circumference and the widest point around the hips for hip girth. Waist-to-hip ratio (WHR) was subsequently calculated.

7.2.3 Lung Function and Respiratory Strength Measurements

Forced vital capacity (FVC) and forced expiratory volume in 1-second (FEV_1) were assessed using a portable dry wedge spirometer (Micro Medical, MicroRPM, UK), according to the British Thoracic Society standards (1994), by an experienced respiratory physiotherapist. Each participant was required to complete three consistent inspirations and exhalations, with the best score being taken. All parameters were expressed as the percentage predicted for age, stature and gender (British Thoracic Society, 1994). For mean inspiratory pressure (MIP), the participant was instructed to exhale slowly and completely, seal their lips firmly around the mouthpiece, and then "pull in hard, like you are trying to suck up a thick milkshake" (Castile & Davis, 2012; Sachs, Enright, Stukovsky, Jiang, & Barr, 2009). Conversely, to measure mean expiratory pressure (MEP), participants were instructed to inhale slowly and completely, seal their lips firmly around the mouthpiece, and exhale as hard as possible (Castile & Davis, 2012; Vitacca et al., 2006).

7.2.4 Handgrip Strength Test

Handgrip strength (HGS), which has been shown to correlate with lung function (Smith et al., 2018; Wells et al., 2014) and upper extremity strength (Bohannon 1998) in CF participants, has been identified as a valid measure of peripheral muscle function. HGS was measured using a hand dynamometer (Takei 5401, Tokyo, Japan),

whereby participants were asked to stand upright with the arm naturally extended straight, pointing to the floor, and squeeze as hard as they could for 10 seconds. A total of four measurements were taken (two from each hand), alternating hands each time, with the overall mean result calculated. Verbal encouragement was given throughout the test.

7.2.5 Physical Activity Analysis

The ActiSleep+ monitor (ActiGraph LLC, Pensacola, FL), shown to be valid and reliable in paediatric populations (Kinder et al., 2012; Ruf et al., 2012), was placed on the right iliac crest and worn 24 hours a day, for seven consecutive days. The monitors were set to sample at 100 Hz. Participants were asked to log whether, and for how long, they removed the monitor (e.g. for water-based activities).

7.2.6 Cardiopulmonary Exercise Testing with Supramaximal Verification Bout

Following familiarisation, each participant completed an incremental ramp test on a cycle ergometer (ViaSprint 150P; ViaSys Healthcare, Hoechberg, Germany) to volitional exhaustion. After completing a three-minute warm-up at 10W, the resistance was progressively increased at a fixed rate based on height (<120 cm, 10 $W \cdot min^{-1}$; 120-150 cm, 15 $W \cdot min^{-1}$; >150 cm, 20 $W \cdot min^{-1}$). Participants were required to maintain a cadence of 70-80 revolutions per minute (rpm) throughout the test, with the test terminated when the cadence decreased by >10 rpm for five consecutive seconds, despite strong verbal encouragement. Following completion of the cardiopulmonary exercise testing (CPET), a five-minute active cool-down, followed by a 10-minute seated recovery was provided. A supra maximal (S_{max}) verification of $\dot{V}O_{2max}$ was then performed, whereby a three-minute baseline at 10 W was followed by a 'step transition' to a constant work rate equivalent to 110% of the peak power output (W_{peak}) achieved during the initial cycle ergometer test (Saynor et al., 2013a, 2013b). Participants were required to maintain this workload until voluntary exhaustion. During the incremental exercise tests, continuous breath-by-breath pulmonary gas exchange data was collected (MetaMax 3B, Cortex Medical, Germany). Participants were required to wear a facemask, breathing through an impeller turbine assemble (Jaeger Triple V, Hoechberg, Germany), were gas volumes were continuously sampled at 100Hz.

7.2.7 Questionnaires

All CF participants completed an age-appropriate version of the Cystic Fibrosis Questionnaire – Revised (CFQ-R; Modi & Quittner, 2003; Quittner et al., 2000), a disease-specific health-related quality of life (HRQOL) questionnaire designed to measure the physical, social and emotional impact of CF on participants. Quality of life dimensions, disease-related symptoms and overall health perceptions were assessed on Likert scales, with scores standardised on each scale ranging from 0 to 100. The CFQ-R child version consists of 35 items grouped into eight dimensions, whereas the adolescent version consists of 50 items grouped into 12 domains. Specific sub-scales include physical functioning, role functioning, energy/fatigue, psychological, emotional and social functioning, eating disturbances, body image, respiratory symptoms, digestive symptoms, weight disturbance, treatment burden, and general health perceptions. Higher scales on subscales indicate better HRQoL. For the respiratory symptom domain, the minimal clinically important difference (MCID) was defined as a change of 4.0 points (Quittner et al., 2009).

Employing self-determination theory (Williams, Deci & Ryan, 1999), all participants completed psychological measures of self-regulation, need satisfaction and perceived competence, in relation to IMT. Following a stem question ("Why do you exercise?"), participants responded to each item on a five-point Likert scale ranging from 1 (not true for me) to 5 (very true for me). These measures were taken at baseline and at post-intervention by using the Behavioural Regulation Questionnaire (BREQ-3; Wilson, Rogers, Rodgers, & Wild, 2006), which is valid and reliable in children (Markland & Tobin, 2004; Sebire, Jago, Fox, Edwards, & Thompson, 2013; Crciun & Rus, 2012; Wilson, Rogers, Rodgers, & Wild, 2006). Psychological needs satisfaction was measured by using four single-item indicators to assess perceived competence in undertaking IMT ("I feel confident in my ability to complete IMT regularly"). Participants responded to each item on a scale ranging from 1 (not at all true) to 7 (very true). All measures are validated for use with clinical populations and modifications of items to the specific context are permitted (Ng et al., 2012; G C Williams et al., 1985).

7.2.8 Interviews

Children were invited to complete a face-to-face, semi-structured interview

following the eight-week intervention. If participants failed to complete the intervention, they were still invited to take part in an interview to ascertain their perceptions. The interviewer (JMC) asked open-ended questions, seeking clarification or elaboration when required. Questions were centred around their experience with IMT, recommendations for future use, and more generic opinions of physical activity (PA) and exercise. The language used was tailored to be age-appropriate and ensure full understanding from younger children. Interviews were audio recorded and transcribed verbatim.

7.3 Data Analysis

7.3.1 Cardiopulmonary Exercise Testing and Supramaximal Verification

$\dot{V}O_2$ and carbon dioxide production ($\dot{V}CO_2$) were interpolated to 15-second averages and peak values taken as the highest moving average $\dot{V}O_2$ measured over 15-seconds. The gas exchange threshold (GET) was determined as the $\dot{V}O_2$ at which there was a non-linear increase in $\dot{V}CO_2$ relative to $\dot{V}O_2$ and an increase in minute ventilation ($\dot{V}E$)/ $\dot{V}O_2$ without an increase in $\dot{V}E/\dot{V}CO_2$ (Beaver, Wasserman, & Whipp, 1985). Given the within participant variability of $\dot{V}O_{2max}$ in children and adolescents with CF (Saynor et al., 2013a), peak $\dot{V}O_2$ was considered maximal if the $\dot{V}O_2$ peak achieved during S_{max} did not exceed that achieved during the ramp-test by ≥ 9% (Causer et al., 2018).

7.3.2 Physical Activity Analysis

Accelerometery data was downloaded using ActiLife (v6.10.4; ActiGraph) and processed into 15-second epochs. Evenson et al. (2008) cut-points were selected due to their acceptability across a range of intensities and ages and have been shown to methodologically rigorous (Trost, Loprinzi, Moore, & Pfeiffer, 2011). Non-wear time was defined as sustained periods of 20 minutes or more of consecutive zero counts (Catellier et al., 2005), with a valid wear time defined as ≥ 9 hours per day, for at least three days (Mattocks et al., 2008), including one weekend day (Aadland et al., 2013), which has previously been used in clinical populations (Mackintosh et al., 2018). Children were required to have worn the ActiSleep+ monitor for at least three days

with one weekend day, which has been shown to have a reliability coefficient of 0.7 (Mattocks et al., 2008b).

7.3.3 Content Analysis

To extend existing knowledge and theory, interview data was analysed via content analysis, in which a deductive and inductive approach was adopted (Hsieh & Shannon, 2005). All interviews were transcribed verbatim by JMC, using a manual approach (Braun & Clarke, 2014), with line-by-line coding on each transcript, which were then placed within the relevant overarching category (i.e. experience of undertaking IMT, competitiveness, mastery, goals, motivations for adherence and top-up period and future suggestions). Similar and/or opposing codes were then organised into themes which provided a detailed account of the children's experience (i.e. factors effecting adherence, feedback loop and future improvements). To ensure methodological rigour, all authors reviewed the data to verify findings were logical and to offer alternative interpretations of data (Boddy et al., 2012; Mackintosh et al., 2011). This process continued until an acceptable consensus had been reached.

7.4 Statistical Analysis

All data was analysed using IBM SPSS (IMB Corp, Version 25.0. Armonk, New York: IBM Corp) and presented as mean ± SD, unless stated otherwise. Statistical significance was accepted as $p < 0.05$. A one-way repeated measures ANOVA was used to analyse any differences in lung function, $\dot{V}O_{2max,}$ questionnaire results and HGS, in response to the IMT intervention from baseline to eight weeks and following the eight-week top-up period. Pearson's correlation coefficients were used to assess the relationship between CFQ-R domains, $\dot{V}O_{2max}$, HGS and lung function. To determine whether IMT had a clinically significant effect, MCIDS were calculated using changes in lung function, HGS and $\dot{V}O_{2max}$ from baseline to follow-up as 0.5 multiplied by the baseline SD. The effect size was calculated using the mean change score divided by the baseline SD, utilising the benchmarks of 0.2 (small), 0.50 (moderate) and 0.80 (large; Cohen, 1988). Scores are shown as the proportion of individuals whose scores exhibited a clinically meaningful increase or decrease, in lung function of ≥ 0.05 SD, with a moderate effect size considered a clinically important effect (Guyatt, 1987).

7.5 Results

Five participants aged 11.0 ± 2.2 years (60% male) with mild CF (FEV1/FVC = 86.4 ± 8.0%) took part in the eight-week IMT intervention (Table 7.1). All of the participants also subsequently agreed to take part in the eight-week top-up period, however, only three were able to be retested due to COVID-19. On average, participants completed 89% of IMT training sessions in the first eight weeks, and 84% in the eight-week top-up period.

Table 7.1. Baseline participant characteristics of children with cystic fibrosis.

Characteristics	Total (*n*= 5)
Age (years)	11.00 ± 2.2
Sex (Girl/Boy)	2/3
Height (cm)	137.6 ± 11.7
Body Mass (kg)	31.7 ± 7.8
Body Mass Index (kg·m^{-2})	16.5 ± 1.6
Waist-to-Hip Ratio (cm)	0.9 ± 0.1

7.5.1 Physical Activity

All children fulfilled the wear time criteria for valid accelerometery. There were similar levels of PA across the intensity spectrum, irrespective of weekday or weekend day in this cohort (Table 7.2). Overall, 40% of children with CF met the current government guidelines for MVPA (60 min·day^{-1}), with greater activity achieved during weekdays (60% ≥ 60 min·day^{-1}) than weekend days (20% ≥ 60 min·day^{-1}; Table 7.2).

Table 7.2. Physical activity levels across one week in children with cystic fibrosis.

	Overall	Weekday	Weekend
	Physical Activity Levels		
Sedentary time (min·day^{-1})	914.5 ± 387.5	850.3 ± 425.5	1100.6 ± 136.8
LPA (min·day^{-1})	149.6 ± 80.5	140.3 ± 83.6	176.6 ± 67.1
MPA (min·day^{-1})	29.7 ± 18.6	30.2 ± 19.4	28.5 ± 17.02
MVPA (min·day^{-1})	56.1 ± 37.5	57.9 ± 38.7	51.0 ± 35.4
VPA (min·day^{-1})	26.4 ± 19.6	27.7 ± 19.7	22.5 ± 19.6

LPA, light physical activity; MPA, moderate physical activity; MVPA, moderate-to-vigorous physical activity; VPA, vigorous physical activity.

7.5.2 Lung Function

After eight weeks of IMT, MIP, MEP and PEF significantly increased by 49.9% ($p = 0.04$), 12.5% ($p = 0.03$), 14.1% ($p = 0.001$), respectively (Figure 7.1). Despite showing trends for improvement in FEV_1, FEV_1%predicted, FVC %predicted and FEV_1/FVC after eight weeks, these were not statistically significant. 80% of CF participants exhibited a large clinically meaningful increase in MIP ($d = 2.0$), MEP ($d = 1.0$) and ID ($d = 1.0$) and moderate clinically meaningful increases in SMIP ($d = 0.7$), while FEV_1 ($d = 0.3$), FEV_1%predicted ($d = 0.4$), PEF ($d = 0.4$) and FEV_1/FVC ($d = 0.4$) showed small clinically meaningful increases. There was a significant correlation between MIP and PEF ($r = 0.879$, $p = 0.05$) and FEV_1/FVC ($r = 0.926$, $p = 0.02$).

There were no significant differences in lung function between eight and eight-week top-up period, despite showing continued trends for improvement in all lung function parameters (Table 7.3). However, despite not being statistically significant, a large clinically meaningful improvement was seen in MEP ($d = 2.3$), moderate clinically meaningful improvement in SMIP ($d = 0.8$), and a small clinically meaningful improvement was exhibited in MIP ($d = 0.3$), ID ($d = 0.2$) and FEV_1/FVC ($d = 0.3$) at the eight-week top-up period.

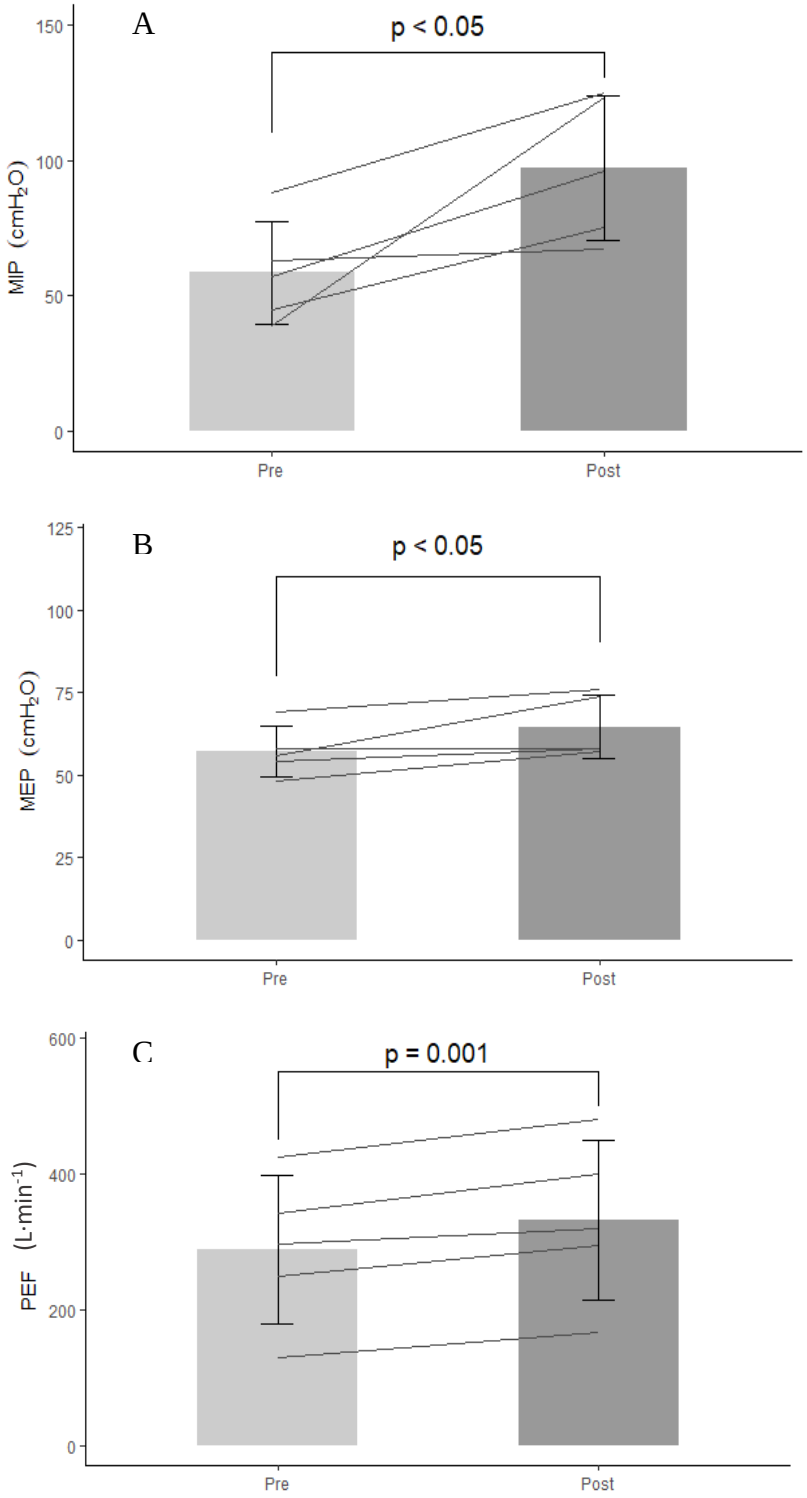


Figure 7.1. Changes in A) MIP, mean inspiratory pressure; B) MEP, mean expiratory pressure and C) PEF, peak expiratory flow, over the first eight weeks of the inspiratory muscle training intervention in children with cystic fibrosis. Grey bars represent mean group response with standard deviation bars. Overlaid lines represent individual responses

7.5.3 Handgrip Strength

There were no statistical or clinically significant changes in HGS following eight weeks or eight-week top-up of IMT (Table 7.3). However, HGS showed a clinically significant increase between eight and 16 weeks (d = 0.6). Furthermore, HGS was strongly correlated with FEV_1 (r = 0.920; p = 0.01) and FVC (r = 0.903, p = 0.04) post-IMT.

7.5.4 Exercise Capacity

$\dot{V}O_{2max}$ significantly increased by 3.1 ± 2.4 $ml \cdot kg^{-1} \cdot min^{-1}$ after eight weeks, with a decrease of 1.3 ± 0.8 $ml \cdot kg^{-1} \cdot min^{-1}$ from the initial eight weeks to the eight-week top-up of IMT. However, the $\dot{V}O_{2max}$ was still 7.9 ± 8.4 8 $ml \cdot kg^{-1} \cdot min^{-1}$ higher than baseline. There was no significant difference between $\dot{V}O_{2max}$ and supramaximal $\dot{V}O_{2}$. Despite the changes in $\dot{V}O_{2max}$ being statistically significant, only 20% of children exhibited a small clinically meaningful improvement in $\dot{V}O_{2max}$ (d = 0.3) following eight-week IMT intervention. $\dot{V}O_{2max}$ significantly correlated with FEV_1 post-IMT (r = 0.902, p = 0.036). There were no statistical or clinically significant changes in W_{peak} following the initial eight weeks or eight-week top-up period (Table 7.3).

Table 7.3. Effect of an eight-week inspiratory muscle training intervention and a subsequent eight-week top-up period on lung function, exercise capacity and handgrip strength in children with cystic fibrosis.

Parameters	Baseline (n = 5)	8-weeks (n = 5)	% of participants with clinically significant increase	% of participants with clinically significant decrease	Effect Size	16 Weeks (n = 3)	% of participants with clinically significant increases	% of participants with clinically significant decreases	Effect Size
				Lung Function					
MIP (cmH_2O)	58.4 ± 19.1	97.2 ± 26.7*	80%	0%	2.0	115 ± 17.4	33%	0%	0.3
MEP (cmH_2O)	57.0 ± 7.7	64.6 ± 9.5*	80%	0%	1.0	85.3 ± 24.2	67%	0%	2.3
FEV_1 (l)	1.8 ± 0.6	2.0 ± 0.6	40%	0%	0.3	2.2 ± 0.5	0%	33%	-0.1
FEV_1 %predicted	61.0 ± 11.8	65.2 ± 7.9	40%	0%	0.4	62.3 ± 5.5	0%	33%	-0.9
FVC (l)	2.2 ± 0.6	2.2 ± 0.6	20%	0%	0.04	2.4 ± 0.7	33%	33%	-0.2
FVC %predicted	72.4 ± 10.0	73.6 ± 9.0	20%	20%	0.1	55.7 ± 13.7	0%	33%	-1.7
PEF ($L \cdot min^{-1}$)	289.0 ± 109.6	332.8 ± 117.3*	40%	0%	0.4	366.0 ± 67.7	0%	67%	-0.3
FEV_1/FVC (%)	86.4 ± 8.0	89.4 ± 8.1	40%	20%	0.4	95.3 ± 4.5	33%	0%	-0.3
				Exercise Capacity					
$\dot{V}O_{2max}$ ($ml \cdot kg^{-1} \cdot min^{-1}$)	35.7 ± 10.7	38.7 ± 10.8*	20%	0%	0.3	43.6 ± 6.1	0%	100%	-0.1
W_{peak}	101.6 ± 40.5	88.0 ± 14.8	0%	0%	0.03	103.5 ± 34.6	0%	0%	0.02
				Handgrip Strength					
Combined (kg)	19.1 ± 13.4	14.1 ± 4.4	0%	20%	-0.3	14.1 ±4.4	67%	0%	0.6

*MIP, mean inspiratory pressure; MEP, mean expiratory pressure; SMIP, sustained maximum inspiratory pressure PTU, pressure time uni, s, seconds; FEV_1, forced expiratory volume in 1-second; FVC, forced vital capacity; PEF, peak expiratory flow; $\dot{V}O_{2max}$, maximal oxygen consumption; W_{peak}, peak power output. *Significance p <0.05.*

7.5.5 Questionnaires

The total CFQ-R score improved, on average, by 6%, though this was not significant (p = 0.06). Whilst there was a trend for improvements in each domain, only the physical functioning domain showed a significant increase of 8.2% (p = 0.02) following eight weeks of IMT. Similarly, from the initial eight weeks to the eight-week top-up, total CFQ-R and the physical function, emotional, eating disturbance and respiratory domains increased, albeit not significantly (Table 7.4).

There was no significant difference following eight weeks of IMT in children's motivation (BREQ) or on their autonomy, competence or relatedness to exercise (Table 7.4). However, participants exhibited a significant improvement in their perceived competence to undertake an IMT intervention in the long-term (p = 0.01).

Table 7.4. Psychological parameters pre- and post- eight weeks of an inspiratory muscle training intervention

				95% Confidence Interval of the Difference		
	Baseline	**8 Weeks**	**Cohen's *d***	**Lower**	**Upper**	**p**
			CFQR			
Total	85.2 ± 4.9	89.9 ± 5.3	-0.9	-11.4	2.1	0.064
Physical functioning	91.1 ± 8.4	98.9 ± 2.5	-1.3	-15.6	0.1	0.026*
Emotional	78.3 ± 3.5	87.5 ± 7.2	-0.9	-21.5	3.2	0.054
Eating disturbances	82.2 ± 24.3	88.9 ± 24.8	-0.3	-33.6	20.2	0.500
Treatment	95.6 ± 9.9	95.6 ± 9.9	0	0	0	1.000
Social functioning	69.5 ± 21.7	81.0 ± 8.9	-0.3	-47.1	24.2	0.395
Body	100 ± 0.1	95.6 ± 9.9	0	-7.9	16.8	0.374
Respiratory	85.0 ± 16.0	85.0 ± 16.0	0	-24.2	11.8	1.000
Digestive	80.0 ± 18.3	86.7 ± 18.3	-1.0	-25.2	11.8	0.500
			BREQ			
Intrinsic Motivation	4.3 ± 0.8	4.2 ± 0.7	0.5	-0.4	0.7	0.391
Introjected Motivation	2.1 ± 0.8	2.3 ± 0.9	-0.3	-1.1	0.7	0.585
Identified Motivation	4.6 ± 0.5	4.1 ± 0.6	2.6	0.2	0.8	0.098
Extrinsic Motivation	3.1 ± 0.9	2.7 ± 0.8	0.6	-0.8	1.6	0.423
			Psychological Needs Satisfaction			
Autonomy	3.8 ± 0.6	3.6 ± 0.6	0.2	-1.3	1.7	0.707
Competence	3.6 ± 0.5	3.4 ± 0.2	0.4	-0.6	1.0	0.465
Relatedness	4.4 ± 0.6	4.2 ± 0.6	0.5	-0.4	0.8	0.337
			Perceived Competence in undertaking IMT			
Perceived Competence	4.1 ± 1.8	5.6 ± 1.6	3.5	3.1	8.2	0.006*

CFQR, cystic fibrosis questionnaire-revised; BREQ, behavioural regulation in exercise questionnaire. ***p** < 0.05*

7.5.6 Qualitative Experiences

A summary of key themes derived from the children's interviews are shown in Table 7.5. All children reported good autonomy and high competency when undertaking the training, attributing this to the simplistic nature of the intervention:

"It was quite simple and easy to use…I could do it easily on my own" [P1]

Good participation and excellent adherence to the training sessions was noted, with children highlighting the home-based nature of the training as a positive:

"I liked being able to use it at home, it meant we didn't have to go somewhere to use it" [P3]

Furthermore, children reported perceived improvements in their physical ability, highlighting this as a critical motivating factor which also contributed to the high adherence in this cohort:

"I think that [noticing improvements in physical ability] made me want to do it as well, I could actually see the changes" [P1]

Another critical motivating factor that promoted adherence was the live, real-time biofeedback they received from the app on their training progress. Indeed, the real-time feedback was highlighted as one of the main positives from the intervention, with children stating that their motivation and effort during each session would have been diminished without the app:

"I think it [feedback from the app] made it more entertaining cause you could see how you were doing visually…I wouldn't have worked [as hard] without the feedback" [P2].

The feedback provided by the app increased the children's determination and drive to set goals in order to beat their previous score:

"You are constantly trying to beat it [previous score]. I like that about it [the training programme], it didn't just show nothing…I said 'alright I'm going to beat it' and I did it properly!" [P3].

Leading to feelings and experiences of positive affect (e.g. *enjoyment, excitement and interested*):

"I'm happy I've done it…It's quite strange to say you have something three times a week that helped [lung function] and it helped my fitness, so I think it was worth it!" [P1]

With regards to future IMT interventions, children discussed their enjoyment of using an app-based training programme and suggested ways in which their experience could be enhanced. Specifically, the ability to compete against others in a virtual group-based training session rather than completing the session individually was suggested:

"If it was multiplayer, so you were against other people would be really fun!" [P2]

Feeding into the children's competitive nature, the ability to gain extrinsic rewards from training to enhance motivation and drive to succeed was also suggested:

"Maybe if you got to the top of the leader board you could get gems to buy different themes for the app…To get people to try harder to get higher [on the leader board] because they want that theme." [P3]

Table 7.5. Key themes derived from interviews with children regarding their experiences of an inspiratory muscle training programme.

Theme	Sub-Theme
Factors affecting adherence	Autonomy and competency
	Convenience of being home-based
	Perceived physical improvements
Feedback loop	Motivational
	Competitive nature
	Goal setting
	Positive affect
Future improvements	Game-based element

7.6 Discussion

The present study found that an eight-week, three times a week, IMT intervention elicited clinically meaningful improvements in respiratory muscle strength and exercise capacity, as well as significantly improving the physical function domain of the CFQ-R. Furthermore, an eight-week top-up period induced additional large clinically meaningful improvements in MIP and the respiratory domain of the CFQ-R. These improvements were associated with excellent adherence, with children reporting being motivated and having perceived competence to undertake IMT. These findings therefore suggest that IMT could be a highly beneficial intervention for youth with CF, with only ~20 minutes, three times per week for eight weeks leading to clinically meaningful adaptations in important health markers that can subsequently be maintained by only one session per week.

Respiratory muscle weakness is hypothesised to contribute to the development of chronic respiratory insufficiency (Adler & Janssens, 2019) due to increased work of breathing, contributing to dyspnoea, ventilatory inefficiency and exercise intolerance in CF (Dekerlegand et al., 2015). Indeed, early childhood represents a critical time in CF during which the disease may progress asymptomatically and aggressive intervention is of high importance to prevent pulmonary deterioration (Vilozni et al., 2016). The current study exhibited large clinically meaningful improvements in MIP after eight weeks of IMT, with smaller clinically meaningful additional effects after 16 weeks. These findings largely agree with previous research whereby significant improvements have been found for MIP, despite differing training protocols (Asher et al., 1982; Sawyer and Clanton, 1993; Santana-Sosa et al., 2014). More specifically, whilst both earlier interventions were implemented at 60% MIP, Asher et al. (1982) incorporated training daily, two times per day, for four weeks (9% improvement in MIP), whereas Sawyer and Clanton. (1993) consisted of training daily, once per day for 10 weeks (13% improvement in MIP). However, despite the lower intensities utilised by Asher et al. (1982) and Sawyer and Clanton. (1993) eliciting improvements in MIP, the magnitude of improvement was considerably greater in the current study (50% improvement in MIP). This supports the hypothesis that high-intensity respiratory training influences inspiratory muscle strength, with greater intensities associated with greater improvements (Reid & Samrai, 1995). It is also pertinent to note that the current intervention only required participants to complete the IMT three

times per week rather than every day, considerably reducing the participant burden and making IMT a more sustainable and feasible long-term intervention than the earlier protocols reported.

To our knowledge, no previous research has found significant improvements in MEP or PEF in children with CF following an IMT intervention. However, IMT enhanced MIP, MEP and reduced airflow obstruction due to an increased PEF in children with asthma (Lima et al., 2008). Although IMT does not directly load the expiratory muscles, it could be hypothesised that the improvements in MEP and PEF are attributable to stronger inspiratory muscles which enable a greater expansion of the thorax (de Medeiros, Fuzari, Rattesa, Brandão, & de Melo Marinho, 2017). This greater expansion may subsequently result in a larger elastic recoil. Furthermore, strong expiratory muscles, as suggested by increased MEP and PEF, have been shown to improve the ability to generate and maintain expiratory force for coughing (Mancopes, Smaoui, & Steele, 2020), which, given that coughing is a natural defence mechanism for airway clearance, would be of benefit to the CF population. Indeed, weak or ineffective coughing can result in secretion retention, infection and deterioration of lung function (Ramos, Krahnke, & Kim, 2014). Although the exploration of cough and cough flow/volume index, which provides an insight into the degree of respiratory impairment, was beyond the scope of this study, IMT has been shown to increase sputum production in adults with CF (Chatham et al., 1997). The improved MEP and PEF in the current study is therefore an important finding which should be explored in depth in future studies.

Despite the significant improvements in respiratory muscle strength, no significant improvements were evident in pulmonary function. Specifically, in accord with previous research in CF (Asher et al., 1982; Sawyer and Clanton, 1993; Jong et al., 2001; Albinni et al., 2004), there was no significant differences in FEV_1 or FVC following eight or 16 weeks of IMT. However, Amelina et al. (2006) found significant improvements in FEV_1 (48% to 51%) and FVC (65% to 68%) at 30% of maximal effort for 10-15 minutes, twice a day for six weeks in adults with CF. However, it is pertinent to note that adults with CF have more severe inspiratory muscle function impairments compared to children (Enright, 2001), and therefore may be more sensitive to adaptations at lower intensities compared to children.

The current study highlighted that a top-up period of IMT once a week was not only able to maintain the improvements obtained in the first eight weeks, but engendered further improvements, resulting in a small and large clinically meaningful improvement in MIP and MEP, respectively. This is line with traditional strength training programmes that suggest the optimal frequency of a training programme is three times a week, with maintenance achieved by continuing once or twice per week for up to 12 weeks (Fleck, 1994; Wernbom et al., 2007). Improvements beyond four weeks of a strength training protocol are considered to be morphological adaptations, including increased capillary beds and muscle fibre hypertrophy (Folland & Williams, 2007; Komi & Hakkinen, 1991). Indeed, increases in the proportion of type I fibres and size of type II fibres have been found following a five week IMT intervention in adults with chronic obstructive pulmonary disease (Ramírez-Sarmiento et al., 2002). It could, therefore, be speculated that the top-up period was sufficient to maintain the earlier structural remodelling of the inspiratory muscles, which could explain the maintained functional improvements.

Given that $\dot{V}O_{2max}$ is a key predictor mortality in CF patients (Nixon et al., 1992; Pianosi et al., 2005; Vendrusculo, Heinzmann-Filho, Piva, Marostica, & Donadio, 2016; Ward, White, Rowe, Stiller, & Sullivan, 2013), our findings of an improved exercise capacity post IMT are of clinical relevance. Indeed, children with CF over 8 years of age with a $\dot{V}O_{2max}$ of < 32 $ml \cdot kg^{-1} \cdot min^{-1}$ have 60% increased mortality rate (Pianosi et al., 2005). Although participants in the current study had an average $\dot{V}O_{2max}$ of 36 $ml \cdot kg^{-1} \cdot min^{-1}$ at baseline, higher than the aforementioned high-risk category threshold, eight weeks of IMT still significantly increased their $\dot{V}O_{2max}$. Whilst Santana-Sosa et al. (2014) reported a 5.4 $ml \cdot kg^{-1} \cdot min^{-1}$ significant improvement in $\dot{V}O_{2max}$ following an eight week IMT intervention in children with CF, their IMT was combined with whole body strength training; the lack of an IMT-only group precludes the differentiation of the effect attributable to IMT *per se*.

It is also noteworthy that only 73% of participants completed all the sessions in the 'whole body' training intervention of Santana-Sosa et al. (2014), compared to the 89% in the current study, suggesting that IMT alone is more tolerable than a 'whole body' exercise training programme in children with CF. Therefore, a home-based, less intensive and more time efficient IMT intervention can exhibit similar improvements

in aerobic capacity to traditional exercise training interventions. Of note, the lack of association between the exercise gains and MEP in the current study contradicts the association between MEP and the six-minute walk distance previously reported in children with CF (Cunha et al., 2006; Gambazza et al., 2018). This discrepancy may be related to inter-study differences in the measurement of exercise capacity.

Impairments in lung function are associated with a decreased HRQoL in CF (Abbott, Hurley, Morton, & Conway, 2013; Wen et al., 2019) but little is known regarding the influence of IMT on HRQoL. In the current participants, CFQ-R increased by 6% after eight-week IMT intervention, with a continued trend for further improvements following the eight week top-up period. Furthermore, the physical functioning domain, which has been shown to be an independent predictor of survival in CF (Abbott et al., 2009), showed a significant 9% increase after initial eight week duration. This is in accord with the qualitative comments in the current study, as well as earlier studies (Chapter 5; McCreery et al., 2018), which highlighted that children perceived improvements in physical ability as a result of the IMT intervention. Interestingly, the respiratory symptom domain exhibited clinically meaningful improvements after 16 weeks of IMT, suggesting that longer interventions may be needed to elicit significant improvements in other CFQ-R domains in children (Hebestreit et al., 2010; Schneiderman-Walker et al., 2000). The clinically meaningful and significant improvements in perceived physical function and respiratory symptom domains highlight the potential for IMT to have a positive impact on individual's HRQoL. This is especially pertinent in children with CF as QoL has been shown to deteriorate in those greater than 12 years of age due to increased disease severity (van Horck et al., 2017).

The improvement in physiological and psychological parameters highlighted in this study could be related to the high adherence reported. IMT has previously been shown to be feasible and acceptable within this population (Chpater 5; McCreery et al., 2018), yet this is the first study to monitor adherence to IMT remotely and objectively. In the current study, an average adherence of 87% was reported throughout the 16 weeks, which is 37% higher than adherence typically reported for traditional treatments in children with CF (Modi & Quittner, 2006). This high adherence may be related to the home-based and time-efficient nature of the training which was stated as a positive by the children. Alternatively, or additionally, the high adherence may be attributed to

the positive perceptions of IMT by children who cited a sense of ‘fun’ and ‘enjoyment,’ along with an enhanced autonomy and mastery, while undertaking IMT, all of which are important factors for long-term engagement (Denford, Van Beurden, O’Halloran, & Williams, 2020; Teixeira, Carraça, Markland, Silva, & Ryan, 2012). Indeed, this is consistent with self-determination theory which suggests motivation for an activity is either intrinsic or extrinsic (Deci & Ryan, 1985).

The feelings of intrinsic motivation reported by children could be related to the live biofeedback provided by the app. The positive and significant improvements in perceptions of competency in the children within this study orient individuals towards the possibility of success, allowing children to adopt mastery-oriented goals (Morris & Kavussanu, 2008). Indeed, mastery-oriented goals have been found to be positively predicted by perceived competence, which, in turn, has been shown to be positively associated with PA and exercise effort (Kinoshita, MacIntosh, & Sato, 2019). If training is deemed too complicated to understand, or perceived as too stressful, it may diminish compliance to treatment (Taylor, 1991). The simplistic nature of the current intervention, coupled with the feedback loop, is therefore likely to be advantageous for intrinsic motivation while simultaneously influencing positive affect and effort. However, despite children voicing improved mastery and autonomy, these self-determination parameters were not significant, which could be a result of the short-intervention duration or small sample size, with previous research highlighting that longer intervention durations are needed to elicit significant changes in self-determination (Teixeira et al., 2012).

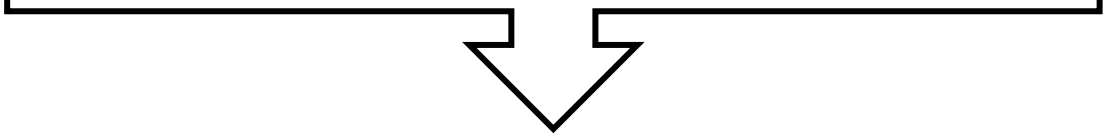
Despite the numerous strengths within this study, there are certain limitations to consider. The small sample size limits statistical power and therefore the interpretation of the data. However, the application of MCID allows for additional patient-orientated insights, and enables studies to be adequately powered with fewer participants (Beaton et al., 2002; Modi et al., 2010). Indeed, considering whether findings are clinically meaningful is arguably more important in terms of driving future treatment decisions (Ranganathan, Pramesh, & Buyse, 2015). Another limitation is the lack of a control group; despite the recruitment of age- and sex-matched controls, COVID-19 precluded study completion.

7.7 Conclusion

In conclusion, IMT elicited clinically meaningful and significant benefits to respiratory muscle strength, exercise capacity and physical and respiratory function domains of the CFQR after eight weeks. Furthermore, a once-a-week top-up period was able to maintain or show trends for improvements in respiratory muscle function parameters. This current study has also highlighted how IMT alone can elicit similar benefits for aerobic capacity as more intensive and time-consuming traditional 'whole body' training interventions. The feedback element of the training programme was discussed as a positive by all children, leading to increased adherence, feelings of mastery, competency and autonomy while undertaking IMT. The combined quantitative and qualitative components provide a unique insight into patient perceptions conveying the feasibility and acceptability of IMT to improve physiological and psychological health of children with CF.

Effects of an Eight-Week, Pro2Fit Inspiratory Muscle Training Programme on the Physiological and Psychological Health of Children with Cystic Fibrosis	
Aims	**Findings**
Determining the influence of inspiratory muscle training on physiological and psychological health and the efficacy of a 16-week top-up period.	Inspiratory muscle training elicited improvements in respiratory muscle strength, exercise capacity and physical functioning domain of the CFQ-R. The 16-week top-up period, maintained improvements in respiratory function

To ascertain whether IMT is effective in other respiratory disease, the same IMT intervention was implemented in adults with bronchiectasis. This population was chosen as bronchiectasis shares a similar pathophysiology with CF and the median age of bronchiectasis diagnosis is 61.8 years.



Effects of a High-Intensity, Pro2Fit Inspiratory Muscle Training Programme on the Physiological and Psychological Health in Adults with Bronchiectasis	
Aims	**Findings**
To investigate the influence of inspiratory muscle training on physiological and psychological health and evaluate participants adherence and ascertain their views and opinions of IMT.	

Chapter 8

The Effects of a High-Intensity PrO2Fit Inspiratory Muscle Training Intervention on the Physiological and Psychological Health in Adults with Bronchiectasis

8.1 Introduction

Bronchiectasis is a chronic pulmonary disease characterised by airflow obstruction due to the destruction of elastic tissue and smooth muscles of the bronchial walls (Onen et al., 2007; Ozalp et al., 2012), arising from a vicious cycle of transmural infection and inflammation (Cole, 1986). Primary symptoms include cough, excessive secretions, dyspnoea, exercise intolerance and fatigue (Koulouris, Retsou, Kosmas, Dimakou, Malagari, Mantzikopoulos, Koutsoukou, Milic-Emili, & Jordanoglou, 2003; Newall, Stickley, & Hill, 2005). These symptoms may, at least in part, be attributable to the respiratory muscle weakness also reported in those with bronchiectasis (Liaw et al., 2011; Moran, Piper, Elborn, & Bradley, 2010; Newall, Stickley et al., 2005), which may lead to discord between respiratory muscle load and capacity (Ozalp et al., 2019). Indeed, decreased respiratory muscle strength is associated with less productive coughing and decreased removal of airway secretions (Moran et al., 2010; Troosters et al., 2005). Effective strategies to target and resolve respiratory muscle weakness are therefore needed for those with bronchiectasis.

Inspiratory Muscle Training (IMT), utilising a restricted airflow breathing technique, has often been used as an adjunct to traditional pulmonary rehabilitation (PR) programmes in chronic obstructive pulmonary disease (COPD), leading to greater improvements in exercise capacity than PR in isolation (Wanke et al., 1994; Weiner, Azgad, & Ganam, 1992). However, whether similar benefits are elicited by IMT in those with bronchiectasis is less clear. Specifically, whilst some report improvements in respiratory muscle strength and endurance, exercise capacity and social aspects of quality of life following IMT (Ozalp et al., 2019), others have reported beneficial effects to be limited to improvements in inspiratory and expiratory muscle strength (Liaw et al., 2011) or there to be no additional benefits to those associated with traditional PR in those with bronchiectasis (Newall, Stockley, et al., 2005). Further work is required to resolve these equivocal findings, which may be related to

considerable methodological differences, such as with regard to the intensity, frequency or duration of the IMT used. Indeed, in those with COPD, interval-based, high-intensity IMT has been shown to elicit greater improvements in respiratory muscle function than low-to-medium intensity protocols (Hill et al., 2006; Sturdy et al., 2003). Alternatively, or additionally, these discrepancies may reflect inter-study differences in participant adherence to the IMT protocol, however, no studies have reported adherence, limiting further conclusions.

The long-term nature of bronchiectasis means patients must cope with the debilitating nature of their disease over the course of their lives. Indeed, patients with bronchiectasis have reported reduced quality of life and increased symptoms of anxiety and depression (Martínez-García, Perpiñá-Tordera, Román-Sánchez, & Soler-Cataluña, 2005; O'leary et al., 2002). Feelings of anxiety have been associated with patients' perceptions of their health and well-being, whereas, in contrast, depression is suggested to be linked to exercise impairment and breathlessness (O'leary et al., 2002). Therefore, interventions that improve both patient perceptions and exercise capacity, whilst relieving symptoms of breathlessness, are of paramount importance to the psychological health of patients with bronchiectasis.

Pulmonary rehabilitation has been recommended for those with bronchiectasis, however, patient perceptions on the effects of PR are limited (Hoffman, Assis, Augusto, Silveira, & Parreira, 2018). Sinnerton and Gillen (2009) found improvements in physical and psychological health post-PR, with enhanced confidence and patients being less dependent on medical resources. However, exacerbations, transport difficulties and lack of motivation were highlighted as barriers to participation in, and adherence to, PR (Sinnerton & Gillen, 2009). In a qualitative study evaluating patient perceptions of home-based IMT in chronic lung disease, Hoffman et al. (2018) found that IMT had a positive impact on activities of daily living, mobility and breathlessness, with patients becoming more confident in managing their disease. Therefore, investigating patient perceptions and motivations to participate in an intervention, in conjunction with determining its physiological and psychological effects, is essential when evaluating the overall effectiveness of an intervention.

Therefore, the aim of the current study was to determine the physiological and psychological effect of an eight-week home-based IMT intervention in adults with bronchiectasis. The secondary aim was to evaluate participants' adherence to the IMT protocol and their experiences and perceptions of this type of pulmonary rehabilitation programme.

8.2 Methods

Ten clinically stable bronchiectasis patients, diagnosed by clinical history including high-resolution tomography, pulmonary functions tests, cough, shortness of breath and exertional dyspnoea, were recruited from an outpatient clinic in South Wales. Eight healthy participants were recruited from University networks and were required to have no pulmonary or respiratory conditions that may impair exercise capacity. Ethical approval was granted by the North West – Liverpool Central Research Ethics Committee (reference 16/NW/0764) and written informed consent was obtained from all participants. Participants were required to attend a testing session at baseline and one following the eight-week intervention. For participants who agreed to do an eight-week IMT top-up, a third visit was required at week 16.

8.2.1 Inspiratory Muscle Training Intervention

The PrO2Fit device (PrO2 Health Incorporated, Rhode Island, USA), was chosen due to its ability to provide biofeedback, remote adherence monitoring and its capacity for greater IMT workloads throughout the full range of inspiration using a decreasing rest period between breaths (Cahalin et al., 2013). Participants were required to breathe through a 2 mm leak from residual value to total lung capacity, while sustaining that breath for as long as possible (Formiga et al., 2018). Prior to completing the intervention, participants were given an ~30-minute training session on how to use the device and the inspiratory manoeuvre technique.

Participants completed high-intensity IMT three times per week, with at least 24 hours between sessions, for eight weeks. After the eight weeks, participants were given the option to complete a further eight weeks during which they were asked to complete IMT once a week. All sessions were performed at home. At the start of every IMT sessions, participants completed a maximal manoeuvre to determine their sustained maximal inspiratory pressure (SMIP), with the subsequent IMT requiring participants to achieve 80% of this SMIP throughout each inspiratory effort. Inspiratory duration

was also measured for each breath. Each IMT session involved up to six blocks of six inspirations, with the rest between inspirations in each block progressively decreasing from 60 seconds to 45, 30, 15, 10, and, finally, 5 seconds. If participants failed to achieve 80% SMIP, the training session was automatically terminated.

8.2.2 Anthropometrics

Physical characteristics including body mass (Seca 220; Hamburg Germany) and stature were measured to the nearest 0.1 kg and 0.01 m, respectively, with body mass index (BMI) subsequently calculated. Waist and hip circumference were measured to the nearest 0.01 m using an anthropometric tape (Seca, UK) at the narrowest point between the base of the ribs and the iliac crest for waist circumference, and the widest point around the hips for hip girth. Waist-to-hip ratio (WHR) was subsequently calculated.

8.2.3 Physiological Measures

Parameters of respiratory function forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), FEV/FEV_1 and peak expiratory flow (PEF) were assessed in a sitting position using a portable spirometer (Micro1, MicroRPM, UK), measured according to the European Respiratory Society Task Force guidelines (Miller et al., 2005). Respiratory muscle strength was measured using a portable electronic mouth pressure device (Micro Medical MicroRPM, UK), with mean inspiratory pressure (MIP) measured at residual volume and mean expiratory pressure (MEP) determined at total lung capacity. Each participant was required to complete three maximal inhalations and exhalations; differences greater than 10% or 10 cm H_2O required an additional effort, with the best inspiration and exhalation selected for subsequent analysis. FEV_1 and FVC were also expressed as the percentage predicted for age, stature and gender (Miller et al., 2005; Quanjer et al., 2012).

As peripheral muscle strength has been reported to be associated with respiratory muscle strength in those with bronchiectasis (Ozalp et al., 2012), handgrip strength (HGS) was measured using a hand dynamometer (Takei 5401, Tokyo, Japan). Participants were required to stand upright, with the arm naturally extended and pointing to the floor, and to squeeze as hard as they could for five seconds, while verbal encouragement was given. A total of four measurements were taken (two from each hand) and the mean result calculated.

If able, participants were asked to complete an incremental ramp test on a cycle ergometer (ViaSpint 150P; ViaSys Healthcare, Germany) to volitional exhaustion. Following a three minute warm-up at 10 W, the resistance was progressively increased at 10 W·min^{-1}. Participants were required to maintain a cadence ~60-70 revolutions per minute (rpm) throughout the test, with the test terminated when the cadence decreased by > 10 rpm, despite strong verbal encouragement. Subjective ratings of perceived exertion (RPE) were recorded every minute (Borg and Dahlstrom, 1962; Borg, 1998; Borg and Linderholm, 2009). Subsequently, participants completed a supramaximal validation bout at 110% of peak power output achieved during the initial cycle ergometer test. Breath-by-breath pulmonary gas-exchange data were collected continuously during the incremental and supramaximal exercise tests (MetaMax 3B, Cortex Medical, Germany). Participants were required to wear a facemask, breathing through an impeller turbine assemble (Jaeger Triple V, Hoechberg, Germany), with gas volumes and flow rates continuously sampled at 100 Hz.

Participants were asked to wear an ActiSleep+ (ActiGraph LLC, Pensacola, FL) tri-axial accelerometer, measuring at 100 Hz on their right mid-axillary line at the level of the iliac crest, 24 hours a day for seven consecutive days. The ActiSleep+ has been shown to be valid and reliable for physical activity (PA) in adult populations (Aadland & Ylvisåker, 2015; Cellini et al., 2013). Additionally, participants completed a self-report log to record whether, and indeed why, the ActiSleep+ was removed (i.e. water-based activities). Troiano et al. (2014) cut-points were used to determine time spent in each intensity (sedentary: < 99 counts·min^{-1}; light: 100-2,019 counts·min^{-1}; vigorous, > 5,999 counts·min^{-1}). Time spent in moderate and vigorous PA was summed to obtain moderate-to-vigorous PA (MVPA; 2,020-5,998 counts·min^{-1}).

8.2.4 Psychological measurements

Employing self-determination theory (Williams, Deci & Ryan, 1999), all participants completed questionnaires to assess treatment self-regulation and perceived competence in relation to IMT, following the initial eight-week intervention. Specifically, the 15-item treatment self-regulation questionnaire was utilised to assess reasons for completing IMT regularly (i.e. “The reason I would undertake IMT is

because I feel that I want to take responsibility for my own health"). The treatment self-regulation questionnaire has three subscales: autonomous regulation, controlled regulation and amotivation. Perceived competence was measured using four single-item indicators (i.e. "I feel confident in my ability to undertake IMT regularly"). Both questionnaires were answered using a Likert scale ranging from one (not at all true) to seven (very true) and are validated for use within clinical populations (Ng et al., 2012).

Finally, participants were invited to complete a face-to-face, semi-structured interview following the eight-week intervention. If participants failed to complete the intervention, they were still invited to take part in an interview to ascertain their perceptions and barriers to completing the intervention. The interviewer (JMC) asked open-ended questions, seeking clarification or elaboration when required. Questions were centred around their experience with IMT, recommendations for future use and more generic opinions of PA and exercise. Interviews were audio recorded and transcribed verbatim.

8.3 Data Analysis

8.3.1 Cardiopulmonary Exercise Testing and Supramaximal Verification

Oxygen consumption ($\dot{V}O_2$) and carbon dioxide production ($\dot{V}CO_2$) were converted to 15 -second averages. The highest moving average of $\dot{V}O_2$ measured over 15 -seconds was taken as the peak value. The gas exchange threshold (GET) was determined as the $\dot{V}O_2$ at which there was a non-linear increase in carbon dioxide consumption relative to $\dot{V}O_2$, with an increase in minute ventilation ($\dot{V}E$)/$\dot{V}O_2$ without a concomitant increase in $\dot{V}E/\dot{V}CO_2$ (Beaver et al., 1985). Peak $\dot{V}O_2$ was considered maximal if the $\dot{V}O_2$ peak achieved during the supramaximal verification did not exceed that achieved during the ramp test by ≥ 9% (Causer et al., 2018).

8.3.2 Interview Analysis

All interviews were transcribed verbatim by JLM, using a manual method (Braun & Clarke, 2014), with interview data analysed using an inductive and deductive approach via direct content analysis (Hsieh & Shannon, 2005). Transcripts were coded line-by-line and then placed in a relevant overarching category. To ensure a detailed account of participants experiences, similar and/or opposing codes were then organised into

themes. An independent author (KAM) undertook a cross examination of the data to challenge the interpretations, ensuring methodological rigour and that findings were logical and to offer alternative interpretations (Boddy et al., 2012; Mackintosh et al., 2011).

8.3.3 Physical Activity Analysis

PA data was downloaded and analysed using ActiLife Software 6 (ActiGraph v6.10.4; Pensacola, FL). Data was integrated into one second epochs, with sustained periods of at least 20 minutes of zero counts considered non-wear time (Catellier et al. 2005). To be included in the subsequent analyses, participants were required to have worn the ActiSleep+ for ≥ 9 hours·day^{-1}, for at least three days, including one weekend day, which has been previously implemented in clinical populations (Ryan, Forde, Hussey, & Gormley, 2015) and shown to have a reliability coefficient of 0.7 (Mattocks et al., 2008).

8.4 Statistical Analysis

All data were analysed using IBM SPSS (IMB Corp, Version 25.0. Armonk, New York: IBM Corp) and are presented as mean ± standard deviation (SD) unless stated otherwise. Statistical significance was accepted as $p < 0.05$. A repeated measures ANOVA was used to determine the influence of IMT, and how this differed by group. Pearson's correlation coefficients were used to assess the relationships between $\dot{V}O_{2max}$, HGS and lung function. The minimal clinically important difference (MCID) was calculated using distribution-based methods. Specifically, the baseline SD multiplied by 0.5 was used to determine whether IMT had a clinically significant effect on lung function, HGS and $\dot{V}O_{2max}$. The change score divided by the baseline SD score was used to calculate effect size, with Cohen's (1988) d thresholds used for interpretation (small = 0.2, moderate = 0.5 and large = 0.8).

8.5 Results

Fourteen adults with clinically stable bronchiectasis agreed to take part in the study. One patient withdrew due to an acute exacerbation, two withdrew due to the inability to use the device and one was unable to make the retesting visits. Due to the impact of

COVID-19, eight healthy participants could not be retested, but they were invited to take part in interviews. Overall, adherence to the IMT protocol was high, with bronchiectasis patients completing significantly more IMT sessions (95%) than the healthy participants (80%) during the first eight weeks.

The healthy participants were younger than those with bronchiectasis who were characterised by a higher BMI at baseline (Table 8.1). Furthermore, healthy participants exhibited a higher MEP ($p = 0.05$), FEV_1 ($p = 0.002$), FVC ($p = 0.002$), FVC %predicted ($p = 0.03$) and $\dot{V}O_{2max}$ ($p = 0.002$; Table 8.2).

Table 8.1. Baseline anthropometrics of adults with bronchiectasis and healthy participants.

Characteristics	Total (n=18)	Bronchiectasis (n=10)	Healthy (n=8)	P value
Anthropometrics				
Age (years)	51.9 ± 17.2	64.5 ± 10.3	36.1 ± 8.5	<0.05*
Sex (female/male)	(5/13)	(3/7)	(2/6)	0.886
Height (cm)	172.6 ± 10.9	169.5 ± 11.2	176.4 ± 9.7	0.183
Weight (kg)	76.9 ± 16.8	81.2 ± 19.7	71.5 ± 11.2	0.238
BMI ($kg \cdot m^{-2}$)	25.8 ± 5.5	28.3 ± 6.3	22.8 ± 1.8	0.024*
WHR (cm)	1.0 ± 0.1	1.0 ± 0.1	0.9 ± 0.6	0.106

BMI, body mass index; WHR, waist-to-hip ratio.

Table 8.2. Effect of an eight-week inspiratory muscle training intervention in adults with bronchiectasis and healthy participants.

Parameters	Baseline		8-week		Change from baseline mean	
	Bronchiectasis (n = 10)	**Healthy (n = 8)**	**Bronchiectasis (n = 10)**	**Healthy (n = 8)**	**Bronchiectasis (n = 10)**	**Healthy (n = 8)**
MIP (cmH_2O)	72.5 ± 44.5	95.3 ± 46.8	92.1 ± 50.8	125.9 ± 35.2	19.6 ± 18.9*	30.6 ± 29.3*
MEP (cmH_2O)	65.7 ± 22.3	107.5 ± 56.8	68.9 ± 25.9	115.6 ± 49.5	3.2 ± 20.3	8.1 ± 28.3
SMIP (PTU)	407.2 ± 354.2	437.0 ± 206.0	473.4 ± 327.0	513.2 ± 238.0	66.1 ± 57.8*	776.2 ± 80.8*
Inspiratory Duration (s)	10.4 ± 5.7	12.2 ± 2.7	14.2 ± 5.3	15.9 ± 4.6	3.8 ± 4.0*	3.8 ± 2.7*
FEV_1 (l)	2.5 ± 0.6	3.8 ± 0.9	2.5 ± 0.6	3.8 ± 1.0	-0.01 ± 0.2	0.01 ± 0.3
FEV_1 %predicted	78.1 ± 15.8	90.6 ± 8.9	78.5 ± 15.5	90.9 ± 15.8	0.4 ± 11.7	0.3 ± 8.3
FVC (l)	3.2 ± 0.6	4.8 ± 1.2	3.2 ± 0.7	4.8 ± 1.2	-0.01 ± 0.2	0.02 ± 0.5
FVC %predicted	80.3 ± 11.9	93.8 ± 12.5	78.3 ± 10.4	94.8 ± 9.1	-2.0 ± 14.1	1.0 ± 7.8
PEF ($L \cdot min^{-1}$)	436.5 ± 127.3	547.4 ± 107.9	441.5 ± 105.0	557.6 ± 110.3	5.0 ± 49.7	10.3 ± 4.8*
FEV_1/FVC	80.3 ± 15.4	82.7 ± 15.3	82.4 ± 14.8	79.3 ± 15.8	2.1 ± 10.2	-3.4 ± 10.6

$\dot{V}O_{2max}$ ($ml \cdot kg^{-1} \cdot min^{-1}$)	11.1 ± 2.6	39.7 ± 11.0	11.0 ± 2.2	44.3 ± 13.6	-0.1 ± 1.5	4.6 ± 4.2*#
Average HGS (kg)	31.8 ± 12.1	40.9 ± 10.3	33.4 ± 10.5	40.8 ± 9.1	1.7 ± 3.3	0.1 ± 4.5

*MIP, mean inspiratory pressure; MEP, mean expiratory pressure; SMIP, sustained maximal inspiratory pressure; PTU, pressure time unit; ID, inspiratory duration; s, seconds; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; PEF, peak expiratory flow; HGS, handgrip strength; $\dot{V}O_{2max}$, maximal oxygen uptake. *p<0.05 change from baseline; #p<0.05 for change between groups.*

One bronchiectasis participant did not meet the wear-time criteria and was therefore removed from PA analysis. On weekdays, bronchiectasis participants spent more time sedentary and less time in VPA and MVPA compared to healthy participants, whilst, conversely, those with bronchiectasis spent less time sedentary on weekend days (Table 8.3).

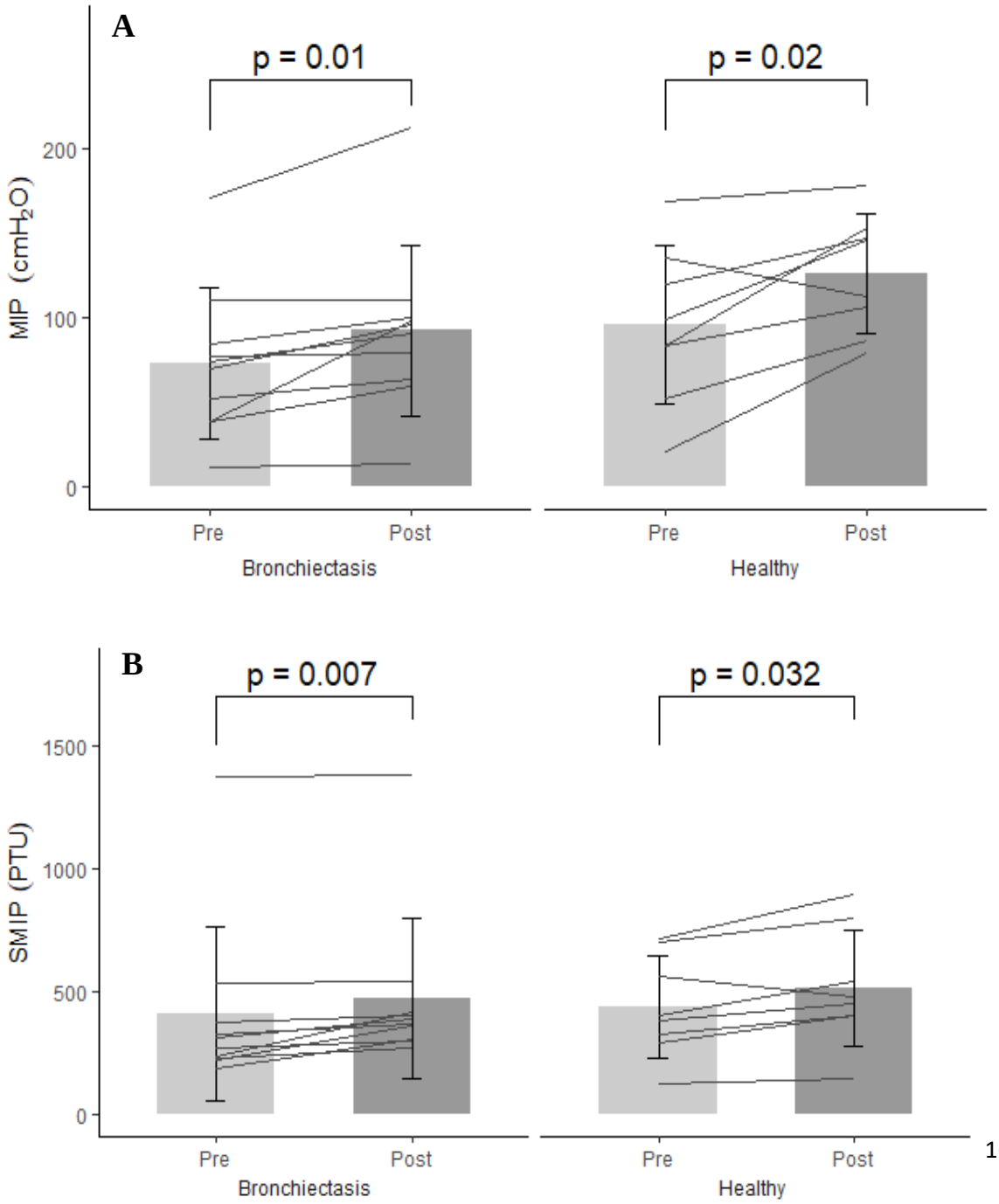
Table 8.3. Baseline physical activity levels in adults with bronchiectasis and healthy participants.

	Total (n=17)	Bronchiectasis (n=9)	Healthy (n=8)	P Value
Overall, min·d^{-1}				
Sedentary Time	1,095.4 ± 249.6	1,158.1 ± 181.1	1,033.0 ± 290.7	0.005*
LPA	106.6 ± 46.3	106 ± 38.9	106.7 ± 52.8	0.981
MPA	46.8 ± 25.6	46.0 ± 26.3	47.5 ±25.1	0.740
MVPA	55.2 ± 32.1	51.4 ± 29.1	59.1 ± 34.6	0.186
VPA	8.5 ± 16.8	5.4 ± 12.0	11.5 ± 20.1	0.043*
Weekday, min·d^{-1}				
Sedentary Time	1,102 ± 224.6	1,144.6 ± 196.7	1,007.0 ± 257.5	0.017*
LPA	104.5 ± 44.1	102.1 ± 30.8	110.0 ± 53.1	0.442
MPA	50.7 ± 24.5	48.0 ± 25.1	56.8 ± 22.4	0.121
MVPA	59.0 ± 31.4	53.1 ± 27.4	72.8 ± 36.1	0.006*
VPA	8.4 ± 16.2	5.0 ± 8.5	16.0 ± 25	0.034*
Weekend, min·d^{-1}				
Sedentary Time	1,064 ± 306.9	1,182.1 ± 1,153.9	947.6 ± 375.7	0.020*
LPA	110.6 ± 52.3	109.1 ± 39.6	112.1 ± 63.6	0.867
MPA	37.2 ± 26.0	36.6 ± 23.7	37.7 ± 28.8	0.901
MVPA	47.0 ± 32.7	42.4 ± 27.7	51.6 ±37.2	0.218
VPA	9.9 ± 19.4	5.8 ± 16.5	13.9 ± 21.7	0.407

LPA, light physical activity; MPA, moderate physical activity; MVPA, moderate-to-vigorous physical activity; VPA, vigorous physical activity.

8.5.1 Effects of Inspiratory Muscle Training

A repeated measures ANOVA with Greenhouse-Geisser correction showed eight weeks of IMT was associated with a main effect of time and group for MIP, SMIP and inspiratory duration, with a significant group-by-time interaction for PEF and $\dot{V}O_{2max}$ ($p < 0.05$). Specifically, bronchiectasis and healthy participants exhibited significant increases in MIP (27% vs. 32%, respectively), SMIP (16% vs. 17%, respectively) and inspiratory duration (36% vs. 30%, respectively) after eight weeks of IMT. The healthy participants also exhibited further improvements in PEF and $\dot{V}O_{2max}$ after eight weeks, which were not evident in the bronchiectasis group (Figure 8.1; Table 8.2). No significant effect of time or group was found in HGS.



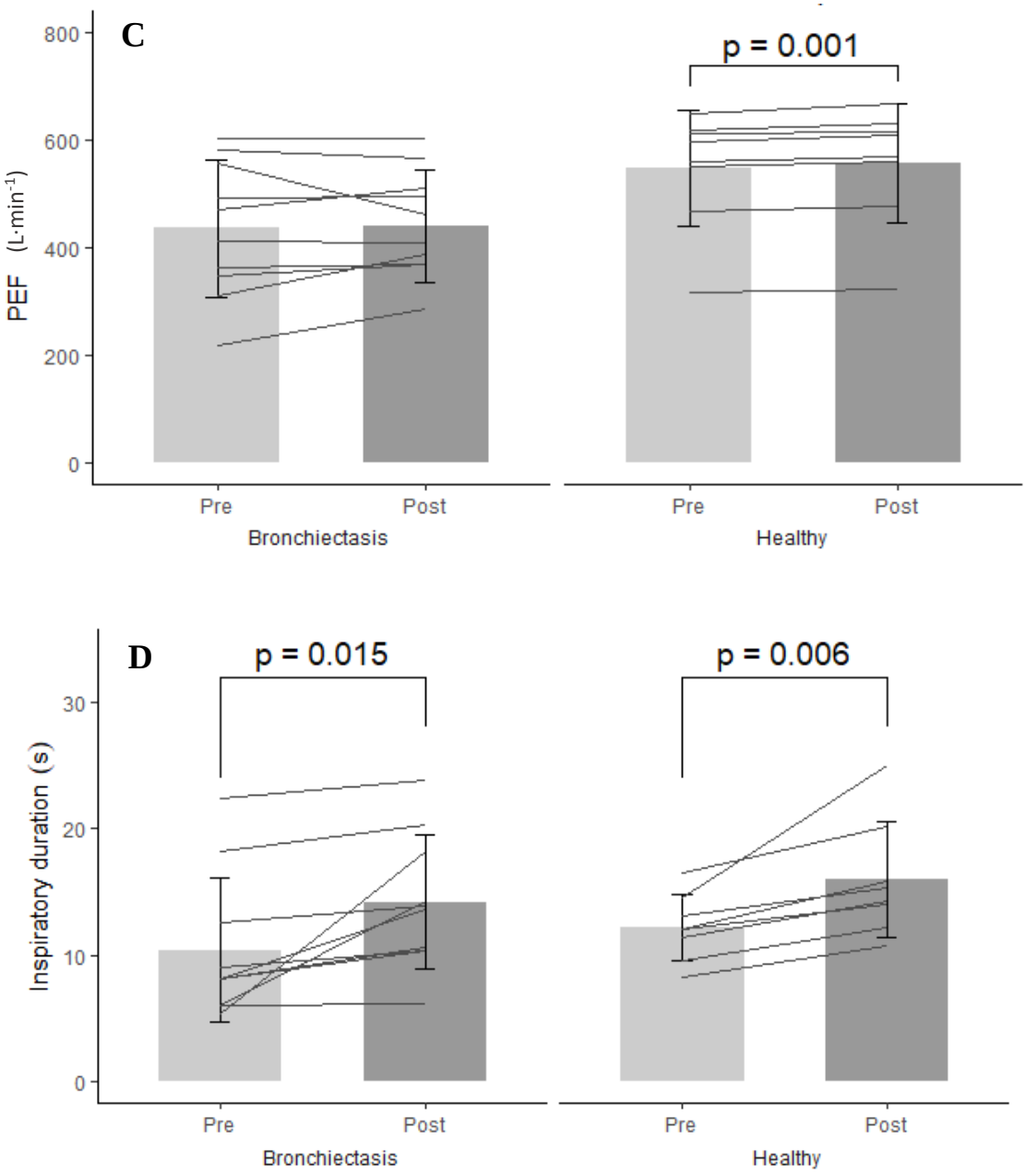


Figure 8.1. Changes in A) MIP, mean inspiratory pressure; B) SMIP, sustained maximal inspiratory pressure; C) PEF, peak expiratory flow and D) inspiratory duration over the eight weeks of an inspiratory muscle training intervention in adults with bronchiectasis and healthy controls. Grey columns represent the mean group response with standard deviation bars. Overlaid lines represent individual responses.

MCID revealed that bronchiectasis patients exhibited small clinically meaningful improvements in MIP, SMIP and HGS (d = 0.4; d = 0.2; d = 0.2, respectively) and a moderate clinically meaningful improvement in inspiratory duration (d= 0.6) following IMT. There were no clinically meaningful improvements in any other parameters (Table 8.4).

Table 8.4. Meaningful clinical differences between baseline, eight weeks and 16 weeks in adults with bronchiectasis.

Parameters	Mean Difference from baseline to 8 weeks (n = 10)	% of participants with clinically significant increase	% of participants with clinically significant decrease	Effect Size	Mean difference from 8 weeks to 16 weeks (n = 3)	% of participants with clinically significant increase	% of participants with clinically significant decrease	Effect Size
Lung Function								
MIP (cmH_2O)	19.6 ± 18.9*	40%	0%	0.4	23.7 ± 27.5	0%	33%	0.5
MEP (cmH_2O)	3.2 ± 20.3	20%	10%	0.1	4.7 ± 4.1	0%	0%	0.2
SMIP (PTU)	66.1 ± 57.8*	50%	0%	0.7	65.8 ± 57.6	0%	0%	0.2
ID (s)	3.8 ± 4.0*	60%	0%	0.2	3.4 ± 4.1	0%	0%	0.1
FEV_1 (l)	0.01 ± 0.2	0%	0%	0.01	0.1 ± 0.1	0%	0%	-0.1
FEV_1 %predicted	0.4 ± 11.7	30%	60%	0.02	7.0 ± 6.7	67%	0%	0.5
FVC (l)	0.01 ± 0.2	10%	0%	-0.02	0.1 ± 0.1	0%	0%	-0.2
FVC %predicted	-2.0 ± 14.1	40%	40%	-0.2	9.0 ± 13.1	33%	0%	0.9
PEF ($L \cdot min^{-1}$)	5.0 ± 49.7	20%	10%	0.04	5.0 ± 9.5	0%	0%	-0.04
FEV_1/FVC	2.1 ± 10.2	10%	0%	0.1	1.3 ± 1.5	0%	0%	0.1

Exercise Capacity $\dot{V}_{O2max}$ (ml·kg^{-1}·min^{-1})	0.1 ± 1.7	10%	10%	-0.04	4.3 ± 5.1	0%	100%	2.0
Handgrip Strength Average HGS (kg)	1.6 ± 3.3	10%	0%	0.1	-0.6 ± 0.6	0%	0%	0.1

*MIP, mean inspiratory pressure; MEP, mean expiratory pressure; SMIP, sustained maximal inspiratory pressure; PTU, pressure time unit; ID, inspiratory duration; s, seconds; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; PEF, peak expiratory flow; HGS, handgrip strength; $\dot{V}_{O2max}$, maximal oxygen uptake. *p<0.05.*

Following the eight-week IMT intervention, MIP significantly correlated with FEV_1 ($r = 0.667$; $p = 0.035$) and FVC ($r = 0.772$; $p = 0.009$), whilst $\dot{V}O_{2max}$ showed significant correlations with FEV_1 ($r = 0.693$; $p = 0.039$) and FEV_1/FVC ($r = 0.795$; $p = 0.018$) in those with bronchiectasis. Contrastingly, in the healthy participants, MIP correlated with MEP ($r = 0.821$; $p = 0.012$), whilst FEV_1 was significantly correlated with FVC ($r = 0.721$; $p = 0.044$).

Compared to healthy participants, those with bronchiectasis exhibited significantly higher levels of autonomy (4.9 ± 1.4 vs 2.1 ± 0.7; $p < 0.01$) and perceived competence (5.5 ± 1.3 vs 4.6 ± 1.1; $p < 0.01$), with lower levels of amotivation (1.4 ± 0.6 vs 4.3 ± 0.4; $p < 0.01$) after eight weeks of IMT.

Table 5. Self-determination measures after eight weeks of inspiratory muscle training.

	8-weeks				95% Confidence Interval		*P* Value between groups
	Bronchiectasis	**Healthy**	**Mean Difference**	**SEM**	**Lower**	**Upper**	
			Treatment Self-Regulation				
Autonomous	4.9 ± 1.4*	2.1 ± 0.7	2.8	0.5	1.7	4.0	<0.01*
Controlled	1.7 ± 0.7	1.5 ± 0.3	0.2	0.3	-0.4	0.8	0.411
Amotivation	1.4 ± 0.6	4.3 ± 0.4*	-2.9	0.3	-3.4	-2.4	<0.01*
Perceived Competence	5.5 ± 1.3*	4.6 ± 1.1	0.9	0.6	-0.31	2.1	0.128

*SEM, standard error of the mean. *p < 0.05 within group differences.*

8.5.2 Eight-Week Top-Up Period

Five bronchiectasis and four healthy participants agreed to do a further eight-week top up period. Two bronchiectasis patients subsequently dropped out of the top-up period; one participant was going on vacation and the other had purchased their own PrO2 and wanted to train more frequently. Two healthy participants also dropped out due to being unable to make the final testing visit. Adherence in those that completed the entire top-up period was 100% and 69% for bronchiectasis and healthy participants, respectively.

There were no significant differences in respiratory muscle strength, lung function parameters, handgrip strength or exercise capacity between or within groups compared to the values following the initial eight weeks after the eight-week top-up period.

8.5.3 Qualitative Experiences

Key themes derived from the interviews with bronchiectasis and healthy participants are presented below. 'B' indicates quotes from bronchiectasis and 'H' from healthy participants.

Relationship with Physical Activity and Exercise

Positives

Most bronchiectasis participants (80%) and all healthy participants (100%) highlighted a positive relationship with PA and exercise, citing experiences of both mental and physical enjoyment:

"I love walking the dogs, because it gets you out into the open air… it is good for you mentally as well I think. It does make you feel better doesn't it? You feel very virtuous when you've done some [PA]." [B10]

"I like the freedom of it… I find it really helpful for my mental health. The knowledge that my body is capable of doing things. I like the sense of achievement." [H1]

Barriers to Exercise

Symptoms associated with bronchiectasis were highlighted as the main barrier to exercise in this cohort of patients:

"Having this bronchiectasis limits the amount of physical activity and exercise I can do… I look forward to it [physical activity and exercise] mentally, but I am very much aware of my limitations very soon… I wish I could do a lot more walking and I would really enjoy that much more if I could." [B3]

With their condition impacting on their activities of daily living:

"I've got to take my time on everything, but anything that's up and down, I mean like the stairs, up is physical, but down is just as hard." [B1]

In line with the healthy participants, barriers such as enjoyment, weather, work and time constraints were also highlighted as reasons for being inactive:

"I don't enjoy it [physical activity], I haven't got the time to do it. It's time more than anything [that is a barrier], you come home from work and you're tired, you don't want to start doing exercises." [B6]

"Time is always the biggest one [barrier to exercise and physical activity]. It always is isn't it? Time and mental sort of motivation… One of the downsides of my job is that I'm spending a lot of time sitting down. I've come from a previously very active job… to then go to a really sedentary job has been really hard and that's really affected my activity." [H5]

Motivations to Exercise

Despite these limitations and the barriers to PA and exercise, patients understood the importance of being physically active and also highlighted their bronchiectasis as a motivator to be active:

"Since the diagnosis I realise I need to be more active in order to keep my lungs healthy and the sputum moving around... So, the more active you are the better it [bronchiectasis] is. I try to be a little bit more active, whereas before [diagnosis] I might have thought 'I won't do any exercise tonight', I think 'right I've got to do it because of the bronchiectasis'." [B10]

Another critical motivator was being healthy for family reasons:

"The idea, certainly with the grandchildren, is to be as fit as you can around them so that you can keep up with them! It has been quite physically demanding [looking after the grandchildren]." [B8]

In line with the bronchiectasis participants, healthy adults also highlighted an understanding of the importance of exercise:

"The benefit [of exercising] is I know it is good for me. It's probably the best drug in the world, if you could bottle it. I do it for my own health and that it makes me feel better about myself." [H5]

External Influences

External influences to exercise also centred around health, implications of ageing and the impact a person's health can have on others:

"I think there is a moral obligation to exercise and at least remain healthy, because it matters to other people what happens to us. Obesity and smoking causes demand on the health service… problems just get worse as you get older and then it drags other people in because they have to look after you… It's a drag on your friends and relatives and you have to consider the effect of your own decisions on other people." [H9]

Furthermore, the social aspect and the influences of others were also highlighted as an external motivator to exercise:

"It depends who you hang around with. If you hang around with lots of sports people you tend to learn off your group. Whereas, if you haven't got that social side to it, then maybe you won't exercise as much." [H1]

Some healthy participants also discussed the pressures they feel to be active, citing external influences such as media, society pressures and weight control:

"If I wasn't particularly active, I think I would feel guilty. I don't know if that is something that is put on me myself or more because of the media aspect… I'm probably going to have more health complications, probably going to be overweight. I don't know if it is a societal thing or a personal thing [pressure to be active], but I'd feel guilty if I didn't [exercise]." [H1]

Inspiratory Muscle Training Intervention

Enjoyment

Bronchiectasis participants expressed 'enjoyment' of undertaking IMT and that it was something they 'looked forward' to doing due to the perception it could help their health:

"I was looking forward to doing it, because I want to do anything that's going to help. I've been so poorly with my chest this year that anything that will help, I will try." [B2]

Motivations

Bronchiectasis patients discussed determination and motivation to do the training, due to the structure of the training programme:

"I was determined, I wanted to do this [IMT]… the main reason is that it gives me that discipline, I am more than happy to follow a training programme and then the motivation followed 'I will do this'." [B3]

Participants enjoyed the high-intensity nature of the training and discussed how the differing levels and reducing rest times were 'challenging' but motivated them to try harder:

"They [decreasing rest times] were good. That really set a goal for you, you know. It was hard, but I was motivated to do it, it did push you a bit more!" [B1]

"That made it harder at the time [levels and decreasing rest times]. I think it was good, it kept it more engaging… it kind of has a reward element to it, I suppose." [H9]

In contrast to bronchiectasis, while some enjoyed the IMT intervention, more healthy participants discussed having less motivation to complete training compared to regular exercise, due to the lack of intrinsic and extrinsic rewards:

"Less motivated to do it [IMT] than I am to do exercise. I think once you've done exercise you feel good about it afterwards, you feel like you have achieved something. Whereas, after doing the PrO2 training, it just felt like something that I had to do, I had to get through, but no reward at the end." [H1]

The reasons for this lack of motivation were due to participant's perceived lack of improvements from undertaking IMT, with healthy participants suggesting that clinical populations or athletes may benefit from this style of training more:

"I'm guessing you might get more significant results if someone sort of sedentary was using it. I don't feel like it was helping me in anything other than being able to do the test better." [H6]

Accessibility

The remote nature of the training programme was a positive for the participants as it allowed easy integration into their daily lives, with participants reporting that if it wasn't home-based, they wouldn't have taken part:

"If I had to go somewhere to use it, I probably would not have done it… I would have had to have made more of an effort and having something small and portable, why would I want to go somewhere else with it?... Having it at home I can do it easily" [B4]

Similarly, the convenience of being able to do it at home was also discussed by healthy participants as a positive of the intervention:

"I think it's better to have it at home than having it elsewhere, it would never have worked [training elsewhere]… It's just convenient really, doing it at your own time at your own pace without anyone watching." [H2]

Healthy participants also discussed the ease of training and how easily it can be integrated into daily routine:

"It's quite portable and convenient as opposed to setting an hour of your day aside to physically go and do exercise… It's a lot more flexible in terms of time of day or motivation. You can adapt to it quite well." [H10]

Feedback

Another highlight of the training was the accompanying app and the live feedback loop it provided. All participants cited this as a critical motivating factor, while giving them a chance to set their own goals:

"You can set your goals then… I found having that sort of feedback was very helpful" [B7]

"It [feedback] changed my behaviour for the better, I was aiming for something, I knew what I was meant to be doing. I think having that goal in mind helps the person try and exercise." [H7]

While it gave participants an opportunity to track their own progress, it also brought out the competitive nature of some participants:

"It is nice to know how you are doing, but it's also nice to have something to compete against. If somebody would have asked me before 'are you competitive'? I would have said no, not really, but yes, in this instance I certainly am!" [B5]

Participants also highlighted if they didn't have this extrinsic motivation, they wouldn't have trained or have been as motivated to try as hard as they perceived they did:

"You wouldn't have pushed yourself as much [if you didn't have the visual feedback]" [B4]

"I wouldn't have tried as hard because you don't know how you've done. You wouldn't be as motivated to try then." [H2]

However, healthy participants also discussed the negative aspects of the feedback element and how it could also potentially be demotivating:

"Then I got really frustrated if I couldn't get to the end." [H4]

Perceived Improvements

Importantly, all bronchiectasis participants perceived an improvement in their physical ability and health after completing IMT, attributing this solely to the training programme:

"I'm not doing anything different in my life other than using the device… Some of the things I do now, the recovery time after doing them is about half [the recovery time] was before. I have never got this far into a winter without a cold turning into a chest infection. My lungs aren't producing the same levels of mucus as they

typically do which is a great improvement. Physically I'm feeling better, now that's [IMT] got to be worth doing." [B8]

Activities of daily living were also perceived to be easier:

"My stamina has got better I would say that, I was quite pleased with that actually. I found it easier walking up the stairs, I was fitter. It's all hills round me and two months ago I wouldn't have been able to do an hour [walk]… but now it's ok!" [B1]

Bronchiectasis participants also voiced the ability to expectorate sputum more easily, which they felt led to a decrease in recurrent respiratory infections:

"What I like about it was that it helped me to clear a lot of sputum much better than the Acapella [an airway clearance device]… I haven't had any infections, and this is my tenth week without antibiotics or infection. I think my record before was three weeks!... When you have bronchiectasis, as long as you can keep your lungs clear, happy days. That is the most important thing." [B2]

Some healthy participants (38%) also discussed perceived improvements post-IMT:

I definitely think my lung capacity is improved… I decided to go for a little run and I was really shocked my breathing had improved… I definitely felt the benefit from it, which was surprising actually. I think it has definitely made a difference. I know a couple of friends of mine are quite jealous." [H10]

However, they could not be confident their perceived improvements were attributable to IMT alone:

"There's definitely been an improvement in my training over time, but I don't know whether that was necessarily because of this device." [H5]

Future Improvements

Adherence

Despite the positives, participants did voice some areas they would like to improve. Specifically, some bronchiectasis patients, despite excellent adherence to the training programme, thought the training programme was 'too long' (30%):

"Tiresome three times a week… it was getting to be a bit of a pain after eight weeks… Possibly if it could get condensed to fit into your lifestyle more." [B4]

Which was also voiced by the healthy participants and would have potentially helped with adherence in this cohort (75%):

"If you could condense it into a shorter training period, that would definitely help in making me complete more sessions." [H5]

Extrinsic Feedback

Participants, irrespective of health status, suggested more extrinsic feedback to help with motivation, while also providing rewards:

"I would have liked something like a smiley face or a 'hip hip hooray! You've done it, well done'!" [B1]

"I think from a sort of motivation point of view, it may sound silly, but just to have a 'well done, that was better than last time, you've improved this much,' 'you're nearly there, keep on going,' and 'you're doing better than you have previously done.' So, that would help motivate you." [H6]

Despite participants exhibiting goal setting, they would also like the app to provide tangible goals that they have to reach:

"If it set you targets to achieve within a certain period. That would make it far more worthwhile." [B4]

"You could have a set target from the data… you know 'can I get closer to the target'? Without targets, it was difficult to know what you could improve on or whether you were improving." [H9]

8.6 Discussion

This study revealed that an eight-week, home-based IMT programme elicited significant and clinically meaningful increases in inspiratory muscle strength and endurance in both bronchiectasis and healthy participants, with healthy participants also significantly enhancing expiratory flow and exercise capacity. Whilst no additional adaptations were shown at 16 -weeks, doing IMT once per week was sufficient to maintain those benefits already elicited. These physiological benefits were enabled by a high adherence to the IMT protocol, with participants reporting that IMT was enjoyable and that they perceived health and well-being benefits. This

therefore suggests that IMT may represent an effective and palatable alternative to traditional pulmonary rehabilitation programmes in those with bronchiectasis.

As bronchiectasis is associated with respiratory muscle weakness (Liaw et al., 2011; Moran et al., 2010; Newall, 2005), the clinically meaningful improvement in MIP observed after eight weeks of IMT in the current study is of clinical importance. Previous research found low intensity IMT (30% MIP) improved MIP by 39% (Newall, 2005), while a progressive overload-based IMT programme (20-70% MIP) elicited improvements of 44% (Ozalp et al., 2019). However, in contrast to the present study, both Newall. (2005) and Ozalp et al. (2019) found significant improvements in MEP of 44% and 12%, respectively. Indeed, whilst the present study found improvements in MEP, these were not statistically significant or clinically meaningful. Such discrepancies may be due to the small sample size in the present study, though it is noteworthy that these findings are in accord with Harver and colleagues (1989) who found that eight weeks of high-intensity IMT improved MIP, but not MEP, in individuals with COPD. As such the physiological effect of IMT on expiratory muscles remains unclear. It has, however, been hypothesised that inspiring against a resistance, as is the case in IMT, could increase the activation of the expiratory muscles by force extension, leading to an increase in MEP (Ozalp et al., 2019). Elsewhere, it has been postulated that increased inspiratory muscle strength results in better thorax expansion, enabling a greater elastic recoil, that could improve MEP and PEF (de Medeiros et al., 2017). Decreased expiratory muscle strength can have detrimental effects in bronchiectasis patients on their effectiveness of coughing and removal of airway secretions (Moran et al., 2010; Troosters et al., 2005), therefore, further research is required to determine the effect, and underlying mechanism, IMT has on respiratory muscle function.

Lung function parameters were not affected by IMT in the present intervention. This is in line with previous research that found eight weeks of high intensity IMT increased MIP, but had no effect on FEV_1 or FVC in those with COPD (Harver et al., 1989), CF (Enright, Chatham, Ionescu, Unnithan, & Shale, 2004) or bronchiectasis (Liaw et al., 2011). Despite there being no significant improvements in respiratory function post-IMT, MIP values were significantly associated with pulmonary function in those with bronchiectasis. It could therefore be postulated that those with inspiratory muscle weakness may suffer from more severe airflow obstruction and greater lung

hyperinflation. This is in accord with previous research that found a positive correlation between MIP and airflow limitation in a COPD population (Jamaati et al., 2013; Nambiar, Ravindra, & Kumar, 2018; Tudorache, Oancea, & Mlădinescu, 2010).

Both SMIP and inspiratory duration are emerging as key clinical markers across several populations (Cahalin & Ross, 2015; Formiga, Campos, & Cahalin, 2018), with suggestions that they are both superior markers of inspiratory performance than MIP (Severin, Arena, Lavie, Bond, & Phillips, 2020). In combination, they provide a more comprehensive assessment of identifiable characteristics of respiratory muscle weakness or fatiguability (Cahalin & Ross, 2015), while potentially providing greater ability to identify outcomes associated with mortality risk in individuals with COPD (Formiga et al., 2018). The significant improvements in SMIP and inspiratory duration exhibited post-IMT in the present study are therefore of particular interest. In COPD, greater SMIP is independently related to reduced airflow limitation, less dyspnoea and increased six minute walk test (6MWT) distance (Formiga et al., 2018). Like SMIP, increased inspiratory duration is reported to be associated with an increase in distance walked in 6MWT (Formiga et al., 2018). Therefore, the current improvements could be postulated to translate to meaningful enhancements in functional exercise capacity.

Exercise intolerance is often reported in those with bronchiectasis, the basis for which is likely to be multifaceted and includes decreased ventilatory efficiency, altered respiratory mechanics, insufficient gas exchange, expiratory flow limitation and increased dynamic hyperinflation (Koulouris, Retsou, Kosmas, Dimakou, Malagari, Mantzikopoulos, Koutsoukou, Milic-Emili, & Jordanoglu, 2003; Ozalp et al., 2012). Furthermore, reduced exercise tolerance has been associated with increased depression (O'leary et al., 2002). In contrast to the healthy participants, IMT was not associated with any change in $\dot{V}_{O2max}$ in those with bronchiectasis in the current study. Whilst this is congruent with some earlier studies (Liaw et al., 2011), others have reported significant improvements in intermittent shuttle walk test (ISWT) distance in a bronchiectasis population (Newall, 2005; Ozalp et al., 2019). It is pertinent to note that the IMT protocol in Newall et al. (2005) was combined with conventional exercise training so it is not possible to discern the independent effect of IMT. Nonetheless, these apparent discrepancies in the effect of IMT on exercise capacity are perhaps more likely to be attributable to the measure of exercise capacity within the studies. Specifically, the current cardiopulmonary exercise testing (CPET) derived values

provide an accurate measure of maximal exercise capacity, the clinical significance of which is increasingly evident with regards to predicting prognosis in numerous clinical conditions (Paolillo & Agostoni, 2017). However, the applicability of this measure to functional capacity and daily activities has been questioned (Houghton, Harrison, Cowley, & Hampton, 2002), with suggestions that measures such as the 6MWT distance may be more applicable to bronchiectasis due to its relatedness to everyday activity (Crapo et al., 2002). This notion is supported by the present study in which, despite exhibiting no significant difference in maximal exercise capacity, bronchiectasis patients reported perceived improvement in their physical ability to undertake activities of daily living. The discrepancies in the effect of $\dot{V}O_{2max}$ are contradictory to what might be expected, given the well-established relationship between baseline fitness and the magnitude of change elicited by traditional exercise interventions (Vollaard et al., 2009). Therefore, it could be speculated that those with bronchiectasis could have different sites or mechanisms of exercise intolerance, that are perhaps less effected by IMT or require a greater dose, be that in terms of intensity, frequency or duration, for beneficial changes to be manifested. Therefore, future IMT studies should consider incorporating measures of functional capacity and assessing the effect of IMT on the underlying causes of functional capacity limitations.

Although the value of patient involvement in clinical research is well established (Supple et al., 2015), few studies have specifically explored the opinions, experiences and/or needs of those with bronchiectasis (Dudgeon, Crichton, & Chalmers, 2018). Moreover, whilst Hoffman et al. (2018) found that individuals with chronic lung disease perceived IMT to be of benefit and to increase their confidence in their disease management, our understanding of patients' motivations to complete IMT is limited. More specifically, no research has previously applied or examined motivation theories within this population. Importantly, IMT elicited high levels of intrinsic motivation in the bronchiectasis participants in this study, who endorsed and valued their involvement in the intervention, reporting satisfaction, interest and engagement. A critical motivating factor for participants desire to train was the live biofeedback, allowing the adoption of mastery orientated goals, which have been shown to be positively associated with effort in PA and exercise interventions (Kinoshita, MacIntosh & Sato, 2019). Furthermore, high levels of motivation were reflected in the increased levels of autonomy and perceived competence and low levels of amotivation

and controlled regulation in bronchiectasis compared to healthy participants. High levels of autonomy have been associated with positive health, behavioural and psychological outcomes, such as adherence to treatment regimens (Manganello, 2008). Contrastingly, controlled forms of amotivation, as reported in the healthy group, have been linked to poorer adherence (Williams, Mcgregor, Zeldman, Freedman, & Deci, 2004). The differences in motivation between groups could explain the better adherence noted in bronchiectasis participants. Indeed, enjoyment, enhanced autonomy and competency are important factors for long-term adherence in clinical populations (Denford et al., 2020; Teixeira et al., 2012). Such high adherence to the IMT protocol in those with bronchiectasis is discordant to research utilising other treatment regimes in this population (McCullough et al., 2014). Adherence to such treatment programmes has also been associated with pulmonary exacerbations (McCullough et al., 2014), reinforcing the potential utility of IMT as a viable rehabilitation strategy for those with bronchiectasis.

Previous research found that patients with bronchiectasis experience feelings of anxiety and fear of exacerbation (Dudgeon et al., 2018). Indeed, the main motivations for being physically active and to undertake IMT in our cohort were centred around the management of their bronchiectasis and their desire to improve their health. Patients reported perceived improvements in their physical ability, a better ability to expectorate sputum in comparison to using traditional methods, such as the Acapella® (Smiths Medical, Wampsville, New York), and a reduction in exacerbations during the intervention, which they attributed solely to IMT. Of importance, impaired clearance of sputum results in a vicious cycle of colonisation and infection of the bronchi with pathogenic organisms, dilation of bronchi, pulmonary exacerbations and further production of sputum (Patterson, 2005) and therefore the ability to remove sputum is a key finding. Indeed, this is congruent with previous research which found that training protocols incorporating ≥ 80% MIP are better at enhancing mucus transport, due to higher flow rate as a result of the higher pressure elicited (Kim, Iglesias, & Sackner, 1987). Conversely, previous research found that sputum clearance only increased with the Acapella®, which was preferred by patients compared to threshold IMT (Naraparaju, Vaishali, Venkatesan, & Acharya, 2010). However, it is pertinent to note that sputum clearance was self-reported in the present study, which

is subject to bias. Future IMT research should therefore utilise sputum volume measurements.

Reductions in reported exacerbations as a result of the IMT intervention is also an important finding. Indeed, the economic burden of exacerbation in those with bronchiectasis resulting in hospitalisations is significant (Goeminne et al., 2019). Unsurprisingly, the convenience of being able to train at home was highlighted as a key enabler, particularly in a population with increasing treatment burdens (Chalmers, Aliberti, & Blasi, 2015). Therefore, the cost-effective, home-based nature of IMT could be advantageous in those with bronchiectasis.

Despite numerous strengths, this study is not without its limitations. The lack of age- and sex-matched controls could explain the discrepancies in exercise capacity and, more specifically, the lack of perceived physical improvement in the healthy cohort. Indeed, the significantly younger healthy population mean such results should be interpreted with caution. Despite the recruitment of age- and sex-matched controls, the onset of COVID-19 precluded the completion of post-intervention testing. Finally, the relatively small sample size limits statistical power and interpretation of the data. However, the application of MCIDs enables studies to be adequately powered with fewer participants (Beaton et al., 2002; Modi et al., 2010), and has been highlighted as more important for future treatment decisions (Ranganathan et al., 2015).

8.7 Conclusion

In conclusion, an eight-week IMT programme significantly increased inspiratory strength, respiratory endurance, perceived competence and autonomy in those with bronchiectasis. Furthermore, bronchiectasis patients perceived an improvement in their physical ability and had high levels of intrinsic and extrinsic motivation to complete IMT. IMT, therefore, appears to be an effective and palatable tool to enhance physiological and psychological health in those with bronchiectasis.

Thesis Map

Study 1	**Determination of Pulmonary Rehabilitation Efficacy in those with Respiratory Disease**	
	Aims Determine effectiveness of PR in various respiratory diseases. Investigate influence of sex and socioeconomic status and their interaction on adherence.	**Findings** PR is applicable to variety of respiratory diseases. Sex differences occur at baseline and post-PR. SES has a negative effect on adherence.
Study 2	**Assessing the Perceptions of a POWERBreathe Inspiratory Muscle Training Intervention in Children with Cystic Fibrosis and their Multidisciplinary Team**	
	Aims Ascertain view and opinions of IMT from children with CF and their multidisciplinary team	**Findings** Children enjoyed IMT and reported perceived improvement to physical ability. MDT suggested monitoring adherence in future interventions.
Study 3	**Effects of a POWERBreathe Inspiratory Muscle Training Intervention on Heart Rate Variability in Children with Cystic Fibrosis: A Pilot Study**	
	Aims Investigate the effects of IMT on cardiac autonomic control, lung function and waulity of life.	**Findings** IMT improved inspiratory muscle strength and respiratory domain of CFQ-R and a reduction in sympathetic modulation.
Study 4	**The Effects of an Eight-Week PRO2 Fit Inspiratory Muscle Training Programme on the Physiological and Psychological Health of Children with Cystic Fibrosis**	
	Aims Determine the influence of IMT on physiological and psychological health and the efficacy of a 16-week top-up period.	**Findings** IMT elicited improvements in respiratory muscle strength, exercise capacity and physical functioning domain of the CFQ-R. The 16-week top-up period maintained improvements in respiratory function.
Study 5	**The Effects of a PRO2 Fit, High-Intensity Inspiratory Muscle Training Programme on the Physiological and Psychological Health of Adults with Bronchiectasis**	
	Aims Influence of IMT on physiological and psychological health. Evaluate participants adherence and ascertain their view and opinions of IMT.	**Findings** IMT significantly improved inspiratory muscle strengths, respiratory endurance in those with bronchiectasis. Participants reported high levels of motivation and perceived confidence and improvement in ability to complete activities of daily living. Adherence was high throughout the intervention.

Chapter 9

Synthesis

The importance of physical activity (PA) and exercise is well-recognised and reported in children and adults with chronic respiratory conditions, however, adherence to pulmonary rehabilitation (PR) programmes is often poor. The purpose of this thesis was to investigate alternative, non-pharmacological strategies that aim to enhance the health and well-being in those with a chronic respiratory condition. This chapter will seek to synthesise the overall outcomes, strengths, limitations and future implications derived from the individual studies presented.

9.1 Summary of Individual Study Findings

Impaired respiratory function is associated with increased mortality and morbidity (Schünemann, Dorn, Grant, Winkelstein, & Trevisan, 2000). PA and exercise are known to improve physiological and psychological health, and reduce mortality and morbidity in numerous chronic conditions (United State Deaprtment of Health and Human Services, 1996). Consequently, PR is advocated as a strategy to improve physical and psychological health in those with chronic obstructive pulmonary disease (COPD) and there is emerging evidence for its application to other respiratory diseases (Holland et al., 2013). However, patients with respiratory diseases present a unique challenge for the appropriate prescription of PR due to the considerable heterogeneity in disease symptoms and the high prevalence of comorbidities (Crisafulli et al., 2008). Therefore, determining the benefit and efficacy of PR in respiratory diseases beyond COPD is of clinical importance and was the first aim of this thesis **(Chapter 4)**. In accord with this aim, in a sample of 1,268 patients, PR was found to equally effective across five respiratory diseases. However, sex-related differences were apparent and low adherence was associated with a low socioeconomic background.

Adherence to PR is essential in order to elicit the associated health benefits, however, the rate of attendance is generally low, with the primary reason for poor adherence suggested to be a lack of resources, geographical distance from treatment centres and the times of scheduled classes (Steiner et al., 2015). Therefore, home-based interventions are a potentially attractive option to overcome these barriers. Treatment

strategies are only effective in the real world if they are considered acceptable and palatable by participants. Therefore, **Chapter 5** explored the experiences and perceptions of IMT in healthy controls and children with CF and their multi-disciplinary team (MDT). Five children, two physiotherapists and one respiratory physician participated in semi-structured interviews, with data transcribed verbatim and thematically analysed. Four key themes emerged from the interviews: (i) acceptability; (ii) facilitators; (iii) barriers; and (iv) recommendations. Findings indicated that children enjoyed the home-based IMT intervention, reporting good adherence, while perceiving a benefit to their physical ability. The MDT had more reservations, specifically regarding the cost of devices and treatment burden. However, they did express interest in investigating longer-term IMT interventions that could provide feedback to patients as well as the ability to monitor adherence remotely.

The aim of **Chapter 6** was to pilot a home-based, inspiratory muscle training (IMT) intervention in children with cystic fibrosis (CF) and its potential effects on physiological and psychological health. Lung function, heart rate variability (HRV) and health-related quality of life (HRQoL) were assessed in ten participants (five CF) across a four-week intervention. Results indicated that IMT elicited increases in strength index and flow rate, while exhibiting a perceived improvement in respiratory symptoms, with indications of change in sympathetic modulation. Importantly, these results were clinically meaningful. These preliminary indications suggested that IMT could benefit respiratory, cardiovascular, and psychological health in children with CF.

Following the feedback from participants and incorporating previous evidence, an IMT intervention was developed in order to establish the effect of IMT on the physiological and psychological health in children with CF. **Chapter 7** examined the impact of an eight-week, home-based, IMT programme, incorporating three training sessions a week. A further eight-week top-up period, with training once a week was offered to participants to ascertain sustainability, long-term adherence and efficacy of a reduces-volume training programme. Physiological measures of lung function, handgrip strength (HGS), exercise capacity, sleep and PA were taken, as well as HRQoL and self-determination theory questionnaires. Participants were also interviewed to gather their perceptions of the training programme. Following eight

weeks of IMT, improvements in mean respiratory strength, exercise capacity and the physical functioning domain of the cystic fibrosis questionnaire (CFQ-R) were evident. After 16 -weeks, which all participants opted to do, lung function parameters showed continued trends for improvement, which were clinically meaningful for respiratory strength and forced expiratory volume in one second/forced vital capacity (FEV_1/FVC). Furthermore, the respiratory symptom domain also showed a clinically meaningful improvement after 16 -weeks. Children reported high levels of autonomy, competency and positive affect and perceived physical improvements in their physical ability. They enjoyed the game-based nature of the app, highlighting the feedback provided by the app as a positive motivating factor.

Finally, to ascertain the effects of IMT in another respiratory disease, **Chapter 8** investigated the same IMT intervention in adults with bronchiectasis. Similar physiological measures were taken, as in **Chapter 7**, with measures of perceived competence, treatment self-regulation and views of IMT also gathered from the bronchiectasis patients. Significant improvements in MIP, sustained maximal inspiratory pressure (SMIP) and inspiratory duration were evident after eight weeks, which were all clinically meaningful. No additional improvements in any parameter were exhibited after 16 -weeks of IMT, but importantly all parameters remained at the levels exhibited post-intervention (eight weeks) and did not return to baseline. Bronchiectasis patients exhibited high levels of autonomy and perceived competency and low levels of amotivation regarding their ability to undertake IMT compared to their healthy counterparts. Furthermore, bronchiectasis patients enjoyed the home-based IMT intervention and perceived improvements to their physical ability, ability to undertake tasks of daily living, increased sputum clearance and a reduction in exacerbations. High levels of intrinsic and extrinsic motivation were also noted, with four participants going on to purchase their own devices following the intervention.

9.2 General Discussion

9.2.1 Feasibility of Pulmonary Rehabilitation in Chronic Respiratory Conditions

PR has been extensively researched in COPD and found to be of physiological and psychological benefit in this population (McCarthy, 2015). However, its application to other respiratory diseases is still unclear, due to small numbers in studies as a result of poor participant uptake and large dropout rates (Michael C Steiner et al., 2017). In

this thesis, irrespective of the type of intervention, specific respiratory condition or age, the magnitude of beneficial effects was considerably smaller than those previously reported to be elicited in COPD participants. In contrast to previous research (Kozu et al., 2011; Michael C Steiner et al., 2017), the retrospective analysis in **Chapter 4** found similar beneficial effects from PR across respiratory diseases. Furthermore, adherence was much higher than reported in previous studies (Arnold, Bruton, & Ellis-Hill, 2006), with only 21% of participants categorised as non-attenders to PR. Due to the retrospective nature of this analysis, ascertaining the reasons for poor adherence was precluded and therefore more research is needed to understand patients' perceptions of PR in respiratory conditions other than COPD. Indeed, it has been recommended that mixed-methods study designs are adopted in future research to understand the novel and complex responses to PR (Witcher et al., 2015). Despite this, evidence in COPD has suggested that the lack of adherence is primarily related to a lack of confidence and self-efficacy, low anticipation of benefits and accessibility to PR programs (Guo & Bruce, 2014). Due to the considerable variations of aetiologies that exist between chronic respiratory conditions, whether these barriers are also evident in other respiratory conditions is unclear.

Chapter 4 also highlighted that socioeconomic status (SES) had an impact on adherence to PR. Lower SES groups are 14 times more likely to have a respiratory disease (Pleasants et al., 2016; Sahni et al., 2017; Schraufnagel et al., 2013) and therefore must be targeted to better improve adherence to PR. One potential strategy to rectify the adherence problem in low SES groups is home-based PR. Home-based PR has been shown to demonstrate effectiveness and equivalence to centre-based PR in COPD (Lahham et al., 2018), whilst also being feasible in those with bronchiectasis (Dal Corso et al., 2017). However, the ability to monitor patient adherence and effort remotely is a potential limitation of home-based PR. Indeed, in **Chapter 5,** the MDT highlighted the desire to be able to monitor patients remotely and track their progress to ensure engagement, while reducing the risk of reporting bias (Jantzen et al., 2016; Ruf et al., 2012b).

Finally, sex differences were evident in **Chapter 4**, with females exhibiting poorer fitness and higher anxiety levels compared to males both pre- and post-PR. Despite sex being a potent determinate of disease aetiology and progression, PR guidelines do not vary by sex. Indeed, a systematic review concluded that sex-related differences in

PR remain unclear (Robles et al., 2014). It is pertinent to note that The British Lung Foundation (2018) found a significant male bias in diagnosis of COPD and therefore more timely access to PR, with being female shown to be a predictor of non-adherence to PR in COPD

In conclusion, **Chapter 4** revealed the benefits to PR in a variety of respiratory diseases. However, it also highlighted the significant barriers that SES and sex can be to PR outcomes and adherence. As such, **Chapter 4** suggested that future areas of interest should be to ascertain the impact of PR on differing respiratory conditions, while research needs to focus on the interaction of sex and SES on key mediators of outcome such as adherence.

9.2.2 Inspiratory Muscle Training Intervention Evaluation

The optimal training frequency, intensity and duration of IMT interventions in CF and bronchiectasis, is unclear (Martin-Valero et al., 2020; Shei et al., 2019). Studies range from 4-12 weeks with adaptations ranging across these time frames. However, neural adaptions are found to occur over the first four weeks of a strength training intervention (Brown et al., 2017; Ramsay et al., 1990), with morphological adaptations evidenced beyond this period (Folland & Williams, 2007). In **Chapter 6,** a four-week IMT programme of 30 breaths, for 15 minutes, twice a day, for 28 days at 40-50% MIP was implemented in children with CF. The improvements elicited in the pilot study were similar to those by Asher et al. (1982), who also found improvements in inspiratory muscle strength in children with CF, though they implemented the IMT at 80% MIP intensity. Furthermore, participants in **Chapter 6** cited the four-week programme as a feasible training schedule and reported good-adherence and enjoyment to the programme. Evidence from other IMT research in CF cited further physiological and psychological improvements in health using higher MIP intensities. Specifically, 60% MIP elicited improvements in respiratory muscle strength, endurance and some effect on exercise performance (Sawyer & Clanton, 1993a), whereas 80% MIP training protocols have elicited greater improvements in sputum clearance, respiratory muscle function and endurance, as well as reduced anxiety and depression (Chatham et al., 1997; Enright, Chatham, Ionescu, Unnithan, & Shale, 2004). In bronchiectasis, 30% MIP produced improvements in respiratory muscle strength (Newall, 2005), whereas an increase to 60% MIP resulted in improvements

in respiratory muscle strength, exercise capacity and health status (Liaw et al., 2011; Ozalp et al., 2019). Previous research has found power increased at 20-40% MIP (Faulkner, 1985), strength at 80-100% MIP, with strength endurance adaptations at 60-80% (Newton & Karmer 1994). Therefore, utilising previous research in these populations coupled with the feedback from MDT and participants in **Chapter 6,** an eight-week, three times a week, 80% MIP, with an eight-week, once a week 80% MIP top-up, IMT training intervention was designed in order to gain maximum physiological and psychological benefits, while being time-efficient.

The training method utilised in **Chapters 7** and **8** could provide further benefits over standard IMT. The PrO2Fit utilises a submaximal isokinetic-like training modality using a progressive work-to-rest ratio. Additionally, the ability to set a one-rep max relative to each individuals' inspiratory muscle strength for each training session, enables an individualised and progressive training nature. This not only allows a constant velocity, but accommodates resistance during inspiratory muscle testing while taking into account the variable nature of disease in CF and bronchiectasis across time, making it appropriate and safe for impaired individuals (Chatham, 2000; Chatham et al., 1997; Enright et al., 2004; Ionescu et al., 1998). Traditional threshold IMT fixes the generation of pressure for each breath via a spring valve, allowing inspiration to occur when a set threshold is overcome and closes the valve when it is no longer achieved. In contrast, PrO2Fit provides a constant and accommodating resistance throughout the whole inspiration, enabling a greater MIP and inspiratory duration to be achieved in comparison to traditional IMT (Cahalin & Arena, 2015). Training loads associated with standard IMT are limited with workloads, with traditional threshold devices exhibiting a maximal resistance of ~42 cmH_2O or less (Cahalin & Arena, 2015; Formiga et al., 2018). In contrast, the PrO2Fit allows a considerably higher level of inspiratory pressure (up to ~300 cmH_2O), throughout a full inspiration (Cahalin & Arena, 2015; Formiga et al., 2018), allowing modulation of all aspects of muscle performance including strength, endurance and work capacity. Previous research has shown it is vitally important to fix the workload to fulfil the principle of overload, which is essential to the training outcomes in both skeletal muscle training and in IMT (Gosselink et al., 2011; Illi, Held, Frank, & Spengler, 2012; Smart, Giallauria, & Dieberg, 2013), therefore, traditional IMT may be suboptimal compared with the PrO2Fit training modality.

Previous research in IMT in children with CF using traditional IMT devices have adopted training durations of two times a day, up to eight weeks (Asher, Pardy, Coates, Thomas, & Macklem, 1982; Bieli, Summermatter, Boutellier, & Moeller, 2017; Santana-Sosa et al., 2014). The training in **Chapter 7** was only performed three times a week, yet still exhibited physiological improvements in respiratory muscle strength, exercise capacity and psychological improvements in physical functioning and the respiratory symptom domains of the CFQ-R, that were maintained in a 16-week top-up period, training once a week. Improvements in MEP and PEF have not been reported post-IMT in CF, while the improvements in exercise capacity were comparable to more intensive and time-consuming interventions (Santana-Sosa et al., 2014). Whilst in **Chapter 8,** bronchiectasis participants only exhibited improvements in MIP, respiratory endurance, perceived competence and motivational levels, the 16-week top-up period was also efficient at maintaining benefits already elicited. The differences exhibited between CF and bronchiectasis could be attributed to the significant age difference and therefore physical ability of participants (McPhee et al., 2016).

In **Chapter 5**, the ability to monitor adherence and patient's effort was highlighted by the MDT. Therefore, the PrO2Fit device was also chosen due to its live biofeedback and ability to remotely monitor adherence and effort. Often traditional methods of IMT do not provide live feedback on training, with participants highlighting in **Chapters 7** and **8** that if they did not have the visual aid, they would consider training to be 'boring' and would be less likely to be motivated to adhere to, and comply with, IMT. Indeed, previous research has found biofeedback from isokinetic training to elicit greater testing and training results in clinical populations. (El Mhandi & Bethoux, 2013; Hammami et al., 2012). This thesis demonstrated the ability to monitor progress in training-elicited potential improvements in autonomy and both intrinsic and extrinsic motivation, as evidenced in **Chapters 7** and **8**. Furthermore, **Chapters 7** and **8** highlighted the perceived competence participants felt in completing IMT in the long-term, which could be related to the feedback provided by the app. Indeed, long-term compliance facilitated by effective training loads has been shown to be further facilitated by optimal feedback to participants in exercise programmes (Chatham, 2000; Chatham, Ionescu, Nixon, & Shale, 2004; Enright et al., 2004;

Enright, Unnithan, Heward, Withnall, & Davies, 2006; Hammami et al., 2012; Ionescu et al., 1998; Mickleborough, Nicholas, Lindley, Chatham, & Ionescu, 2010).

In conclusion, the IMT intervention designed in this thesis is feasible, applicable and well-adhered to within CF and bronchiectasis populations. Furthermore, the intensity, duration and frequency are sufficient to attain physiological improvements in strength and endurance, psychological improvements in HRQoL, and enhance self-determination measures.

9.2.3 Participant Perspectives of Inspiratory Muscle Training Intervention

The mixed-methods design of **Chapters 7 and 8** allows a better understanding of the connections, or, contradictions, between qualitative and quantitative data (Shorten & Smith, 2017). Furthermore, the use of interviews provide participants with a strong voice and an opportunity to share their experiences across the intervention period, facilitating different avenues of exploration that enriches evidence and enables questions regarding intervention efficacy, feasibility and enjoyment to be answered more deeply (Wisdom & Creswell, 2013). To date, this is the first thesis to investigate patient and MDT perceptions of IMT in CF and bronchiectasis and implement these opinions into research design.

Treatments in CF and bronchiectasis are highly prescribed, therefore gaining the views of patients in intervention research is essential in order to improve the quality of care and efficacy (Chalmers, Aliberti, & Blasi, 2015; Johnson, 2011). CF patients reportedly spend 108 minutes per day on a range of therapies, regardless of age or severity of disease (Sawicki, Sellers, & Robinson, 2009c). Bronchiectasis patients also have a high treatment burden, which has shown to impact compliance and adherence to prescribed treatments (Chalmers et al., 2015; McCullough et al., 2014). It is therefore a highly important finding that participants reported that a short eight-week, time-efficient IMT intervention was feasible and easily implemented into their daily routine. Both children and adults demonstrated high adherence to IMT, which was better than the adherence levels previously reported to treatment strategies within these cohorts (McCullough et al., 2014; Modi & Quittner, 2006). This improved adherence could be attributed to the app and the live biofeedback, with both children and adults exhibiting both intrinsic and extrinsic motivation, and low amotivation. The addition of feedback to an IMT intervention was highlighted by MDT in **Chapter 5**

and fed forward to the intervention design. Specifically, in bronchiectasis patients, previous research has highlighted that they want to feel in control of their symptoms and disease (Dudgeon et al., 2018), with patients reporting perceived competence in undertaking IMT in both short- and long-term interventions. Despite perceived competence not being significant in children with CF, interviews highlighted children felt competent, while reporting increased autonomy and mastery in undertaking IMT. Increased levels of autonomy has been associated with positive health, behavioural and psychological outcomes and is therefore important to long-term adherence and compliance to treatment interventions (Manganello, 2008). Children reported that the IMT device and app were easy to use, which is essential to adherence, as training that is deemed too complicated to understand, or perceived as too stressful, has been shown to reduce compliance in the CF population (Taylor, 1991).

Children with CF and adults with bronchiectasis also perceived improvements in their physical functioning, attributing this to the inclusion of IMT into their daily routine. Despite not exhibiting quantitative improvements in their exercise capacity, bronchiectasis adults felt their ability to undertake activities of daily living improved, while children who significantly improved their exercise capacity, noticed improvements in their sporting abilities. Furthermore, bronchiectasis participants also reported increased sputum clearance and a reduction in pulmonary exacerbations. This was not reported by children with CF, potentially due to the near normal lung function and the overall good health of participants in **Chapter 7.** Further investigation is warranted on how this perceived improvement could affect patients' anxiety and depression in the bronchiectasis population. Finally, the qualitative results in **Chapter 8** are in line with previous research in advanced lung disease, with perceived improved breathlessness, mobility, breathing control and abilities in daily activities after eight weeks of IMT (Hoffman et al., 2018). Overall, the qualitative data has further strengthened the evidence of the quantitative data, and shown IMT to be well-adhered to, and enjoyed, in these patient populations. Research should continue to gain insights into patient perceptions of interventions to ensure better programme structure and compliance.

9.3 Thesis Strengths

A major strength of the thesis is patient involvement in the design and implementation of IMT. In **Chapter 5,** the pilot study, views and opinions of patients were sought to help design the future IMT studies implemented within this thesis. Furthermore, the perceptions of IMT gathered from **Chapters 7 and 8** highlight the feasibility and acceptability of IMT in both CF and bronchiectasis. The eight-week, three times a week, intervention period was deemed appropriate to fit into treatment schedules in these populations. Interview data presented in this thesis can help influence the design of future IMT interventions to ensure maximum patient recruitment and retention in studies.

Interview analysis from **Chapter 5** highlighted the MDTs desire to track adherence, progress and compliance to IMT objectively, to reduce the risk of patient reported bias. Indeed, objective adherence to IMT has not been reported previously in clinical populations and therefore is a major strength of both **Chapters 7 and 8**. The ability for the PrO2Fit to monitor adherence remotely allows reliability in assessing participants' adherence to study protocol, while enabling dose-response to be effectively investigated (Formiga et al., 2018).

Another novel feature of the PrO2fit is the visual feedback provided by the app, while also storing past training sessions. This not only enables participants to track their progress, but objective monitoring of home-based IMT from a distance by researchers and clinicians. This therefore reduces the supervision required for IMT to be efficacious. Indeed, **Chapters 7 and 8** highlighted the perceived competency and autonomy reported by participants in undertaking the unsupervised training sessions. Furthermore, the live biofeedback induced feelings of mastery, with participants exhibiting goal-setting behaviour, increasing their motivation to train, which could be attributed to the high adherence reported in both chapters. The high adherence reported in **Chapters 7 and 8** is another strength to this thesis, not least given the lack of adherence to usual treatments in both CF (Modi & Quittner, 2006) and bronchiectasis patients (McCullough et al., 2014).

9.4 Thesis Limitations

There are several limitations within this thesis, which should be acknowledged. Firstly, the small sample sizes within **Chapter 5, 6, 7 and 8** limit the statistical power and therefore the ratification of the findings. A larger sample would have increased the generalisability of the findings, while allowing more in-depth analysis of IMT's effectiveness across the age and disease severity ranges in CF and bronchiectasis. However, the findings within **Chapters 6, 7 and 8** were supported by the application of minimal clinically important difference (MCID) calculations, allowing studies to be adequately powered with fewer participants (Modi et al., 2010), instead of relying solely on statistical significance (Beaton et al., 2002). It is important to consider whether there is a tendency in clinical studies to undervalue findings stemmed from small samples. Such bias towards larger sample sizes could inadvertently direct research interest and focus away from studies involving under-served and hard-to-reach populations (Manganello, 2008).

An additional limitation is the lack of age- and sex-matched controls in **chapters 5, 6, 7 and 8**. Matching on factors such as age and sex improves study efficiency by enhancing statistical precision (Pearce, 2016). Furthermore, matched control groups would have aided in the assessment of efficacy and by discriminating outcomes found post-IMT from those caused by other factors, such as course the of disease, participant expectation or other treatments (Malay & Chung, 2012). Age- and sex-matched controls were recruited for **Chapters 7 and 8,** however, due to the onset of COVID-19 they could not complete the intervention.

Finally, the lack of longitudinal follow-up to determine whether the physiological and psychological improvements exhibited from IMT in **Chapters 5, 7 and 8** were maintained, would have been beneficial. Whilst improvements in physiological health were maintained during a top-up period in **Chapters 7 and 8**, whether these parameters were maintained in the long-term remains to be elucidated. Furthermore, one of the biggest concerns regarding utilising technology in a clinical setting is whether individuals will sustain their engagement with technology over time (Ledger & McCaffrey, 2014). The application of longer interventions and longitudinal follow-up in future research is therefore needed.

9.5 Implications for Future Research

The work completed in this thesis, alongside current and emerging literature, has developed several recommendations that should be considered for future research.

9.5.1 Patient Involvement in Clinical Research

As recruitment for clinical research studies is a major challenge (Anderson, Borfitz, & Getz, 2018; Tohid et al., 2017), **Chapters 6, 7 and 8** suggest the importance of ascertaining the views and opinions of participants undertaking the research. Furthermore, to date, these are the first studies to investigate the perceptions of IMT in chronic respiratory conditions. Future studies should implement short-term pilot studies to ascertain patients' perceptions of an intervention prior to long-term interventions. This will allow research to determine the feasibility and acceptability of an intervention, and simultaneously foster autonomy in providing input regarding the potential palatability of interventions, not least in terms of their frequency, intensity and duration. Indeed, compromising on the optimal intervention dose may be more effective if participants will adhere to it, than striving for the optimal dose that no participants will engage in.

9.5.2 Determining Optimal Inspiratory Muscle Training Programmes

As discussed in **Chapter 2**, research surrounding the optimal frequency, intensity and duration of IMT in clinical populations remains to be determined. Such uncertainty has arisen as a result of the, considerable inter-study variation resulting in equivocal results regarding the effect of IMT in CF and bronchiectasis. It is hypothesised that the individual participant variations in disease, age and underlying comorbidities are the cause of the varying effects of IMT. As the focus on the importance of patient-centred clinical outcomes and the drive towards personalised/precision medicine continues to increase, it could be argued that IMT should be utilised on a case-by-case basis. Based on individual needs, protocols that aim to target the strength and/or endurance deficits, may in turn elicit optimal physiological and psychological benefits to that individual.

9.5.3 Implementing Respiratory Muscle Strength Measures into Standard Clinical Care

Impairment of the respiratory muscles is a common finding in those with respiratory disease (Laghi & Tobin, 2003; ATS, 1999). Indeed, in respiratory disease, inspiratory muscle weakness may cause a disparity between muscle load and capacity, resulting in dyspnoea, reduced exercise capacity and the development of hypoventilation and respiratory failure (Moxham, 1991; Gibson, 1995; Trooster et al., 2005). Expiratory muscle weakness can impact on cough efficiency, affecting the removal of secretions from the airway, resulting in respiratory infection in those with a chronic respiratory condition (Arora & Gal, 1981; Irwin et al., 1998). However, diagnosis of respiratory muscle weakness is often delayed as standard screening protocols do not assess muscle strength (Parshall et al., 2012; Caruso et al., 2015). This is surprising given that the assessment of respiratory muscle strength may be clinically useful to monitor changes in disease over time, helping to identify risk of hypoventilation and determining the impact of interventions (Moran et al., 2010). Additionally, since the relationship between lung volumes and inspiratory muscle strength is non-linear (de Troyer et al., 1980), mean inspiratory pressure (MIP) measurements can identify inspiratory muscle weakness earlier than would be possible based on changes in lung volumes (Caruso et al., 2015).

To quantify respiratory muscle strength, volitional and non-invasive measures of MIP and mean expiratory mouth pressures (MEP) are the mostly widely accepted and commonly used methods (ATS/ERS, 2002). Importantly, the equipment is low-cost, low-complexity and portable, with the test being quick and easy to perform, which is essential in busy respiratory clinics (Caruso et al., 2015). Given the ease of testing and the valuable indices of MIP and MEP, the implementation of frequent respiratory muscle strength testing in standard clinical care would be advantageous to monitor health, disease progression and identify risks in chronic respiratory conditions.

9.5.4 Prognostic Value of Handgrip Strength Testing

Muscle dysfunction is a common manifestation in chronic lung diseases, secondary to multiple mechanisms, including, but not limited to, diet changes, systemic inflammation, reduced muscle repair, oxidative stress, drug use, aging, and muscle deconditioning (Lima et al., 2019). Muscle dysfunction may appear early in lung

impairment or manifest over time, resulting in PA limitations and a reduction in activities of daily living, resulting in deterioration of QoL (Chaves et al., 2007; Ziegler et al., 2007; Pleguezuelos et al., 2016). Loss of peripheral skeletal muscle mass and progressive decline in muscle strength (Blau et al., 2002) are caused by a reduction in ventilatory capacity, which promotes adaptive changes in skeletal muscle mass, therefore contributing to exercise intolerance in respiratory disease (Chaves et al., 2007; Garcia et al., 2017).

Handgrip strength (HGS) is a rapid, simple, cost-effective measure of upper limb muscle force and is an overall indicator of physical capacity (Lima et al., 2019). Moreover, HGS is not limited to assessing the upper limbs and has been found to be a good predictor of mortality, with various respiratory and cardiovascular co-morbidities associated with reduced HGS (Leong et al., 2015). Several studies have evidenced a positive association between HGS and lung function in those with COPD (Martinez et al., 2017) and CF (Rovedder et al., 2019). Furthermore, HGS is correlated with six-minute walk distance in COPD (Kyomoto et al., 2019) and bronchiectasis (Ozalp et al., 2012), and absolute VO_{2peak} in children with CF (Wells et al., 2014). Despite HGS prognostic value, it is infrequently used as a functional measure in those with respiratory disease, perhaps because it is often associated with a complex battery of tests (Martinez et al., 2017; Lima et al., 2019). Finally, HGS can serve as a test to identify those with poor upper limb strength that can be referred for more extensive exercise capacity testing, a health and disease monitoring process and a marker for intervention success in respiratory disease (Han et al., 2018). Therefore, the use of HGS tests in standard clinical care is warranted.

9.5.5 Application of Inspiratory Muscle Training in Conjunction with Pulmonary Rehabilitation

The efficacy of PR and IMT has been discussed throughout this thesis, however, the effects of both of these rehabilitation modalities in combination are worth consideration and further research. In COPD, IMT has been found to be an important adjunct to PR, with reduced respiratory muscle strength, resulting in greater improvements in exercise capacity than reported with PR in isolation (Wanke et al., 1994; Weiner et al., 1992). These additional gains in exercise capacity may be related to the increase in inspiratory muscle strength at the end of the training programme, or

to the reduction in perceived dyspnoea during exercise (Weiner, Magadle, Berar-Yanay, Davidovich, & Weiner, 2000). During exercise, the inspiratory muscles have demonstrated increased loading in both CF (Goetghebeur et al., 2002) and bronchiectasis patients (Koulouris, Retsou, Kosmas, Dimakou, Malagari, Mantzikopoulos, Koutsoukou, Milic-Emili, & Jordanoglu, 2003) due to tidal expiratory flow limitation, increased dyspnoea and reduced exercise tolerance. The consequences of expiratory flow limitation have also been well documented in COPD, where the combination of PR and IMT has been shown to be effective (Newall, Stockley, et al., 2005b). It can therefore be postulated that combined PR and IMT could possibly be effective in both CF and bronchiectasis due to similar disease pathologies (Schafer, Grise, Chandrasekaran, Chotirmall, & Hartle, 2018).

In CF, there has been one reported study combing exercise training and IMT. Santana-Sosa et al. (2014) combined IMT with aerobic and strength training exercises for four weeks. Children significantly increased their peak oxygen uptake, inspiratory and 'whole body' muscle strength, while exhibiting a shift towards a healthier body composition (Santana-Sosa et al., 2014). Furthermore, inspiratory muscle and leg press strength were maintained after detraining, while a positive trend was noted in children's HrQoL (Santana-Sosa et al., 2014). It could be hypothesised that the combination of central adaptations, such as the potential effect of IMT on maximal ventilatory capacity, coupled with the peripheral adaptations, higher leg muscle strength, and delayed fatigue during testing, could explain the improvement in peak oxygen consumption. Indeed, it was concluded that the evidence in Santana-Sosa et al. (2014) study supported the need to prescribe a 'complete' exercise intervention as early as possible, across disease severities and ages within the CF population. Despite these findings, this is the only study to date to investigate the combination of exercise and IMT in CF.

In line with CF, only one study has reported the beneficial effects of combined PR and IMT training in bronchiectasis (Newall, Stockley, et al., 2005b). Exercise training sessions, incorporating treadmill walking, cycle ergometry and stair climbing, were combined with IMT across eight weeks. IMT increased respiratory muscle strength significantly, but did not provide immediate benefits beyond the effects of exercise training alone (Newall, Stockley, et al., 2005b). However, in the PR-IMT group improvements in both exercise capacity and health status observed, were maintained

three months after training cessation, whereas those in the PR-sham group were not maintained, highlighting the potential additive effect of IMT.

Overall, both studies (Newall, 2005; Santana-Sosa et al., 2014) highlight that combined PR methodologies and IMT training are feasible and applicable within these populations. Whilst it is impossible to identify the specific influence of IMT in Santana-Sosa and colleagues (2014) study due to lack of sham IMT group, Newall et al. (2005) highlighted the potential additive effect of IMT long-term. However, both studies acknowledge the small sample sizes and the normal to mildly reduced inspiratory muscle strength at baseline in participants (Newall, Stockley, et al., 2005b; Santana-Sosa et al., 2014b). Indeed, it was argued by Newall et al. (2005) that the lack of additional benefit of IMT in conjunction with exercise training was due to the lack of functional weakness in their cohort, which has also been evidenced elsewhere (Larson et al., 1999). Furthermore, the optimal combination of exercise training and IMT needs to be investigated. Indeed, the high-intensity nature reported in Newall et al. (2005) may have induced the maximal attainable benefits in exercise capacity, therefore the addition of IMT may elicit no further benefit. Conversely, the addition of a strength training protocol utilised by Santana-Sosa et al. (2014) may have only elicited peripheral adaptions due to the increase in leg strength, thereby delaying fatigue during testing. Furthermore, the optimal intensity, duration and frequency of IMT in both populations still remains to be elucidated.

In conclusion, while there is emerging evidence supporting the use of combined PR and IMT in both short- and long-term health outcomes, further research is warranted to investigate the optimal combination of training methods, across ages and disease severities in both CF and bronchiectasis populations.

9.5.6 Potential Application of Inspiratory Muscle Training to Coronavirus Disease

Coronavirus disease 2019 (COVID-19) is a global pandemic, causing significant damage to the lungs and airways, potentially leading to acute respiratory distress syndrome and, if severe enough, respiratory failure (Honce & Schultz-Cherry, 2019). Those who are at higher susceptibility of developing severe respiratory complications from COVID-19 include those who are obese, older age, and smoke, as well as those who suffer from cardiometabolic and lung diseases (Arentz et al., 2020; Livingston &

Bucher, 2020; Wu & McGoogan, 2020). There are also people who do not possess these characteristics that develop severe respiratory complications, and, as such, there are other factors that contribute to the risk of poorer outcomes from COVID-19 that are yet to be elucidated (Severin et al., 2020).

Despite impaired respiratory muscle performance being considered rare (A. Rodrigues et al., 2017; Sclauser Pessoa et al., 2014), it is frequently evident in patients with poorer health characteristics, such as obesity and chronic respiratory condition (Severin et al., 2020). Indeed, a reduction in respiratory muscle strength, and changes in airway resistance and chest wall compliance, due to the increased demand imposed on the respiratory muscles, have been found in patients with chronic lung disease and obesity (ATS/ERS Statement, 2002; Laveneziana et al., 2019; Sood, 2009). Therefore, patients with these underlying complications that sustain an acute viral infection, such as COVID-19, can experience increased risk of respiratory failure, due to further imbalances between respiratory muscle-force-generating capacity and imposed demands required for breathing (Levine et al., 2008).

Those who suffer from acute respiratory distress syndrome and respiratory failure require mechanical ventilation to unload the respiratory musculature, which has been demonstrated in COVID-19 (Severin et al., 2020). However, mechanical ventilation has been shown to adversely change the respiratory muscles, inducing rapid atrophy and profound weakness, resulting in ventilator-induced diaphragm dysfunction (VIDD; Berger et al., 2016; Vassilakopoulos, Zakynthinos, & Roussos, 1998). Evidence has shown VIDD results in unsuccessful weaning from mechanical ventilation due to lower diaphragm thickness (American Society of Anesthesiologists Task Force, 2012), and an imbalance between respiratory muscle-force-generating capabilities and demand imposed for spontaneous breathing (Martin et al., 2011; Purro et al., 2000; Sklar et al., 2020), causing increased risk of further complications (American Society of Anesthesiologists Task Force, 2012) .

Those who are in poor health post-COVID-19 and at greater risk of a viral infection, may demonstrate respiratory muscle weakness and, therefore, be at an increased risk of poorer clinical trajectory, if acute respiratory distress syndrome continues (Severin et al., 2020). Therefore, respiratory muscle training, which improves respiratory muscle strength, exercise capacity, diaphragm thickness and dyspnoea in several

populations (Edwards, Maguire, Graham, Boland, & Richardson, 2012; R Gosselink et al., 2011; Illi et al., 2012; Pazzianotto-Forti, Mori, Zerbetto, & et, 2019; H. Souza, Rocha, Pessoa, & Al., 2014) may be of pertinence post-COVID infection. To date, no studies have investigated the impact of respiratory muscle training in those who have suffered a viral infection. However, a recent study found that just five days of a preoperative respiratory muscle training protocol significantly reduced pulmonary complications and time spent in hospital (Elkins & Dentice, 2015). Furthermore, in patients at risk of prolonged hospitalisation, four weeks of respiratory muscle training at 50% of MIP reduced hospital stay duration, mortality and risk of intubation (Nikoletou et al., 2016). In patients that required mechanical ventilation, a respiratory muscle training invention improved weaning outcome, (Langer et al., 2015) and reduced post-operative respiratory conditions (Martin et al., 2011). Nonetheless, the role of respiratory muscle training to mitigate the effects of respiratory complications from viral infections has yet to be investigated. The current evidence of the apparent connection of impaired respiratory muscle performance, mechanical ventilation and respiratory complications, coupled with the strong evidence of the beneficial effects of respiratory muscle training, warrants further exploration regarding whether it can reduce the risk of severe complications during and or after a viral infection (Severin et al., 2020).

9.5.7 The Fatigue Index Test (FIT)

Respiratory muscle fatigue is the cause of the onset of ventilatory impairment, often accompanied by hypoxemia and hypercapnia (Tsukamoto, Maruyama, Kato, Uchida, & Kubo, 2019) and a major cause of respiratory failure in CF (Dunnink, Doeleman, Trappenburg, & de Vries, 2009) and bronchiectasis (Ozalp et al., 2019). Multiple measures, such as electrical or magnetic stimulation, have been employed to quantify respiratory muscle fatigue in chronic respiratory conditions, however, such testing is difficult, uncomfortable and time-consuming (ATS/ERS, 2002). The Fatigue Index Test (FIT) is a novel method of quantifying the propensity for inspiratory muscle fatigue in clinical practice (Formiga, Vital, Urdaneta, Campos, & Cahalin, 2019). The FIT score is a calculated utilising the equation below:

$$FIT\ Score = \frac{(Summation\ of\ Inspiratory\ Power\ x\ Total\ Inspiratory\ Time)}{(Power_{500} \times\ Time_{500})}$$

Equation 9.1

The FIT is based upon the parameters measured during a single inspiratory breath, where $Power_{500}$ is equal to the power expended to inspire 500 ml of air and $Time_{500}$ is the time to inspire 500 ml of air. The 500 ml is set a default because it is the equivalent of average resting tidal volume (Hallett & Ashurst, 2018). However, this baseline may need to be altered to reflect underlying lung volumes and health status (Chatham, 2018). The FIT Score compares capacity in measurement of total single inspiratory breath work performed to demand the average tidal volume of 500 ml. Therefore, the FIT Score is related to propensity to inspiratory muscle fatigue and may be an indicator of approaching respiratory failure in chronic conditions. According to this equation, those presenting with greater MIP measured at residual volume will achieve shorter T_{500} times, which will result in a greater FIT score for a given total time, whereas a high MIP with rapid and acute fall of power output will result in a lower FIT Score and less endurance (Chatham et al., 1999). A recent study examined the relationship between the FIT Score and COPD-related outcomes (Formiga et al., 2019). A higher propensity to inspiratory muscle fatigue, as reflected by lower FIT Scores, was associated with more severe airflow obstruction, reduced functional exercise capacity, impaired HRQoL, increased symptomatology and greater risk of mortality in COPD (Formiga et al., 2019). Despite limited evidence, and no studies to date in other respiratory conditions, the FIT Score potentially promises a valuable and quick indicator of overall health in individuals with chronic respiratory disease. Further research is warranted and encouraged to gain insight into the FIT Score and its quantification of respiratory muscle fatigue.

9.6 Overall Conclusion

This thesis provides evidence that an alternative PR strategy, such as IMT, is an applicable, feasible, safe and time-efficient form of exercise that can improve physiological and psychological health in those with CF and bronchiectasis. The home-based nature, coupled with enjoyment and the ability to monitor progress, led to increased motivation and high adherence within our participant cohort. Whilst it is acknowledged that the small sample sizes may limit the generalisability the current findings to the wider CF and bronchiectasis population, this thesis provides a strong foundation to develop further investigations and interventions, drawing on the strengths of the IMT study protocol and patient feedback to help enhance future directions of IMT research. Indeed, this thesis presents evidence that IMT can be a useful therapeutic tool in chronic respiratory conditions and has scope in future PR strategies.

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Appendix A

Information Sheets and Consent/Assent Forms

Applied Sports Technology Exercise and Medicine Research Centre (A-STEM)

Sport and Health Portfolio, College of Engineering

Swansea University
Prifysgol Abertawe

ADOLESCENT PARTICIPANT INFORMATION SHEET

(Version 1, Date 17/10/2015)

Project Title:

Determining physical activity levels in young cystic fibrosis patients **Contact Details:**

Dr Melitta McNarry

Email: [redacted]

Telephone: [redacted]

Dr Kelly Mackintosh

Email: [redacted]

Telephone: [redacted]

Jessica McCreery

Email: [redacted]

1. Invitation Paragraph

Thank you for being interested in our project. Please read this information sheet carefully and think about whether you are happy to take part. If you are happy to take part, thank you. If you prefer not to take part, this is not a problem and we thank you for thinking about it. Your care will not be influenced if you do or do not decide to take part.

2. What is the purpose of the study?

The four week program you completed before was to see whether making your muscles stronger, made life easier for you. What we would like to do is ask you some questions on how the training went, how you felt about using the resistive device and whether it made life easier for you. This will help us in future studies with children and adults with cystic fibrosis.

3. Why have you been chosen?

You have been asked if you would like to take part because you have completed a four week program with the resistive training device.

4. What will happen to you if you take part?

You will be asked to come to your normal Cystic Fibrosis Clinic at Singleton Hospital once. You will then be asked some questions on the four week program you completed. There is no right or wrong answer to these questions, all we want to know are your thoughts.

5. What are the possible disadvantages of taking part?

There may be some questions you are not sure on how to answer or need longer to think about, but that's ok we will give you plenty of time to answer and help you as much as we can!

6. What are the possible benefits of taking part?

You will help us see whether this type of training is good for people with cystic fibrosis and whether it makes them feel better. This will help us make future studies better for people with cystic fibrosis.

7. Will my taking part in the study be kept confidential?

All personal information collected will be kept completely confidential. That is, only members of the research team will have access to it. Any direct quotes used will be given a fake name so that no one will know who originally said it. After the study is finished, all private information will be deleted.

8. What if I have any questions?

If you have any questions, please contact us on the details at the beginning of this sheet. You can also ask one of the researchers when you come in to visit the Clinic.

Applied Sports Technology Exercise and Medicine Research Centre (A-STEM)
Sport and Health Portfolio, College of Engineering

PARENT/GUARDIAN PARTICIPANT INFORMATION SHEET
(Version 1, Date 17/10/2015)

Project Title:
Determining physical activity levels in young cystic fibrosis patients

Contact Details:

Dr Melitta McNarry
Email: [redacted]
Telephone: [redacted]

Dr Kelly Mackintosh
Email: [redacted]
Telephone: [redacted]

Jessica McCreery
Email: [redacted]

1. Invitation Paragraph
Thank you for being interested in our project. Please read this information sheet carefully and think about whether you are happy for your child to take part. If you are happy for them to take part, thank you. If you prefer them not to take part, this is not a problem and we thank you for thinking about it. Your child's care will not be influenced if they do or do not decide to take part.

2. What is the purpose of the study?
The four week program that was completed before was to see whether making muscles stronger for people with cystic fibrosis, made life easier for them. The questions we will ask is about their feelings and views on how the training went, how they felt about using the resistive device and whether it made life easier for them. This will help us in future studies with children and adults with cystic fibrosis

3. Why has your child been chosen?

Your child has been asked if they have previously taken part in a four week resistive breathing study.

4. What will happen to your child if they take part?

They will be asked to come to their normal Paediatric Cystic Fibrosis Clinic at Singleton Hospital once. They will then be asked some questions based on their four week program which they previously completed. The questions will be solely centered on their opinions and experiences of the previous study. There is no right or wrong answers to these questions!

5. What are the possible disadvantages of taking part?

Your child may get stuck on a question or find it difficult to answer. We will give them as much help as we can and plenty of time to answer the questions. All questions will be catered towards children and their level of understanding.

6. What are the possible benefits of taking part?

The information gathered will help us determine whether this type of training is good for people with cystic fibrosis. It will also help us in future studies with children and adults with cystic fibrosis.

7. Will my child taking part in the study be kept confidential?

All personal information collected will be kept completely confidential. That is, only members of the research team will have access to it. Any direct quotes used will be given a fake name so that no one can identify who originally said it. After the study is finished, all private information will be deleted.

8. What if my child or I have any questions?

If your child or you have any questions, please contact us on the details at the beginning of this sheet. You can also ask one of the researchers when you come in to visit the Clinic.

Applied Sports Technology Exercise and Medicine Research Centre (A-STEM)

Sport and Health Portfolio, College of Engineering

UNDER 12 YEARS OLD INFORMATION SHEET CONTROL

(Version 1.2, Date 09/03/2017)

Project Title:

Investigating the influence of an Inspiratory Muscle Training program on lung function and quality of life in children and adults with Cystic Fibrosis.

Contact Details:

Dr Melitta McNarry

Email: [redacted]

Telephone: [redacted]

Dr Kelly Mackintosh

Email:

Telephone: [redacted]

Jessica McCreery

Email: [redacted]

Telephone: [redacted]

Thank you for being interested in our project. Please read this information sheet carefully and think about whether you are happy to take part. If you are happy to take part, thank you. If you prefer not to take part that is ok. If you have any questions, please contact us on the details at the beginning of this sheet. You can also ask one of the researchers when you come in to visit the Clinic.

What is the purpose of this study?

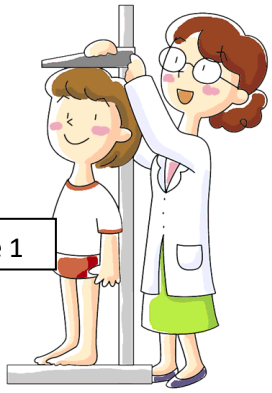
We want to see if we can make your breathing muscles stronger. To do this we will ask you to use a special device into which you breathe in and out. The

point of this study is to see if breathing through this device makes you feel better and able to exercise for longer afterwards.

What will happen to you if you take part?

You will be invited to attend 4 sessions. These will take place at Swansea University or Morriston Hospital, we can help cover cost of travel to these sessions.

Each visit will take about 1.5 hours. During the first visit, we will show you all the equipment being used during the study and you can ask any questions you may have. After this, we will measure how tall you are when you are standing and sitting down and how much you weigh on a special machine (picture right). We will also measure your waist and hip size and see how strong your lungs are when you breathe in as hard as you possibly can!



Picture 1

Visit 1

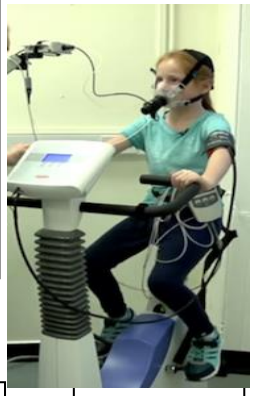
Ask any questions

Get to know the equipment

Take height and weight (Picture 1)
How strong are you (Picture 2)

Cycle as long as you can (Picture 3)

Questionnaire



Picture 3

Visit 2 (week 2)

Return movement monitors

Picture 2

Visit 3 (week 4)

Take height and weight

Cycle as long as you can

How strong are you?

Visit 4 (week 8)

Take height and weight

Cycle as long as you can

Questionnaire

Picture 5

Visit 5 (week 16)

Take height and weight

Cycle as long as you can

How strong are you?

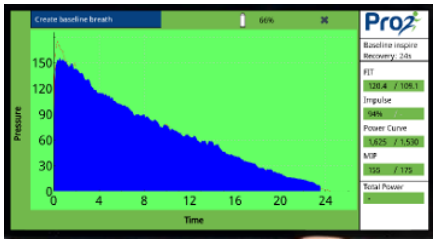
Picture 4

To measure how strong, you are you will be asked to squeeze a hand grip machine as hard as you can (picture 2). We will then ask you to cycle on the bike with a mask on that you breathe through and some stickers on your chest to see how fast your heart beats. While you cycle, it will get slowly harder and harder, like cycling up hill, and we will encourage you to keep going for as long as you can.

Breathing Device

You will then be given your own breathing device (picture on left), which you can link to your mobile or tablet through an app. This means you can track your progress during training and see how well you are doing!

We want you to use this device three times a week, every week for 8 weeks. During these sessions, you will start each session by doing a maximum effort breath into the device. You should do this standing up and by blowing out all the air in your lungs and then taking the biggest breath in you possibly can as hard, fast and long as you can! After this, you will do sets of 6 breaths at a time, with the time between each breath getting shorter as you keep going through each set. As you breathe in, you are trying to match the effort shown on the app (picture on right) all the way through the breath. You will find it gets harder and harder as you go through and we want you to try and get as far through the sets as you can each day.



At the end of 8 weeks you can decide if you want to keep training for another 8 weeks or stop, this is completely your choice.

After wearing this monitor for a week you can send this monitor back to us. When you are wearing the monitor, you do NOT need to do anything differently, just your normal routine

Questionnaires

At the end of 8 weeks you still sit down with one of the researchers and talk about your thoughts and feelings on the IMT program. There is no right or wrong answer to these questions, all we want to know are your thoughts. This chat will be recorded and what you say will be written down and then destroyed.

If you are 10+ years old at one training session in weeks 1, 4 and 8 some questions will pop up on the IMT app for you to answer before and after your training sessions. There is no right or wrong answer to these questions, we just want to know how you are feeling on that day. Answers will be based on a scale:

Please indicate how much each reason is true for you, using the following scale:

1	2	3	4	5	6	7
not at all true			somewhat true			very true

What are the possible disadvantages of taking part?

The bike exercise may make you feel tired and the mask may feel a little uncomfortable. The visits will take up some time, however we can time them at times that best suit you. The sticky pads that are stuck to your chest may be slightly uncomfortable when removed, but it's just like removing a sticky plaster! You may find breathing against the resistance device strange at first but, like any exercise, the more you do it the more you will feel comfortable with it.

What are the possible benefits of taking part?

It might help us find ways to help children and adults with Cystic Fibrosis. Cystic Fibrosis is a disease that causes the body to make thick sticky slime which hurts a persons lungs.

What happens if something goes wrong?

We don't expect any problems to occur, but if something does go wrong during the study you will be asked to stop. We will get the doctors to check you to make sure you are ok and to see if you can continue or not.

Will my taking part in the study be kept secret?

All personal information collected will be kept completely secret. That is, only members of the research team will have access to it. You will be given a special number so that no one knows who your results belong to. Interview recordings will be written up and then the audio recordings will be destroyed. After the study is finished, all private information will be deleted.

Applied Sports Technology Exercise and Medicine Research Centre (A-STEM)

Sport and Health Portfolio, College of Engineering

12- 15 YEARS OLD INFORMATION SHEET CONTROL

(Version 1.2, Date 09/03/2017)

Project Title:

Investigating the influence of an Inspiratory Muscle Training program on lung function and quality of life in children and adults with Cystic Fibrosis.

Contact Details:

Dr Melitta McNarry

Email: [redacted]

Telephone: [redacted]

Dr Kelly Mackintosh

Email: [redacted]

Telephone: [redacted]

Jessica McCreery

Email: [redacted]

Telephone: [redacted]

Thank you for being interested in our project. Please read this information sheet carefully and think about whether you are happy to take part. If you have any questions, please just ask one of the researchers or contact us in the details above. If you are happy to take part, thank you. If you prefer not to take part, this is not a problem and we thank you for thinking about it.

What is the purpose of this study?

We think that if we make breathing muscles stronger, it might make everyday life easier. To make the breathing muscles stronger, we will ask you to use a special device into which you breathe in and out. The point of this study is to see if breathing through this device makes you feel better and able to exercise for longer afterwards.

What will happen to you if you take part?

You will be invited to attend 4 testing sessions. (See Diagram below) These will take place at Swansea University or Morriston Hospital, we can help cover cost of travel to these sessions.

Each visit will take about 1.5 hours. During the first visit, we will show you all the equipment being used during the study and you can ask any questions you may have. After this, we will measure how tall you are when you are standing and sitting down and how much you weigh on a special machine (picture right). We will also measure your waist and hip size and then see how strong your lungs are when you breathe in as hard as you possibly can! To measure how strong, you are you will be asked to squeeze a hand grip machine as hard as you can (picture 1).

We will then ask you to cycle on the bike with a mask on that you breathe through and some stickers on your chest to see how fast your heart beats. While you cycle, it will get slowly harder and harder, like cycling up hill, and we will encourage you to keep going for as long as you can.

Picture 1

Visit 1

Ask questions

Get to know the equipment

Take height and weight

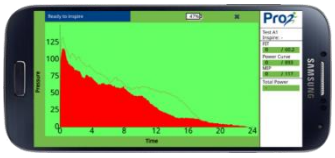
How strong are you? (Picture 1)

Cycle as long as you can (Picture 2)

Questionnaires

Get to know the breathing device (Picture 3)

Given a monitor to measure how much you move (Picture 4)



Picture 3

Visit 2 (week 2)

Return movement monitors

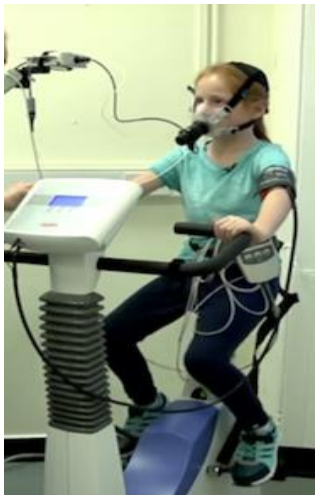
Visit 3 (week 4)

Take height and weight

Cycle as long as you can

How strong are you?

Picture 2



Visit 4 (week 8)

Take height and weight

Cycle as long as you can

Questionnaire

One-to-one talk

How strong are you?

Picture 4

Visit 5 (week 8 of top-up/detraining)

Take height and weight

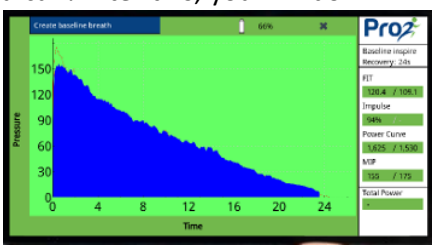
Cycle as long as you can

How strong are you?

Breathing Device

You will then be given your own IMT device (picture on left), which you can link to your mobile or tablet through an app. This means you can track your progress during training and see how well you are doing!

We want you to use this device three times a week, every week for 8 weeks. During these sessions, you will start each session by doing a maximum effort breath in to the device. You should do this standing up and blowing out all the air in your lungs and then taking the biggest breath in you possibly can as hard, fast and long as you can! After this, you will do sets of 6 breaths at a time, with the time between each breath getting shorter as you keep going through each set. As you breathe in, you are trying to match the effort shown on the app all the way through the breath (picture on right). You will find it gets harder and harder as you go through and we want you to try and get as far through the sets as you can each day.



At the end of 8 weeks you can decide if you want to keep training for another 8 weeks or stop, this is completely your choice!

Questionnaires

At one training session in weeks 1, 4 and 8 some questions will pop up on the IMT app for you to answer before and after your training sessions. There is no right or wrong answer to these questions, we just want to know how you are feeling on that day. Answers will be based on a scale:

Please indicate how much each reason is true for you, using the following scale:

1	2	3	4	5	6	7
not at all true			somewhat true			very true

At the end of 8 weeks you still sit down with one of the researchers and talk about your thoughts and feelings on the IMT program. There is no right or wrong answer to these questions, all we want to know are your thoughts. This chat will be recorded and what you say will be written down and then destroyed

Monitors

We will then give you a monitor to wear. The monitor shown in the picture on the right, will be worn on a belt around your waist but you will need to take it off when you shower or swim and write down how long you didn't have it on for. After wearing the monitor for a week you can send it back to us. When you are wearing the monitor, you do not need to do anything differently. We just want you to do whatever you would normally do each day.

What are the possible disadvantages of taking part?

The bike exercise may make you feel tired and the mask may feel a little uncomfortable, however you will complete a warm-up and cool-down exercise before and after all exercise testing. We will give you some rest breaks and water will be available. Coming to the labs will take up some time, however we can schedule testing for times that best suit you. The sticky pads that are stuck to your chest may be slightly uncomfortable when removed, but it's just like removing a sticky plaster! You may find breathing against the resistance device strange at first but, like any exercise, the more you do it the more you will feel comfortable with it.

What are the possible benefits of taking part?

Any information that is gained from the research will help children and adults with cystic fibrosis and other scientists. Cystic Fibrosis is a disease that causes the body to make thick sticky slime which hurts a persons lungs.

What happens if something goes wrong?

We don't expect any problems to occur, but if something does go wrong during the study you will be asked to stop. We will get the doctors to check you to make sure you are ok and to see if you can continue or not.

Will my taking part in the study be kept confidential?

All personal information collected will be kept completely confidential. That is, only members of the research team will have access to it. You will be given a unique number so that no one knows who your results belong to. Interview recordings will be written up and then will be destroyed. After the study is finished, all private information will be deleted.

Applied Sports Technology Exercise and Medicine Research Centre (A-STEM)

Sport and Health Portfolio, College of Engineering

PARENT/GUARDIAN PARTICIPANT INFORMATION SHEET

CONTROL

(Version 1.2, Date 09/03/2017)

Project Title:

Investigating the influence of an Inspiratory Muscle Training program on lung function and quality of life in children and adults with Cystic Fibrosis.

Contact Details:

Dr Melitta McNarry

Email: [redacted]

Telephone: [redacted]

Dr Kelly Mackintosh

Email:

Telephone: [redacted]

Jessica McCreery

Email: [redacted]

Telephone: [redacted]

Thank you for being interested in our project. Please read this information sheet carefully and think about whether you are happy for your child to take part. If you are happy for them to take part, thank you. If you prefer them not to take part, this is not a problem and we thank you for thinking about it. Your child's care will not be influenced if they do or do not decide to take part. If you have any questions, please just ask one of the researchers or contact us in the details above.

What is the purpose of this study?

We think that if we make your child's breathing muscles stronger, it might make their everyday life easier. This involves breathing through a resistive device to train your child's muscles. After this your child may be asked to do another 8 weeks of training or stop. The aim of this study is to investigate 1) the effects of training the lung muscles on how your child feels and how well they exercise and 2) the subsequent effects of a detraining or top-up period.

What will happen to your child if they take part?

Your child will be invited to attend 4 testing sessions. These will take place at Swansea University or Morriston Hospital, we can help cover cost of travel to these sessions.

Each testing visit will take approximately 1.5 hours. During the first visit, we will show your child all the equipment being used during the study and they can ask any questions they may have. We will measure their height, weight on a machine (picture right), waist and hip size. We will also measure their lung function to determine how strong their lungs are. To measure the strength of your child's hand and forearm muscles they will be asked to complete a handgrip test (picture 1).

We will then ask them to cycle on the bike with a mask (to measure oxygen and carbon dioxide levels) and chest stickers (to measure heart rate). While they cycle it will slowly get harder, like cycling up hill, we will encourage them to keep going for as long as they possibly can.

Picture 1

Visit 1

Ask questions

Get to know the equipment

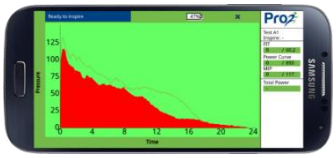
Take height and weight

Handgrip strength (picture 1)

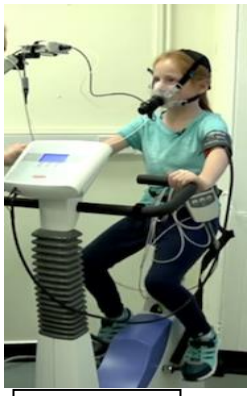
Bike Programme (Picture 2)

Questionnaires

Get to know the breathing device (Picture 3)



Picture 3



Picture 2

Visit 2 (week 2)

Return Physical Activity Monitors

Visit 3 (week 4)

Height and Weight Measurements

Bike Programme

Handgrip strength

Visit 4 (week 8)

Height and Weight Measurements

Bike Programme

Visit 5 (week 8 of top-up/detraining)

Height and Weight Measurements

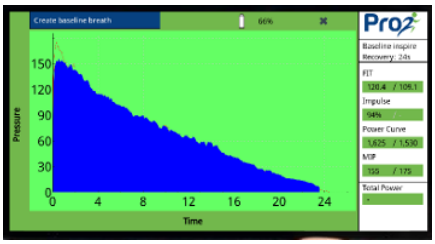
Bike Programme

Picture 4

IMT Device

Your child will then be given their own IMT device (picture on left), which can be linked to a mobile or tablet through an app. This means they can track their progress during training and see how well they are doing!

IMT involves your child breathing through the device, which provides a resistance when they breathe. This makes their muscles work harder and therefore makes them stronger! We will ask them to do the training 3 times a week for 8 weeks. They will start each session by doing a maximum effort breath in to the device. This should be done standing up, blowing all the air out of their lungs and then inhaling through the device for as hard and as long as they can! After this, your child will do 6 sets of breaths at a time, there are 6 levels in total and the time they have between each breath at each level reduces. As they breathe in, they are trying to match the effort shown on the app all the way through the breath (picture on right). Your child will find it gets harder as they go through and we want them to try and get as far through the sets as they possibly can each day.



At the end of 8 weeks your child can decide if they want to keep training for another 8 weeks or stop. This is completely their choice and whatever choice they make their care will not be changed.

Questionnaires

At one training session in weeks 1, 4 and 8 some questions will pop up on the IMT app for your child to answer before and after their training sessions. There is no right or wrong answer to these questions, we just want to know how they are feeling on that day. The questionnaires will be centred around completing IMT and their health. Answers will be based on a points scale (like the one below):

Please indicate how much each reason is true for you, using the following scale:

1	2	3	4	5	6	7
not at all true			somewhat true			very true

At the end of 8 weeks your child will sit down with one of the researchers and talk about their thoughts and feelings on the IMT program. There is no right or wrong answer to these

questions, all we want to know are their thoughts. This chat will be recorded and what they say will be written down and then audio recording will be destroyed

At the end of the 8 weeks, your child will be given the option to continue training for another 8 weeks or stop. This decision is entirely up to your child and their care will not be changed if they do or do not decide to continue training.

Monitors

We will then give your child a monitor to wear. The monitor shown in the picture on the right, will be worn on a belt around their waist but they will need to take it off when they shower or swim and write down how long they didn't have it on for. After your child wears the monitor for a week they can send it back to us. When your child is wearing these monitors, they do not need to do anything differently. We just want them to do whatever they would normally do each day.

What are the possible disadvantages of taking part?

The bicycle test may make them feel tired and the mask may feel a little uncomfortable, however a warm-up and cool-down exercise will be completed before and after all exercise. Sufficient rest breaks will be provided and water readily available. Coming to the labs is a time commitment, however testing can be scheduled round times that suit you and your child best. The sticky pads that are stuck to their chest may be slightly uncomfortable when removed, but it's just like removing a sticky plaster! They may find the breathing against a resistance strange at first but, like any exercise, the more they do it the more they will feel comfortable with it. The study and all the protocols within it are covered by Swansea University's indemnity policy.

What are the possible benefits of taking part?

Knowledge that is gained from this research will contribute to the wider scientific community and possibly help children and adults with Cystic Fibrosis.

What happens if something goes wrong?

We don't envisage any problems occurring, however if something does go wrong during the study your child will be asked to stop and checked by their medical team to determine whether they can continue or not.

8. Will my child taking part in the study be kept confidential?

All personal information collected will be kept completely confidential. That is, only members of the research team will have access to it. Your child will be given an individual code to ensure confidentiality and anonymity. All audio recordings will be destroyed after transcription. After the study is finished, all private information will be deleted.

UNDER 12 YEARS OLD INFORMATION SHEET CYSTIC FIBROSIS

(Version 1.4, Date 09/03/2017)

Project Title:

Investigating the influence of an Inspiratory Muscle Training program on lung function and quality of life in children and adults with Cystic Fibrosis.

Contact Details:

Dr Melitta McNarry

Email: [redacted]

Telephone: [redacted]

Dr Kelly Mackintosh

Email:

Telephone: [redacted]

Jessica McCreery

Email: [redacted]

Telephone: [redacted]

Thank you for being interested in our project. Please read this information sheet carefully and think about whether you are happy to take part. If you are happy to take part, thank you. If you prefer not to take part that is ok! Your care will not be changed if you do or do not decide to take part. If you have any questions, please contact us on the details at the beginning of this sheet. You can also ask one of the researchers when you come in to visit the Clinic.

What is the purpose of this study?

As you have Cystic Fibrosis we want to see if we can make your breathing muscles stronger. To do this we will ask you to use a special device into which

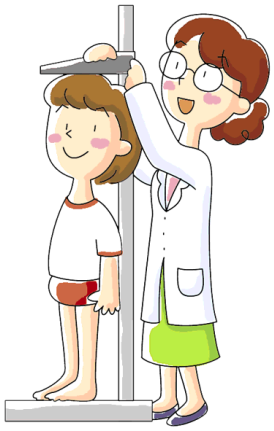
you breathe in and out. The point of this study is to see if breathing through this device makes you feel better and able to exercise for longer afterwards.

What will happen to you if you take part?

You will be invited to attend 4 sessions. These will take place at Swansea University or Morriston Hospital, we can help cover cost of travel to these sessions.

Each visit will take about 1.5 hours. During the first visit, we will show you all the equipment being used during the study and you can ask any questions you may have. After this, we will measure how tall you are when you are standing and sitting down and how much you weigh on a special machine (picture right). We will also measure your waist and hip size and then see how strong your lungs are when you breathe in as hard as you possibly can!

Picture 1



Visit 1

Ask any questions

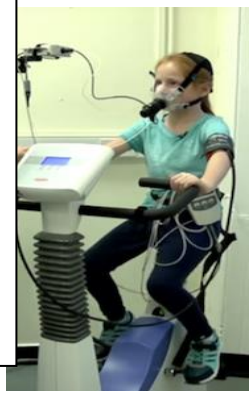
Get to know the equipment

Take height and weight (Picture 1)

How strong are you? (Picture 2)

Cycle as long as you can (Picture 3)

Questionnaire



Visit 2 (week 2)

Return movement monitors

Picture 2

Visit 3 (week 4)

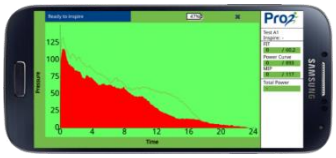
Take height and weight

Cycle as long as you can

How strong are you?

Cough experiment

Picture 3



Picture 4

Visit 4 (week 8)

Take height and weight

Cycle as long as you can

How strong are you?

Picture 5

Visit 5 (week 16)

Take height and weight

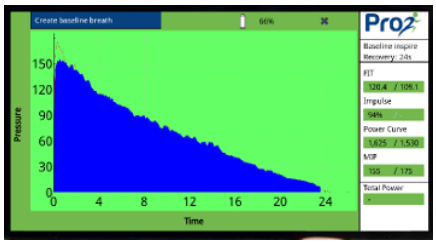
Cycle as long as you can

To measure how strong, you are you will be asked to squeeze a hand grip machine as hard as you can (picture 2). We will then ask you to cycle on the bike with a mask on that you breathe through and some stickers on your chest to see how fast your heart beats. While you cycle, it will get slowly harder and harder, like cycling up hill, and we will encourage you to keep going for as long as you can.

Breathing Device

You will then be given your own breathing device (picture on left), which you can link to your mobile or tablet through an app. This means you can track your progress during training and see how well you are doing!

We want you to use this device three times a week, every week for 8 weeks. During these sessions, you will start each session by doing a maximum effort breath out into the device. You should do this standing up and by blowing out all the air in your lungs and then taking the biggest breath in you possibly can as hard, fast and long as you can! After this, you will do sets of 6 breaths at a time, with the time between each breath getting shorter as you keep going through each set. As you breathe in, you are trying to match the effort shown on the app (picture on right) all the way through the breath. You will find it gets harder and harder as you go through and we want you to try and get as far through the sets as you can each day. At home, we also want you to be a scientist and do your own experiment! We want you to measure how much stuff you can cough up from your lungs after training. All you have to do is cough into a pot and weigh it on a set of kitchen scales!



At the end of 8 weeks you can decide if you want to keep training for another 8 weeks or stop. This is your choice and whatever choice you make your care will not be changed

After wearing this monitor for a week you can send this monitor back to us. When you are wearing the monitor, you do NOT need to do anything differently, just your normal routine

Questionnaires

At the end of 8 weeks you still sit down with one of the researchers and talk about your thoughts and feelings on the IMT program. There is no right or wrong answer to these questions, all we want to know are your thoughts. This chat will be recorded and what you say will be written down and then destroyed.

If you are 10+ years old at one training session in weeks 1, 4 and 8 some questions will pop up on the IMT app for you to answer before and after your training sessions. There is no right or wrong answer to these questions, we just want to know how you are feeling on that day. Answers will be based on a scale:

Please indicate how much each reason is true for you, using the following scale:

1	2	3	4	5	6	7
not at all true			somewhat true			very true

What are the possible disadvantages of taking part?

The bike exercise may make you feel tired and the mask may feel a little uncomfortable. The visits will take up some time, however we can time them at times that best suit you. The sticky pads that are stuck to your chest may be slightly uncomfortable when removed, but it's just like removing a sticky plaster! You may find breathing against the resistance device strange at first but, like any exercise, the more you do it the more you will feel comfortable with it.

What are the possible benefits of taking part?

It might help us find ways to help future people with CF!

What happens if something goes wrong?

We don't expect any problems to occur, but if something does go wrong during the study you will be asked to stop. We will get the doctors to check you to make sure you are ok and to see if you can continue or not. If you are unhappy with anything that happens you can contact Dr McNarry (details above) or alternatively Professor Mike McNamee.

Will my taking part in the study be kept secret?

All personal information collected will be kept completely secret. That is, only members of the research team will have access to it. You will be given a special number so that no one knows who your results belong to. Interview recordings will be written up and then the audio recordings will be destroyed. After the study is finished, all private information will be deleted.

12- 15 YEARS OLD INFORMATION SHEET CYSTIC FIBROSIS

(Version 1.4, Date 09/03/2017)

Project Title:

Investigating the influence of an Inspiratory Muscle Training program on lung function and quality of life in children and adults with Cystic Fibrosis.

Contact Details:

Dr Melitta McNarry

Email: [redacted]

Telephone: [redacted]

Dr Kelly Mackintosh

Email:

Telephone: [redacted]

Jessica McCreery

Email: [redacted]

Telephone: [redacted]

Thank you for being interested in our project. Please read this information sheet carefully and think about whether you are happy to take part. If you have any questions, please just ask one of the researchers or contact us in the details above. If you are happy to take part, thank you. If you prefer not to take part, this is not a problem and we thank you for thinking about it. Your care will not be changed if you do or do not decide to take part.

What is the purpose of this study?

As you have Cystic Fibrosis we think that if we make your breathing muscles stronger, it might make your everyday life easier. To make your breathing muscles stronger, we will ask you to use a special device into which you breathe in and out. The point of this study is to see if breathing through this device makes you feel better and able to exercise for longer afterwards.

What will happen to you if you take part?

You will be invited to attend 4 testing sessions (See Diagram below). These will take place at Swansea University or Morriston Hospital, we can help cover cost of travel to these sessions.

Each visit will take about 1.5 hours. During the first visit, we will show you all the equipment being used during the study and you can ask any questions you may have. After this, we will measure how tall you are when you are standing and sitting down and how much you weigh on a special machine (picture right). We will also measure your waist and hip size and then see how strong your lungs are when you breathe in as hard as you possibly can! To measure how strong, you are you will be asked to squeeze a hand grip machine as hard as you can (picture 1).

We will then ask you to cycle on the bike with a mask on that you breathe through and some stickers on your chest to see how fast your heart beats. While you cycle, it will get slowly harder and harder, like cycling up hill, and we will encourage you to keep going for as long as you can.

Picture 1

Visit 1

Ask questions

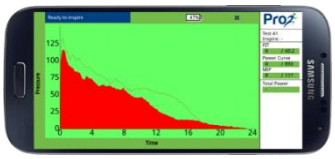
Get to know the equipment

Take height and weight

How strong are you? (Picture 1)

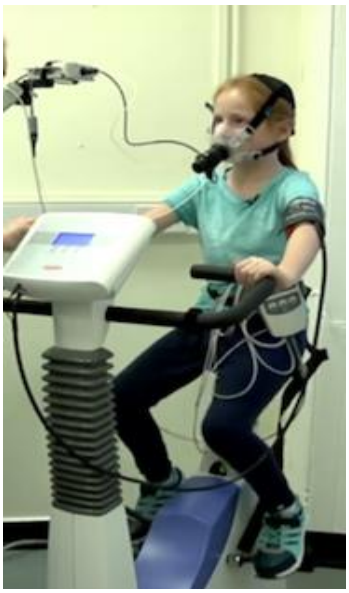
Cycle as long as you can (Picture 2)

Questionnaires



Picture 3

Picture 2



Visit 2 (week 2)

Return movement monitors

Visit 3 (week 4)

Take height and weight

Cycle as long as you can

How strong are you?

Cough experiment

Picture 4

Visit 4 (week 8)

Take height and weight

Cycle as long as you can

Questionnaire

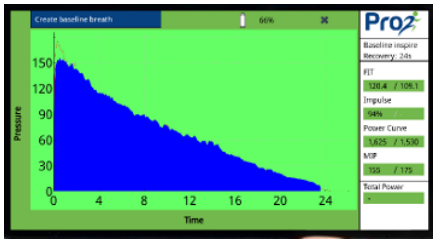
Visit 5 (week 8 of top-up/detraining)

Take height and weight

Breathing Device

You will then be given your own IMT device (picture on left), which you can link to your mobile or tablet through an app. This means you can track your progress during training and see how well you are doing!

We want you to use this device three times a week, every week for 8 weeks. During these sessions, you will start each session by doing a maximum effort breath in to the device. You should do this standing up and blowing out all the air in your lungs and then taking the biggest breath in you possibly can as hard, fast and long as you can! After this, you will do sets of 6 breaths at a time, with the time between each breath getting shorter as you keep going through each set. As you breathe in, you are trying to match the effort shown on the app all the way through the breath (picture on right). You will find it gets harder and harder as you go through and we want you to try and get as far through the sets as you can each day. At home, we also want you to be a scientist and do your own experiment! We want you to measure how much you can cough up from your lungs after training. All you have to do is cough into a pot and weigh it on a set of kitchen scales!



At the end of 8 weeks you can decide if you want to keep training for another 8 weeks or stop. This is your choice and whatever choice you make your care will not be changed.

Questionnaires

At one training session in weeks 1, 4 and 8 some questions will pop up on the IMT app for you to answer before and after your training sessions. There is no right or wrong answer to these questions, we just want to know how you are feeling on that day. Answers will be based on a scale:

Please indicate how much each reason is true for you, using the following scale:

1	2	3	4	5	6	7
not at all true			somewhat true			very true

At the end of 8 weeks you still sit down with one of the researchers and talk about your thoughts and feelings on the IMT program. There is no right or wrong answer to these

questions, all we want to know are your thoughts. This chat will be recorded and what you say will be written down and then destroyed

Monitors

We will then give you a monitor to wear. The monitor shown in the picture on the right, will be worn on a belt around your waist but you will need to take it off when you shower or swim and write down how long you didn't have it on for. After wearing the monitor for a week you can send it back to us. When you are wearing the monitor, you do not need to do anything differently. We just want you to do whatever you would normally do each day.

What are the possible disadvantages of taking part?

The bike exercise may make you feel tired and the mask may feel a little uncomfortable, however you will complete a warm-up and cool-down exercise before and after all exercise testing. We will give you some rest breaks and water will be available. Coming to the labs will take up some time, however we can schedule testing for times that best suit you. The sticky pads that are stuck to your chest may be slightly uncomfortable when removed, but it's just like removing a sticky plaster! You may find breathing against the resistance device strange at first but, like any exercise, the more you do it the more you will feel comfortable with it.

What are the possible benefits of taking part?

Any information that is gained from the research will help other people with CF and other scientists!

What happens if something goes wrong?

We don't expect any problems to occur, but if something does go wrong during the study you will be asked to stop. We will get the doctors to check you to make sure you are ok and to see if you can continue or not. The University indeminity policy covers any adverse events. If you are unhappy with anything that happens during the study you can contact Dr McNarry (details above) or alternatively if you prefer to speak to someone independent, you can contact Prof Mike McNamee chair of the A-STEM Ethics committee.

Will my taking part in the study be kept confidential?

All personal information collected will be kept completely confidential. That is, only members of the research team will have access to it. You will be given a unique number so that no one knows who your results belong to. Interview recordings will be written up and then will be destroyed. After the study is finished, all private information will be deleted.

Applied Sports Technology Exercise and Medicine Research Centre (A-STEM)

Sport and Health Portfolio, College of Engineering

PARENT/GUARDIAN PARTICIPANT INFORMATION SHEET

CHILD CYSTIC FIBROSIS

(Version 1.4, Date 09/03/2017)

Project Title:

Investigating the influence of an Inspiratory Muscle Training program on lung function and quality of life in children and adults with Cystic Fibrosis.

Contact Details:

Dr Melitta McNarry

Email: [redacted]

Telephone: [redacted]

Dr Kelly Mackintosh

Email:

Telephone: [redacted]

Jessica McCreery

Email: [redacted]

Telephone: [redacted]

Thank you for being interested in our project. Please read this information sheet carefully and think about whether you are happy for your child to take part. If you are happy for them to take part, thank you. If you prefer them not to take part, this is not a problem and we thank you for thinking about it. Your child's care will not be influenced if they do or do not decide to take part. If you have any questions, please just ask one of the researchers or contact us in the details above.

What is the purpose of this study?

As your child has Cystic Fibrosis we think that if we make your child's breathing muscles stronger, it might make their everyday life easier. This involves breathing through a resistive device to train your child's muscles. After this your child may be asked to do another 8 weeks of training or stop. The aim of this study is to investigate 1) the effects of training the lung muscles on how your child feels and how well they exercise and 2) the subsequent effects of a detraining or top-up period.

What will happen to your child if they take part?

Your child will be invited to attend 4 testing sessions. These will take place at Swansea University or Morriston Hospital, we can help cover cost of travel to these sessions.

Each testing visit will take approximately 1.5 hours. During the first visit, we will show your child all the equipment being used during the study and they can ask any questions they may have. We will measure their height, weight on a machine (picture right), waist and hip size. We will also measure their lung function to determine how strong their lungs are. To measure the strength of your child's hand and forearm muscles they will be asked to complete a handgrip test (picture 1).

We will then ask them to cycle on the bike with a mask (to measure oxygen and carbon dioxide levels) and chest stickers (to measure heart rate). While they cycle it will slowly get harder, like cycling up hill, we will encourage them to keep going for as long as they possibly can.

Visit 1

Ask questions

Get to know the equipment

Take height and weight

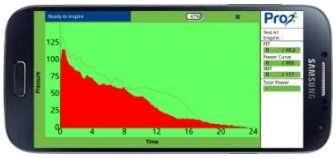
Handgrip strength (picture 1)

Bike Programme (Picture 2)

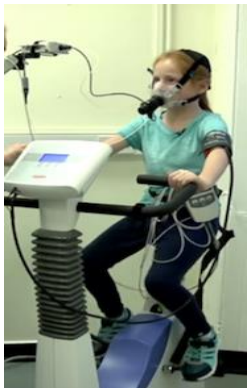
Questionnaires

Get to know the breathing device (Picture 3)

Picture 1



Picture 3



Picture 2

Visit 2 (week 2)

Return Physical Activity Monitors

Visit 3 (week 4)

Height and Weight Measurements

Bike Programme

Visit 4 (week 8)

Height and Weight Measurements

Bike Programme

Questionnaires

One-to-one talk

Handgrip strength

Sputum production

Visit 5 (week 8 of top-up/detraining)

Height and Weight Measurements

Bike Programme

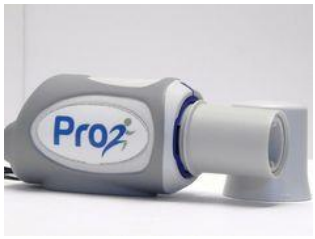
Handgrip strength

Sputum production

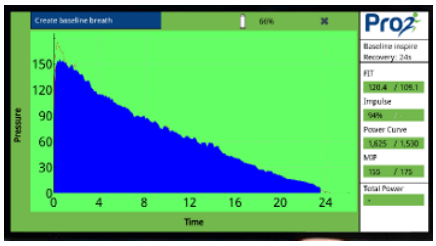
Picture 4

IMT Device

Your child will then be given their own IMT device (picture on left), which can be linked to a mobile or tablet through an app. This means they can track their progress during training and see how well they are doing!



IMT involves your child breathing through the device, which provides a resistance when they breathe. This makes their muscles work harder and therefore makes them stronger! We will ask them to do the training 3 times a week for 8 weeks. They will start each session by doing a maximum effort breath in to the device. This should be done standing up, blowing all the air out of their lungs and then inhaling through the device for as hard and as long as they can! After this, your child will do 6 sets of breaths at a time, there are 6 levels in total and the time they have between each breath at each level reduces. As they breathe in, they are trying to match the effort shown on the app all the way through the breath (picture on right). Your child will find it gets harder as they go through and we want them to try and get as far through the sets as they possibly can each day. At home, we want your child to do their own experiment. We ask if you and your child could take a measurement of their sputum production after exercise. All they have to do is cough into a pot and weigh and record the weight on a set of kitchen scales and dispose of it as your normally do.



At the end of 8 weeks your child can decide if they want to keep training for another 8 weeks or stop. This is completely their choice and whatever choice they make their care will not be changed.

Questionnaires

At one training session in weeks 1, 4 and 8 some questions will pop up on the IMT app for your child to answer before and after their training sessions. There is no right or wrong answer to these questions, we just want to know how they are feeling on that day. The questionnaires will be centred around completing IMT and their health. Answers will be based on a points scale (like the one below):

Please indicate how much each reason is true for you, using the following scale:

1	2	3	4	5	6	7
not at all true			somewhat true			very true

At the end of 8 weeks your child will sit down with one of the researchers and talk about their thoughts and feelings on the IMT program. There is no right or wrong answer to these

questions, all we want to know are their thoughts. This chat will be recorded and what they say will be written down and then audio recording will be destroyed

At the end of the 8 weeks, your child will be given the option to continue training for another 8 weeks or stop. This decision is entirely up to your child and their care will not be changed if they do or do not decide to continue training.

Monitors

We will then give your child a monitor to wear. The monitor shown in the picture on the right, will be worn on a belt around their waist but they will need to take it off when they shower or swim and write down how long they didn't have it on for. After your child wears the monitor for a week they can send it back to us. When your child is wearing these monitors, they do not need to do anything differently. We just want them to do whatever they would normally do each day.

What are the possible disadvantages of taking part?

The bicycle test may make them feel tired and the mask may feel a little uncomfortable, however a warm-up and cool-down exercise will be completed before and after all exercise. Sufficient rest breaks will be provided and water readily available. Coming to the labs is a time commitment, however testing can be scheduled round times that suit you and your child best. The sticky pads that are stuck to their chest may be slightly uncomfortable when removed, but it's just like removing a sticky plaster! They may find the breathing against a resistance strange at first but, like any exercise, the more they do it the more they will feel comfortable with it. The study and all the protocols within it are covered by Swansea University's indemnity policy.

What are the possible benefits of taking part?

Knowledge that is gained from this research will contribute to the wider scientific community so you can help other people with CF.

What happens if something goes wrong?

We don't envisage any problems occurring, however if something does go wrong during the study your child will be asked to stop and checked by their medical team to determine whether they can continue or not. The University indeminity policy covers any adverse events. If you are unhappy with anything that happens during the study you can contact Dr McNarry (details above) or alternatively if you prefer to speak to someone independent, you can contact Prof Mike McNamee chair of the A-STEM Ethics committee.

Will my child taking part in the study be kept confidential?

All personal information collected will be kept completely confidential. That is, only members of the research team will have access to it. Your child will be given an individual code to ensure confidentiality and anonymity. All audio recordings will be destroyed after transcription. After the study is finished, all private information will be deleted.

16 YEARS PLUS INFORMATION SHEET CONTROL

(Version 1.2, Date 09/03/2017)

Project Title:

Investigating the influence of an Inspiratory Muscle Training program on lung function and quality of life in children and adults with Cystic Fibrosis.

Contact Details:

Dr Melitta McNarry

Email: [redacted]

Telephone: [redacted]

Dr Kelly Mackintosh

Email:

Telephone: [redacted]

Jessica McCreery

Email: [redacted]

Telephone: [redacted]

Thank you for being interested in our project. Please read this information sheet carefully and think about whether you are happy to take part. If you have any questions, please just ask one of the researchers or contact us in the details above. If you are happy to take part, thank you. If you prefer not to take part, this is not a problem and we thank you for thinking about it.

What is the purpose of this study?

We think that if we make breathing muscles stronger, it might make everyday life easier. This involves breathing through a resistive device to train your muscles. The aim of this study is to investigate 1) the effects of training the lung muscles on how you feel and how well you exercise and 2) the subsequent effects of a detraining or top-up period.

What will happen to you if you take part?

You will be invited to attend 4 testing sessions. These will take place at Swansea University or University Hospital, Llandough, we can help cover cost of travel to these sessions.

Each testing visit will take approximately 1.5 hours. During the first visit, we will show you all the equipment being used during the study and you can ask any questions you may have. We will measure your height, weight on a machine (picture right), waist and hip size. We will also measure your lung function to determine how strong your lungs are. To measure the strength of your hand and forearm muscles you will be asked to complete a handgrip test (picture 1).

We will then ask you to cycle on the bike with a mask (to measure your oxygen and carbon dioxide levels) and chest stickers (to measure your heart rate). While you cycle it will slowly get harder, like cycling up hill, we will encourage you to keep going for as long as you can.

Visit 1

Ask questions

Get to know the equipment

Take height and weight

Handgrip strength (Picture 1)

Bike Programme (Picture 2)

Questionnaires

Get to know the breathing device (Picture 3)

Picture 1

Picture 2

Visit 2 (week 2)

Return Physical Activity Monitors

Picture 4

Visit 3 (week 4)

Height and Weight Measurements

Bike Programme

Handgrip strength

Visit 4 (week 8)

Height and Weight Measurements

Bike Programme

Questionnaires

One-to-one talk

Handgrip strength

Visit 5 (week 8 of top-up/detraining)

Height and Weight Measurements

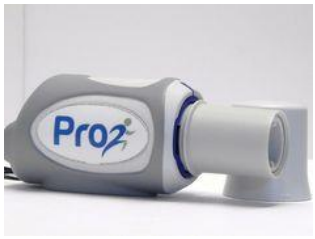
Bike Programme

Handgrip strength

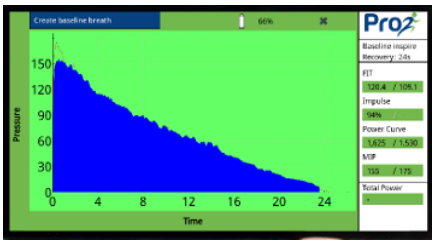
Sputum collection

IMT Device

You will then be given your own IMT device (picture on left), which you can link to your mobile or tablet through an app. This means you can track your progress during training and see how well you are doing!



IMT involves you breathing through the device, which provides a resistance when you breathe. This makes your muscles work harder and therefore makes them stronger! We will ask you to do the training 3 times a week for 8 weeks. You will start each session by doing a maximum effort breath in to the device. This should be done standing up, blowing all the air out of your lungs and then inhaling through the device for as hard and as long as you can! After this, you will do 6 sets of breaths at a time, there are 6 levels in total and the time you have between each breath at each level reduces. As you breathe in, you are trying to match the effort shown on the app all the way through the breath (picture on right). You will find it gets harder as you go through and we want you to try and get as far through the sets as you can each day.



At the end of 8 weeks you can decide if you want to keep training for another 8 weeks or stop, this is completely your choice!

Questionnaires

At one training session in weeks 1, 4 and 8 some questions will pop up on the IMT app for you to answer before and after your training sessions. There is no right or wrong answer to these questions, we just want to know how you are feeling on that day. Answers will be based on a scale:

Please indicate how much each reason is true for you, using the following scale:

1	2	3	4	5	6	7
not at all true			somewhat true			very true

At the end of 8 weeks you still sit down with one of the researchers and talk about your thoughts and feelings on the IMT program. There is no right or wrong answer to these questions, all we want to know are your thoughts. This chat will be recorded and what you say will be written down and then destroyed.

Monitors

We will then give you a monitor to wear. The monitor shown in the picture on the right, will be worn on a belt around your waist but you will need to take it off when you shower or swim and write down how long you didn't have it on for. After wearing the monitor for a week you can send it back to us. When you are wearing the monitor, you do not need to do anything differently. We just want you to do whatever you would normally do each day.

What are the possible disadvantages of taking part?

The bike exercise may make you feel tired and the mask may feel a little uncomfortable, however you will complete a warm-up and cool-down exercise before and after all exercise testing. We will give you some rest breaks and water will be available. Coming to the labs will take up some time, however we can schedule testing for times that best suit you. The sticky pads that are stuck to your chest may be slightly uncomfortable when removed, but it's just like removing a sticky plaster! You may find breathing against the resistance device strange at first but, like any exercise, the more you do it the more you will feel comfortable with it.

What are the possible benefits of taking part?

Any information that is gained from the research will help children and adults with cystic fibrosis and other scientists.

What happens if something goes wrong?

We don't expect any problems to occur, but if something does go wrong during the study you will be asked to stop. We will get the doctors to check you to make sure you are ok and to see if you can continue or not.

Will my taking part in the study be kept confidential?

All personal information collected will be kept completely confidential. That is, only members of the research team will have access to it. You will be given a unique number so that no one knows who your results belong to. Interview recordings will be written up and then will be destroyed. After the study is finished, all private information will be deleted.

16 YEARS PLUS INFORMATION SHEET CYSTIC FIBROSIS AND BRONCHIECTASIS

(Version 1.4, Date 09/03/2017)

Project Title:

Investigating the influence of an Inspiratory Muscle Training program on lung function and quality of life in children and adults with Cystic Fibrosis.

Contact Details:

Dr Melitta McNarry

[redacted]

Telephone: [redacted]

Dr Kelly Mackintosh

Email:

Telephone: [redacted]

Jessica McCreery

Email: [redacted]

Telephone: [redacted]

Thank you for being interested in our project. Please read this information sheet carefully and think about whether you are happy to take part. If you have any questions, please just ask one of the researchers or contact us in the details above. If you are happy to take part, thank you. If you prefer not to take part, this is not a problem and we thank you for thinking about it. Your care will not be influenced if you do or do not decide to take part.

What is the purpose of this study?

As you have Cystic Fibrosis or bronchiectasis we think that if we make your breathing muscles stronger, it might make your everyday life easier. This involves breathing through a resistive device to train your muscles. The aim of this study is to investigate 1) the effects of training the lung muscles on how you feel and how well you exercise and 2) the subsequent effects of a detraining or top-up period.

What will happen to you if you take part?

You will be invited to attend 4 testing sessions. These will take place at Swansea University or University Hospital, Llandough, or Glangwili Hospital we can help cover cost of travel to these sessions.

Each testing visit will take approximately 1.5 hours. During the first visit, we will show you all the equipment being used during the study and you can ask any questions you may have. We will measure your height, weight on a machine (picture right), waist and hip size. We will also measure your lung function to determine how strong your lungs are. To measure the strength of your hand and forearm muscles you will be asked to complete a handgrip test (picture 1).

We will then ask you to cycle on the bike with a mask (to measure your oxygen and carbon dioxide levels) and chest stickers (to measure your heart rate). While you cycle it will slowly get harder, like cycling up hill, we will encourage you to keep going for as long as you can.

Picture 1

Visit 1

Ask questions

Get to know the equipment

Take height and weight

Handgrip strength (Picture 1)

Bike Programme (Picture 2)

Questionnaires

Get to know the breathing device (Picture 3)

Physical Activity Tracker (Picture 4)

Picture 2

Picture 3

Visit 2 (week 2)

Return Physical Activity Monitors

Visit 3 (week 4)

Height and Weight Measurements

Bike Programme

Handgrip strength

Sputum collection

Picture 4

Visit 4 (week 8)

Height and Weight Measurements

Bike Programme

Questionnaires

One-to-one talk

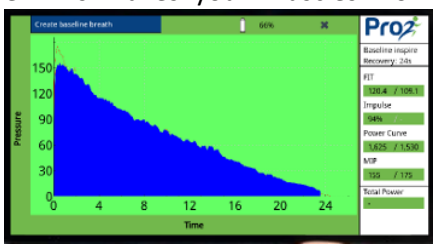
Handgrip strength

Visit 5 (week 8 of top-up/detraining)
Height and Weight Measurements
Bike Programme
Handgrip strength
Sputum collection

IMT Device

You will then be given your own IMT device (picture on left), which you can link to your mobile or tablet through an app. This means you can track your progress during training and see how well you are doing!

IMT involves you breathing through the device, which provides a resistance when you breathe. This makes your muscles work harder and therefore makes them stronger! We will ask you to do the training 3 times a week for 8 weeks. You will start each session by doing a maximum effort breath in to the device. This should be done standing up, blowing all the air out of your lungs and then inhaling through the device for as hard and as long as you can! After this, you will do 6 sets of breaths at a time, there are 6 levels in total and the time you have between each breath at each level reduces. As you breathe in, you are trying to match the effort shown on the app all the way through the breath (picture on right). You will find it gets harder as you go through and we want you to try and get as far through the sets as you can each day. At home, we also ask if you could take a measurement of your sputum production after exercise. All you have to do is cough the sputum into a pot and weigh and record the weight on a set of kitchen scales and dispose of it as you normally do.



At the end of 8 weeks you can decide if you want to keep training for another 8 weeks or stop. This is your choice and whatever choice you make your care will not be changed.

Questionnaires

At one training session in weeks 1, 4 and 8 some questions will pop up on the IMT app for you to answer before and after your training sessions. There is no right or wrong answer to these questions, we just want to know how you are feeling on that day. Answers will be based on a scale:

Please indicate how much each reason is true for you, using the following scale:

1	2	3	4	5	6	7
not at all true			somewhat true			very true

At the end of 8 weeks you still sit down with one of the researchers and talk about your thoughts and feelings on the IMT program. There is no right or wrong answer to these questions, all we want to know are your thoughts. This chat will be recorded and what you say will be written down and then destroyed.

Monitors

We will then give you a monitor to wear. The monitor shown in the picture on the right, will be worn on a belt around your waist but you will need to take it off when you shower or swim and write down how long you didn't have it on for. After wearing the monitor for a week you can send it back to us. When you are wearing the monitor, you do not need to do anything differently. We just want you to do whatever you would normally do each day.

What are the possible disadvantages of taking part?

The bike exercise may make you feel tired and the mask may feel a little uncomfortable, however you will complete a warm-up and cool-down exercise before and after all exercise testing. We will give you some rest breaks and water will be available. Coming to the labs will take up some time, however we can schedule testing for times that best suit you. The sticky pads that are stuck to your chest may be slightly uncomfortable when removed, but it's just like removing a sticky plaster! You may find breathing against the resistance device strange at first but, like any exercise, the more you do it the more you will feel comfortable with it.

What are the possible benefits of taking part?

Any information that is gained from the research will help other people with CF and other scientists!

What happens if something goes wrong?

We don't expect any problems to occur, but if something does go wrong during the study you will be asked to stop. We will get the doctors to check you to make sure you are ok and to see if you can continue or not. The University indeminity policy covers any adverse events. If you are unhappy with anything that happens during the study you can contact Dr McNarry (details above) or alternatively if you prefer to speak to someone independent, you can contact Prof Mike McNamee chair of the A-STEM Ethics committee.

Will my taking part in the study be kept confidential?

All personal information collected will be kept completely confidential. That is, only members of the research team will have access to it. You will be given a unique number so that no one knows who your results belong to. Interview recordings will be written up and then will be destroyed. After the study is finished, all private information will be deleted.

GP Information Sheet

(Version 1.2; Date – 07/03/2017)

Research Study: **Investigating the influence of an Inspiratory Muscle Training program on lung function and quality of life in children and adults with Cystic Fibrosis.**

Dear …….,

Your patient has been invited to participate in the above study because they have Cystic Fibrosis or bronchiectasis.

The purpose of the study is to determine whether a home based inspiratory muscle training programme can improve lung function, physiological response to exercise and quality of life in both adults and children with Cystic Fibrosis and bronchiectasis. We have already completed a pilot study with children which was well received and we would now like to investigate a larger population to determine inspiratory muscle trainings effectiveness in progression from childhood to adulthood.

Your patient has been assessed in their Cystic Fibrosis Unit at Singleton Hospital/ Llandough University Hospital Glangwili Hospital by their care team and is considered eligible to participate. He/she will be asked to attend Singleton Hospital/ Llandough University Hospital/ Glangwili Hospital or Swansea University Bay Campus on four occasions with the following occurring:

Anthropometrics and Maximal Cardiopulmonary Exercise Test (CPET)

Anthropometric data including age, height, body mass, sex and waist and hip circumference will be recorded. Patients' resting pulmonary function measurements will also be recorded, including forced vital capacity (FVC), FEV_1, Peak Expiratory Flow (PEF) using a flow-volume loop spirometer and will follow British Thoracic Society guidelines. Measures of respiratory muscle strength (maximum inspiratory pressure (MIP) and maximum expiratory pressure (MEP)) will then be obtained using a respiratory pressure meter.

Participants will be familiarised with exercising on a cycle ergometer, maintaining a constant pedal rate [revolutions per minute (RPM)] at a given power output. The maximal CPET on a cycle ergometer has been demonstrated to be safe and effective for this population (e.g. Saynor et al., 2013a, 2013b, 2014a, 2014b, under review). Adjustments will be made to the seat, pedals and handlebars to insure maximum comfort for each individual patient and will be recorded for future visits. Prior to the test beginning heart rate, resting pulmonary gas measurements, heart rate variability and oxygen saturation will be measured. The intensity of exercise will be dependent on patients' age, height, weight and health status. The test involves a maximal exercise test to voluntary exhaustion using an incremental ramp protocol on a cycle ergometer. It will be followed by a supramaximal verification test to exhaustion (S_{max}) following recovery from the ramp test.

The test will begin with unloaded pedalling (0.W) for a baseline period of 3 minutes. Following, this the power output will increase incrementally (10-20 $W.min^{-1}$) in a fixed interval based on height (10 $W.min^{-1}$ <120cm; 15 $W.min^{-1}$ 120-150cm; 20 $W.min^{-1}$ >150cm), independent of sex. All participants will pedal at a cadence of 70-80 rpm and be verbally encouraged to continue until voluntary exhaustion which is defined as volitional exhaustion or drop of pedal cadence by >10rpm despite strong verbal encouragement. A recovery period consisting of 5 minutes of unloaded pedalling (0W) will be followed by a 10 minute passive recovery, seated in an upright position. One further bout of supramaximal exercise will follow consisting of 3 minutes pedalling at 20 W and a 'step' transition to 110% of the peak power achieved during the ramp test. This will require patients to cycle at this intensity with a pedal rate of 70-80rpm until exhaustion, as defined above. Active recovery will follow with a power output of 20W. Throughout the testing patients will be observed by a researcher and a doctor will be present at all times. The CPET is relative for all patients and they have the right to stop the test whenever they want.

Breath-by-breath changes in pulmonary gas exchange, ventilation, heart rate variability, HR and SpO2 will be recorded continuously during all exercise testing and recovery period. Subjective ratings of perceived exertion (RPE) and perceived dyspnoea (RPD) will also be obtained. Gas exchange responses will be interpolated to 1 second intervals and averaged every 15 seconds. HR will be determined on beat-by-beat basis and will be averaged every 15 seconds, HR variability will be monitored using an3 lead electrocardiogram (ECG) and impedance cardiography (ICG).

Inspiratory Muscle Training

Participants will be given their own personal Inspiratory Muscle Training device (PrO2 hand-held wireless device) to prevent cross contamination. The training programme will initially be 8 weeks with 3 training sessions a week, unsupervised in their own home. Before each session patients are asked to establish a 1 rep max (baseline) and they train based on 80% of that number. The programme consists of 6 levels (A-F) with 6 inspirations at each level for a total of 36 breaths. At each level recovery times decrease (A=20s, B= 30s, C= 20s, D= 15s, E= 10s, F= 5s). The training programme takes approximately 20-30 minutes depending on the individual's advancement through the training levels. Each patient baseline is reassessed every time they train, therefore they still work 80% of what they are capable on that day. At one training session in weeks 1, 4 and 8 participants will be requested to answer questions on feeling scale, arousal scale and profile of mood states before and after their IMT session. They will be prompted to complete these questions by the app and should take no longer than 10 minutes to complete. After 8 weeks of training participants will have the option to continue a top-up training for a further 8 weeks (1 IMT session a week) or undergo a detraining period where they will stop IMT and continue with their normal routine. This decision is entirely their choice and their decision will not influence their care or future participation in studies.

In addition to the above measures, patients will undertake some psychological questionnaire measures on self-determination theory, quality of life, affective valence and one to on interviews to determine their thoughts and feelings on the intervention. Patients physical activity and sleep will also be monitored for 7 days using an accelerometer and ECG that is attached via the chest via two electrodes. None of these pose any risk to patients.

Handgrip

Handgrip strength is a validated measure of peripheral muscle function, which has been shown to be correlated to lung function in Cystic Fibrosis patients (Ziai et al, 2014) and upper extremity strength (Bohannon, R.W. 1998). Handgrip strength will be measured using a hand dynamometer (Takei 5401, Tokyo, Japan). Subjects will be asked to stand upright with the arm naturally extended straight pointing to the floor and be asked to squeeze as hard as they can. A total of 4 measurements will be required (2 from each hand) alternating hands each time. Verbal encouragement will be given throughout and the device can be altered to suit the grip distance of each individual subject.

Bioelectrical Impedance Analysis

Bioelectrical Impedance calculates body composition and free fat mass (FFM) measurements through a safe electrical signal being sent throughout the body. Recent studies have documented an association between FFM depletion and poor respiratory muscle strength or impaired pulmonary function (Enright et al, 2007 and King et al, 2010).

Patients height, weight, gender and age will be entered into the Bioelectrial Impedance Device (Tanita BC-418ma). Patients will then be asked to stand on the weighing platform with bare feet and asked to grasp the grips with both hands. Subjects will be required to empty their bowels, refrain from vigorous exercise or alcohol within 12 hours of BIA and be measured at least 2 hours after their last meal. Any patient on diuretic medications, pacemaker or any other medical electrical device implanted will not be able to undertake BIA.

Sputum Clearance

Patients will be supplied with a sterile pot and will be asked to rinse mouth and gargle with sterile water prior to collection. Patients will be instructed to cough deeply, then breathe deeply and cough deeply to produce sputum from the airway into a sterile pot. This pot will then be measured and the wet weight recorded. Patients can complete this in their home and measure with any set of scales. Their sputum can then be disposed with as they normally do.

Outline of Visits

Visit 1/baseline will be prior to exercise programme beginning. It will consist of incremental CPET, lung function, BIA, hand-grip strength and anthropometric measurements. CFQ and CFQ-child questionnaire, basic needs satisfaction scale, treatment self-regulation questionnaire, perceived competence scale and health care climate questionnaire. Patients will be given their own ActiHeart and ActiSleeps and IMT training device. Patients will also measure their sputum clearance in their home as a baseline sputum clearance pre IMT training.

Visit 2/Week 1 will be 7 days later for patients to return their accelerometers. Week 1 of IMT training, participants will complete the feeling scale, arousal scale and profile of mood states questions on the IMT app. Patients will also measure their sputum clearance in their home post exercise session.

Visit 3/Week 4 will be at week 4 of the training programme and consist of the incremental CPET, BIA, handgrip strength and lung function measurements for reassessment. Participants will complete the feeling scale, arousal scale and profile of mood states questions on the IMT app and measure their sputum clearance in their home post exercise session. They will also complete basic needs satisfaction

scale, treatment self-regulation questionnaire, perceived competence scale and health care climate questionnaire.

Visit 4/week 8 of the training programme participants will complete the feeling scale, arousal scale and profile of mood states questions on the IMT app and measure their sputum clearance in their home post exercise session. Following the end of the initial 8 weeks of training, participants will be retested in; incremental CPET, lung function measurements, BIA, handgrip strength, CFQ and CFQ-child questionnaires and interview measurements for assessment. They will also complete basic needs satisfaction scale, treatment self-regulation questionnaire, perceived competence scale and health care climate questionnaire. Patients will also make the decision to either continue a top-up period of training for a further 8 week or detrain.

Visit 5/Week 16 top-up/detraining participants will return for an incremental CPET, BIA, handgrip strength and lung function measurements for reassessment. Patients will also measure their sputum clearance in their home post exercise session.

Your patient has been made aware that they are free to withdraw from the study at any point, without having to give a reason, and this will not affect their medical care or legal rights. All data generated from this study will be treated with the strictest confidentiality and will not be used for any other purpose.

Thank you for taking time to read the above information. If you have any questions regarding the study, please do not hesitate to contact us and we will discuss it further.

Your Sincerely,

Jessica McCreery, Dr Melitta McNarry, Dr Kelly Mackintosh

College of Engineering

Swansea University

[redacted]

Swansea University
Prifysgol Abertawe

Applied Sports Technology Exercise and Medicine Research Centre (A-STEM)

Sport and Health Portfolio, College of Engineering

PARTICIPANT ASSENT FORM

(Version 1.2, Date: 05/12/2013)

Project Title:

Determining physical activity levels in young cystic fibrosis patients

Contact Details:

Dr Melitta McNarry

Email: [redacted]

Telephone: [redacted]

Dr Kelly Mackintosh

[redacted]

Telephone: [redacted]

Please initial box

1. I have read and understood the information sheet for this study and have been able to ask any questions I have. ☐
2. I know that it is my choice to take part and that I am can stop doing so at any time, without giving any reason, and without any problems. ☐
3. I understand that some of the information I give may be looked at by people at Swansea University or the hospital. I am happy for these people to see my results. ☐
4. I am happy for my GP to be informed that I am doing this study ☐
5. I understand that the interviews will be recorded and that the anonymized data from these interviews will be retained. ☐
6. I agree to take part in the above study. ☐

Name of Parent/Guardian	Date	Signature
_____	_____	_____
Name of Person taking consent	Date	Signature
_____	_____	_____
Researcher	Date	Signature
_____	_____	_____

Swansea University
Prifysgol Abertawe

Applied Sports Technology Exercise and Medicine Research Centre (A-STEM)

Sport and Health Portfolio, College of Engineering

PARENT/GUARDIAN CONSENT FORM

(Version 1.2, Date: 05/12/2013)

Project Title:

Determining physical activity levels in young cystic fibrosis patients

Contact Details:

Dr Melitta McNarry

Email: [redacted]

Telephone: [redacted]

Dr Kelly Mackintosh

Email:

Telephone: [redacted]

Please initial box

1. I confirm that I have read and understood the information sheet dated 05/11/2013 (version number 1.1) for the above study and have had the opportunity to ask questions. ☐

2. I understand that my child's participation is voluntary and that they are free to withdraw at any time, without giving any reason and without their medical care, school work or legal rights being affected. ☐

3. I understand that sections of any of data obtained may be looked at by responsible individuals from the Swansea University or from regulatory authorities where it is relevant to my child taking part in research. I give permission for these individuals to have access to these records. ☐

4. I am happy for my child's GP to be informed of their participation in this ☐

study.

5. I understand that the interviews will be recorded and that the anonymized data from these interviews will be retained. ☐

6. I agree for my child to take part in the above study. ☐

Name of Parent/Guardian	Date	Signature
_____	_____	_____
Name of Person taking consent	Date	Signature
_____	_____	_____
Researcher	Date	Signature
_____	_____	_____

Applied Sports Technology Exercise and Medicine Research Centre (A-STEM)

Sport and Health Portfolio, College of Engineering

ADOLESCENT ASSENT FORM

(Version 1.2; Date – 05/02/2019)

Project Title:

Investigating the influence of an Inspiratory Muscle Training program on lung function and quality of life in children and adults with Cystic Fibrosis and non-CF Bronchiectasis .

Contact Details:

Jessica McCreery

[redacted]

[redacted]

Dr Melitta McNarry

Email: [redacted]

Telephone: [redacted]

Dr Kelly Mackintosh

Email:

Telephone: [redacted]

Please Initial Box

1. I have read and understood the information sheet for this study and have been able to ask any questions I have ☐
2. I know that it is my choice to take part and that I can stop doing so at any time, without giving any reason, and without any problems. ☐
3. I understand that some of the information I give may be looked at by ☐

people at Swansea University or the hospital. I am happy for these people to see my results

4. I am happy for my GP to be informed that I am doing this study. ☐

5. I agree to take part in the above study, ☐

Name of Parent/Guardian	Date	Signature
_____	_____	_____
Name of Person taking consent	Date	Signature
_____	_____	_____
Researcher	Date	Signature
_____	_____	_____

Applied Sports Technology Exercise and Medicine Research Centre (A-STEM)

Sport and Health Portfolio, College of Engineering

PARENT/GUARDIAN CONSENT FORM

(Version 1.2; Date – 05/02/2019)

Project Title:

Investigating the influence of an Inspiratory Muscle Training program on lung function and quality of life in children and adults with Cystic Fibrosis and non-CF Bronchiectasis.

Contact Details:

Jessica McCreery

[redacted]

[redacted]

Dr Melitta McNarry

Email: [redacted]

Telephone: [redacted]

Dr Kelly Mackintosh

Email:

Telephone: [redacted]

Please Initial Box

1. I confirm I have read and understood the information sheet Dated 28/03/2016 (Version 1) for the above study and had the opportunity to ask questions. ☐

2. I understand that my child's participation is voluntary and that they are free to withdraw at any time, without giving reason and without their medical care, school work or legal rights being affected. ☐

3. I understand that sections of any data obtained may be looked at by Responsible individuals from Swansea University or from regulating Authorities where it is relevant to my child taking part in research. I Give permission for these individuals to have access to these records. ☐

4. I am happy for my child's GP to be informed of their participation in this Study. ☐

5. I agree for my child to take part in the above study, ☐

Name of Parent/Guardian	Date	Signature
_____	_____	_____
Name of Person taking consent	Date	Signature
_____	_____	_____
Researcher	Date	Signature
_____	_____	_____

ADULT CONSENT FORM

(Version 1.2; Date – 05/02/2019)

Project Title:

Investigating the influence of an Inspiratory Muscle Training program on lung function and quality of life in children and adults with Cystic Fibrosis and non-CF Bronchiectasis.

Contact Details:

Jessica McCreery

[redacted]

Dr Melitta McNarry

Email: [redacted]

Telephone: [redacted]

Dr Kelly Mackintosh

Email:

[redacted]

Please Initial Box

6. I confirm I have read and understood the information sheet Dated 28/03/2016 (Version 1) for the above study and had the opportunity to ask questions. ☐

7. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving reason and without my medical care, work or legal rights being affected. ☐

8. I understand that sections of any data obtained may be looked at by Responsible individuals from Swansea University or from regulating ☐

authorities where it is relevant to my involvement in research. I give permission for these individuals to have access to these records.

9. I am happy for my GP to be informed of my participation in this Study. ☐

10. I agree to take part in the above study, ☐

Name of Parent/Guardian	Date	Signature
_____	_____	_____
Name of Person taking consent	Date	Signature
_____	_____	_____
Researcher	Date	Signature
_____	_____	_____

Appendix B

Questionnaires and Interview Questions

Treatment Self-Regulation Questionnaire - Adults

TSRQ (exercise/modified for IMT) The following question relates to the reasons why you would start to complete IMT regularly or continue to do so. Different people have different reasons for doing that, and we want to know how true each of the following reasons is for you. All 15 response are to the one question.

Please indicate the extent to which each reason is true for you, using the following 7-point scale:

1 2 3 4 5 6 7

not at all true — somewhat true — very true

The reason I would complete IMT regularly is:	Likert Scale Number
Because I feel that I want to take responsibility for my own health.	
Because I would feel guilty or ashamed of myself if I did not complete the IMT regularly.	
Because I personally believe it is the best thing for my health.	
Because others would be upset with me if I did not.	
I really don't think about it.	
Because I have carefully thought about it and believe it is very important for many aspects of my life.	
Because I would feel bad about myself if I did not complete IMT regularly.	
Because it is an important choice I really want to make.	

Because I feel pressure from others to do so.	
Because it is easier to do what I am told than think about it.	
Because it is consistent with my life goals.	
Because I want others to approve of me.	
Because it is very important for being as healthy as possible.	
Because I want others to see I can do it.	
I don't really know why.	

Perceived Competence - Adults

Perceived Competence (Exercising Regularly/Modified for IMT) Please indicate the extent to which each statement is true for you, assuming that you were intending either to begin now a permanent regimen of exercising regularly or to permanently maintain your regular exercise regimen.

In answering the questions, please use the following scale:

1 2 3 4 5 6 7

not at all true — somewhat true — very true

Question:	Likert Scale Number
I feel confident in my ability to complete IMT regularly.	
I now feel capable of completing IMT regularly.	
I am able to complete IMT regularly over the long term.	
I am able to meet the challenge of completing IMT regularly.	

BREQ - Physical activity among school age children.

Why are you active?

Boys and girls can be **active** by doing all sorts of things:

- Exercise (walking, keep fit, gym)
- Playing out, doing active things (like playing in the park)
- Sports (like football, tennis, netball, swimming)

The following pages have some reasons why you might be active.

Please Highlight the Relevant Box

I am active because...						
1.	being active is fun	Not true for me	Not really true for me	Sometimes true for me	Often true for me	Very true for me
2.	it is important to me to do active things	Not true for me	Not really true for me	Sometimes true for me	Often true for me	Very true for me
3.	when I'm not active I feel bad	Not true for me	Not really true for me	Sometimes true for me	Often true for me	Very true for me
4.	other people say I should be	Not true for me	Not really true for me	Sometimes true for me	Often true for me	Very true for me
5.	I enjoy being active	Not true for me	Not really true for me	Sometimes true for me	Often true for me	Very true for me
6.	I value the benefits of being active	Not true for me	Not really true for me	Sometimes true for me	Often true for me	Very true for me
7.	when I don't do activity I feel bad about myself	Not true for me	Not really true for me	Sometimes true for me	Often true for me	Very true for me
8.	if I'm not, other people will not be pleased with me	Not true for me	Not really true for me	Sometimes true for me	Often true for me	Very true for me
9.	I like being active	Not true for me	Not really true for me	Sometimes true for me	Often true for me	Very true for me

10.	in life it is important to be active	Not true for me	Not really true for me	Sometimes true for me	Often true for me	Very true for me
11.	I want to show other people how good I am	Not true for me	Not really true for me	Sometimes true for me	Often true for me	Very true for me
12.	other people pressure me to be active	Not true for me	Not really true for me	Sometimes true for me	Often true for me	Very true for me

The next section has some sentences describing how people feel about BEING ACTIVE and DOING ACTIVE THINGS (like active games, playing out and doing sports). Please read each sentence and tell us how like you each one is.

15.	I can decide which activities and sports I want to do.	Not like me at all	Not really like me	Sometimes like me	Quite a lot like me	Really like me
16.	I have a say in what activities and sports that I want to do	Not like me at all	Not really like me	Sometimes like me	Quite a lot like me	Really like me
17.	I feel I am active because I want to be	Not like me at all	Not really like me	Sometimes like me	Quite a lot like me	Really like me
18.	I have to force myself to be active	Not like me at all	Not really like me	Sometimes like me	Quite a lot like me	Really like me
19.	I feel free when I'm active	Not like me at all	Not really like me	Sometimes like me	Quite a lot like me	Really like me
20.	I have some choice in what activity and sport I want to do	Not like me at all	Not really like me	Sometimes like me	Quite a lot like me	Really like me
21.	When it comes to playing active games, I think I am pretty good.	Not like me at all	Not really like me	Sometimes like me	Quite a lot like me	Really like me
22.	I think I do well compared to other children	Not like me at all	Not really like me	Sometimes like me	Quite a lot like me	Really like me
23.	After working at a new activity for a while, I feel that I can do it pretty well.	Not like me at all	Not really like me	Sometimes like me	Quite a lot like me	Really like me
24.	I am happy with how good I am at doing active games.	Not like me at all	Not really like me	Sometimes like me	Quite a lot like me	Really like me
25.	When it comes to being active, I have good skills.	Not like me at all	Not really like me	Sometimes like me	Quite a lot like me	Really like me

26.	I can't do physical activities very well.	Not like me at all	Not really like me	Sometimes like me	Quite a lot like me	Really like me

27.	I am included by others in active games/sports	Not like me at all	Not really like me	Sometimes like me	Quite a lot like me	Really like me
28.	I feel like I am part of a team	Not like me at all	Not really like me	Sometimes like me	Quite a lot like me	Really like me
29.	I am supported by others	Not like me at all	Not really like me	Sometimes like me	Quite a lot like me	Really like me
30.	Other children want me to be active with them	Not like me at all	Not really like me	Sometimes like me	Quite a lot like me	Really like me
31.	I have close bonds with others	Not like me at all	Not really like me	Sometimes like me	Quite a lot like me	Really like me
32.	I fit in well with others	Not like me at all	Not really like me	Sometimes like me	Quite a lot like me	Really like me

Perceived Competence

Perceived Competence (Exercising Regularly/Modified for IMT) Please indicate the extent to which each statement is true for you, assuming that you were intending either to begin now a permanent regimen of exercising regularly or to permanently maintain your regular exercise regimen.

In answering the questions, please use the following scale:

1 2 3 4 5 6 7

not at all true | somewhat true | very true

Question	Likert Scale Number
I feel confident in my ability to complete IMT regularly.	
I now feel able to complete IMT regularly.	
I am able to complete IMT regularly over the long term.	
I am able to meet the challenge of completing IMT regularly.	

Cystic Fibrosis Questionnaire Revised – Children Ages 6 to 11 (Interviewer Format)

This questionnaire is formatted for use by an interviewer. Please use this format for younger children. For older children who seem able to read and answer the questions on their own, such as 12 and 13 year olds, use this questionnaire in its self-report format.

There are directions for the interviewer for each section of the questionnaire. Directions that you should *read* to the child are indicated by quotation marks. Directions that you are to *follow* are underlined and set in italics.

Interviewer: *Please ask the following questions*

A. What is your date of birth?

Date | | | | | | | | |

Day Month Year

B. Are you?

☐ Male ☐ Female

C. During the **past two weeks**, have you been on holiday or out of school for reasons **NOT** related to your health?

☐ Yes ☐ No

D. Which of the following best describes your racial background?

- ☐ White - UK
- ☐ White - other
- ☐ Indian/ Pakistani
- ☐ Chinese/ Asian
- ☐ African
- ☐ Caribbean
- ☐ Other [not represented above or people whose predominant origin cannot be determined/ mixed race]
- ☐ Prefer not to answer this question

What year are you in now at school?

(If summer, year you just finished)

- ☐ Reception
- ☐ Year 1
- ☐ Year 2
- ☐ Year 3
- ☐ Year 4
- ☐ Year 5
- ☐ Year 6
- ☐ Year 7

Interviewer: *Please read the following to the child:* "These questions are for children like you who have cystic fibrosis. Your answers will help us understand what this disease is like and how your treatments help you. So, answering these questions will help you and others like you in the future." "For each question that I ask, choose one of the answers on the cards I'm about to show you." *Present the orange card to the child.* "Look at this card and read with me what it says: **very true, mostly true, somewhat true, not at all true**." "Here's an example: If I asked you if it is **very true, mostly true, somewhat true, not at all true** that elephants can fly, which one of the four answers on the card would you choose?" *Present the blue card to the child.* "Now, look at this card and read with me what it says: **always / often / sometimes / never**." "Here's another example: If I asked you if you go to the moon **always, often, sometimes, or never**, which answer on the card would you choose?" *Present the orange card to the child.* "Now, I will ask you some questions about your everyday life." ***"Tell me if you find the statements I read to you to be*** *very true, mostly true, somewhat true, or not at all true****."***

Please tick the box indicating the child's response.

"During the past **two weeks**":	**Very True**	**Mostly True**	**Somewhat True**	**Not a all Tru**
1. You were able to walk as fast as others	☐	☐	☐	☐
2. You were able to climb stairs as fast as others	☐	☐	☐	☐
3. You were able to run, jump, and climb as you wanted	☐	☐	☐	☐
4. You were able to run as quickly and for as long as others	☐	☐	☐	☐
5. You were able to participate in sports that you enjoy (e.g., swimming, football, dancing or others)	☐	☐	☐	☐
6. You had difficulty carrying or lifting heavy things such as books, your school bag, or a rucksack	☐	☐	☐	☐

Interviewer: *Present the blue card to the child.*

Please tick the box indicating the child's response.

"And during these past **two weeks**, tell me how often":	**Always**	**Often**	**Sometimes**	**Nev**
7. You felt tired	☐	☐	☐	☐
8. You felt mad	☐	☐	☐	☐
9. You felt grouchy	☐	☐	☐	☐
10. You felt worried	☐	☐	☐	☐
11. You felt sad	☐	☐	☐	☐
12. You had trouble falling asleep	☐	☐	☐	☐
13. You had bad dreams or nightmares	☐	☐	☐	☐
14. You felt good about yourself	☐	☐	☐	☐
15. You had trouble eating	☐	☐	☐	☐
16. You had to stop fun activities to do your treatments	☐	☐	☐	☐
17. You were forced to eat	☐	☐	☐	☐

Interviewer: *Present the orange card to the child.*

*"**Now tell me if you find the statements I read to you to be** very true, mostly true, somewhat true, **or** not at all true**."***

Please tick the box indicating the child's response.

"During the past **two weeks**":	**Very True**	**Mostly True**	**Somewhat True**	**Not all Tr**
18. You were able to do all of your treatments	☐	☐	☐	☐
19. You enjoyed eating	☐	☐	☐	☐
20. You got together with friends a lot	☐	☐	☐	☐
21. You stayed at home more than you wanted to	☐	☐	☐	☐
22. You felt comfortable sleeping away from home (at a friend or family member's house or elsewhere)	☐	☐	☐	☐

Children Ages 6 to 11 (Interviewer Format)

"During the past **two weeks**":	**Very True**	**Mostly True**	**Somewhat True**	**Not all Tı**
23. You felt left out	☐	☐	☐	☐
24. You often invited friends to your house	☐	☐	☐	☐
25. You were teased by other children	☐	☐	☐	☐
26. You felt comfortable discussing your illness with others (friends, teachers)	☐	☐	☐	☐
27. You thought you were too short	☐	☐	☐	☐
28. You thought you were too thin	☐	☐	☐	☐
29. You thought you were physically different from others your age .	☐	☐	☐	☐
30. Doing your treatments bothered you	☐	☐	☐	☐

Interviewer: *Present the blue card to the child again*

Please tick the box indicating the child's response.

"Tell me how often in the past **two weeks**":	**Always**	**Often**	**Sometimes**	**Nev**
31. You coughed during the day	☐	☐	☐	☐
32. You woke up during the night because you were coughing	☐	☐	☐	☐
33. You had to cough up mucus	☐	☐	☐	☐
34. You had trouble breathing	☐	☐	☐	☐
35. Your stomach hurt.....	☐	☐	☐	☐

*Please make sure **all** the questions have been answered.*

Cystic Fibrosis Questionnaire Revised – Children Ages 12 to 13 (Self Report Form)

These questions are for children like you who have cystic fibrosis. Your answers will help us understand what this disease is like and how your treatments help you. So, answering these questions will help you and others like you in the future.

Please answer all the questions. There are **no** right or wrong answers! If you are not sure how to answer, choose the response that seems closest to your situation.

A. What is your date of birth?

Date | | | | | | | | |

Day Month Year

B. Are you?

☐ Male ☐ Female

C. During the **past two weeks**, have you been on holiday or out of school for reasons **NOT** related to your health?

☐ Yes ☐ No

D. Which of the following best describes your racial background?

- ☐ White - UK
- ☐ White - other
- ☐ Indian/ Pakistani
- ☐ Chinese/ Asian
- ☐ African
- ☐ Caribbean
- ☐ Other [not represented above or people whose predominant origin cannot be determined/ mixed race]
- ☐ Prefer not to answer this question

E.What year are you now in school?

- ☐ Not in school
- ☐ Year 6
- ☐ Year 7
- ☐ Year 8

- ☐ Year 9
- ☐ Year 10
- ☐ Year 11

Please tick the box matching your response.

In the past **two weeks**:

	Very True	**Mostly True**	**Somewhat True**	**Not a all Tru**
1. You were able to walk as fast as others	☐	☐	☐	☐
2. You were able to climb stairs as fast as others	☐	☐	☐	☐
3. You were able to run, jump, and climb as you wanted	☐	☐	☐	☐
4. You were able to run as quickly and for as long as others	☐	☐	☐	☐
5. You were able to participate in sports that you enjoy (e.g., swimming, football, dancing or others)	☐	☐	☐	☐
6. You had difficulty carrying or lifting heavy things such as books, your school bag, or a rucksack	☐	☐	☐	☐

Please tick the box matching your response.

And during these past **two weeks**, indicate how often:

	Always	**Often**	**Sometimes**	**Nev**
7. You felt tired	☐	☐	☐	☐
8. You felt mad	☐	☐	☐	☐
9. You felt grouchy	☐	☐	☐	☐

10. You felt worried	☐	☐	☐	☐
11. You felt sad	☐	☐	☐	☐
12. You had trouble falling asleep	☐	☐	☐	☐
13. You had bad dreams or nightmares	☐	☐	☐	☐
14. You felt good about yourself	☐	☐	☐	☐
15. You had trouble eating	☐	☐	☐	☐

Please tick the box matching your response.

And during these past **two weeks**, indicate how often:

	Always	**Often**	**Sometimes**	**Never**
16. You had to stop fun activities to do your treatments	☐	☐	☐	☐
17. You were forced to eat	☐	☐	☐	☐

Please tick the box matching your response.

During the past **two weeks**:	**Very True**	**Mostly True**	**Somewhat True**	**Not at all True**
18. You were able to do all of your treatments	☐	☐	☐	☐
19. You enjoyed eating	☐	☐	☐	☐
20. You got together with friends a lot	☐	☐	☐	☐
21. You stayed at home more than you wanted to	☐	☐	☐	☐
22. You felt comfortable sleeping away from home (at a friend or family member's house or elsewhere)	☐	☐	☐	☐
23. You felt left out	☐	☐	☐	☐

24. You often invited friends to your house	☐	☐	☐	☐
25. You were teased by other children	☐	☐	☐	☐
26. You felt comfortable discussing your illness with others (friends, teachers)	☐	☐	☐	☐
27. You thought you were too short	☐	☐	☐	☐
28. You thought you were too thin	☐	☐	☐	☐
29. You thought you were physically different from others your age	☐	☐	☐	☐
30. Doing your treatments bothered you	☐	☐	☐	☐

Please tick the box matching your response.

Let us know how often in the past **two weeks**:	**Always**	**Often**	**Sometimes**	**Never**
31. You coughed during the day	☐	☐	☐	☐
32. You woke up during the night because you were coughing	☐	☐	☐	☐
33. You had to cough up mucus	☐	☐	☐	☐
34. You had trouble breathing	☐	☐	☐	☐
35. Your stomach hurt	☐	☐	☐	☐

Please make sure all the questions have been answered.

Cystic Fibrosis Questionnaire Revised – Adolescents and Adults (Patients 14 Years Old and Older)

Understanding the impact of your illness and treatments on your everyday life can help your healthcare team keep track of your health and adjust your treatments. For this reason, this questionnaire was specifically developed for people who have cystic fibrosis. Thank you for your willingness to complete this form.

Instructions: The following questions are about the current state of your health, as you perceive it. This information will allow us to better understand how you feel in your everyday life.

Please answer all the questions. There are **no** right or wrong answers! If you are not sure how to answer, choose the response that seems closest to your situation.

A. What is your date of birth?

Date | | | | | | | | | |

Day Month Year

B. What is your gender?

- ☐ Male ☐ Female

C. During the **past two weeks**, have you been on holiday or out of school or work for reasons **NOT** related to your health?

- ☐ Yes ☐ No

D. What is your current marital status?

- ☐ Single/never married
- ☐ Married
- ☐ Widowed
- ☐ Divorced
- ☐ Separated
- ☐ Remarried
- ☐ With a partner

E. Which of the following best describes your racial background?

- ☐ White - UK
- ☐ White - other
- ☐ Indian/ Pakistani
- ☐ Chinese/ Asian
- ☐ African
- ☐ Caribbean
- ☐ Other [not represented above or people whose predominant origin cannot be determined/ mixed race]
- ☐ Prefer not to answer this question

F. What is the highest level of education you have completed?

- ☐ Some secondary school or less
- ☐ GCSEs/ O-levels
- ☐ A/AS-levels
- ☐ Other higher education
- ☐ University degree
- ☐ Professional qualification or post-graduate study

G. Which of the following best describes your current work or school status?

- ☐ Attending school outside the home
- ☐ Taking educational courses at home
- ☐ Seeking work
- ☐ Working full or part time (either outside the home or at a home-based business)
- ☐ Full time homemaker
- ☐ Not attending school or working due to my health
- ☐ Not working for other reasons

Section II. Quality of Life

Please tick the box indicating your answer.

*During the past **two weeks**, to what extent have you had difficulty:*	**A lot of difficulty**	**Some difficulty**	**A little difficulty**	**No difficu**
1. Performing vigorous activities such as running or playing sports	☐	☐	☐	☐
2. Walking as fast as others	☐	☐	☐	☐
3. Carrying or lifting heavy things such as books, shopping, or school bags	☐	☐	☐	☐
4. Climbing one flight of stairs	☐	☐	☐	☐
5. Climbing stairs as fast as others	☐	☐	☐	☐

***During the past two weeks**, indicate how often:*	**Always**	**Often**	**Sometimes**	**Neve**
6. You felt well	☐	☐	☐	☐
7. You felt worried	☐	☐	☐	☐
8. You felt useless	☐	☐	☐	☐
9. You felt tired	☐	☐	☐	☐
10. You felt full of energy	☐	☐	☐	☐
11. You felt exhausted	☐	☐	☐	☐
12. You felt sad	☐	☐	☐	☐

*Thinking about the state of your health over the last **two weeks**:*

13. To what extent do you have difficulty walking?
1. You can walk a long time without getting tired
2. You can walk a long time but you get tired
3. You cannot walk a long time because you get tired quickly
4. You avoid walking whenever possible because it's too tiring for you

14. How do you feel about eating?
1. Just thinking about food makes you feel sick
2. You never enjoy eating
3. You are sometimes able to enjoy eating
4. You are always able to enjoy eating

15. To what extent do your treatments make your daily life more difficult?
1. Not at all
2. A little
3. Moderately
4. A lot

16. How much time do you currently spend each day on your treatments?
1. A lot
2. Some
3. A little
4. Not very much

17. How difficult is it for you to do your treatments (including medications) each day?
a. Not at all
b. A little
c. Moderately
d. Very

18. How do you think your health is now?
a. Excellent
b. Good
c. Fair
d. Poor

Please select a box indicating your answer.

*Thinking about your health during the past **two weeks**, indicate the extent to which each sentence is true or false for you.*	**Very true**	**Somewhat true**	**Somewhat false**	**Very false**
19. I have trouble recovering after physical effort	☐	☐	☐	☐
20. I have to limit vigorous activities such as running or playing sports	☐	☐	☐	☐
21. I have to force myself to eat	☐	☐	☐	☐
22. I have to stay at home more than I want to	☐	☐	☐	☐
23. I feel comfortable discussing my illness with others	☐	☐	☐	☐
24. I think I am too thin	☐	☐	☐	☐
25. I think I look different from others my age	☐	☐	☐	☐
26. I feel bad about my physical appearance	☐	☐	☐	☐
27. People are afraid that I may be contagious	☐	☐	☐	☐
28. I get together with my friends a lot	☐	☐	☐	☐
29. I think my coughing bothers others	☐	☐	☐	☐
30. I feel comfortable going out at night	☐	☐	☐	☐
31. I often feel lonely	☐	☐	☐	☐
32. I feel healthy	☐	☐	☐	☐
33. It is difficult to make plans for the future (for example, going to college, getting married, getting promoted at work, etc.)	☐	☐	☐	☐
34. I lead a normal life	☐	☐	☐	☐

Section III. School, Work, or Daily Activities

Questions 35 to 38 are about school, work, or other daily tasks.

35. To what extent did you have trouble keeping up with your schoolwork, professional work, or other daily activities during the past **two weeks**?

1. You have had no trouble keeping up
2. You have managed to keep up but it's been difficult
3. You have been behind
4. You have not been able to do these activities at all

36. How often were you absent from school, work, or unable to complete daily activities during the last two weeks because of your illness or treatments?

☐ Always ☐ Often ☐ Sometimes ☐ Never

37. How often does CF get in the way of meeting your school, work, or personal goals?

☐ Always ☐ Often ☐ Sometimes ☐ Never

38. How often does CF interfere with getting out of the house to run errands such as shopping or going to the bank?

☐ Always ☐ Often ☐ Sometimes ☐ Never

Section IV. Symptom Difficulties

Please select a box indicating your answer.

*Indicate how you have been feeling during the past **two weeks**.*	**A great deal**	**Somewhat**	**A little**	**Not at all**
39. Have you had trouble gaining weight?	☐	☐	☐	☐
40. Have you been congested?	☐	☐	☐	☐
41. Have you been coughing during the day?	☐	☐	☐	☐
42. Have you had to cough up mucus? ☐		☐	☐	☐ **Go to Question**

44 43. Has your mucus been mostly: ☐ Clear ☐ Clear to yellow ☐ Yellowish-green ☐ Green with traces of blood ☐ Don't know

*How often during the past **two weeks:***	**Always**	**Often**	**Sometimes**	**Never**
44. Have you been wheezing?	☐	☐	☐	☐
45. Have you had trouble breathing?	☐	☐	☐	☐
46. Have you woken up during the night because you were coughing?	☐	☐	☐	☐
47. Have you had problems with wind?	☐	☐	☐	☐
48. Have you had diarrhoea?	☐	☐	☐	☐
49. Have you had abdominal pain?	☐	☐	☐	☐
50. Have you had eating problems?	☐	☐	☐	☐

Please make sure you have answered all the questions.

Applied Sports Technology Exercise and Medicine Research Centre (A-STEM)

Sport and Health Portfolio, College of Engineering

Interview Questions – Study 3

Version 1.1

Thank you for agreeing to talk to me. Today we are going to have a chat about your thoughts and feelings on completing the four week programme with the Powerbreathe training device (show device). In this interview remember, there is no right or wrong answer and if you are confused or don't understand the question just let me know. I have a terrible memory so I am going to record our interview so I can listen to it again later. Are you happy to go ahead?

1. **What do you think physical activity is?**
   Follow-Up – What are your thoughts about doing that physical activity/exercise?

   Can you talk me through how much exercise you do weekly? (before School, after school, P.E. classes, weekends, clubs, how they get to school)
   What do you like/not like about doing exercise?

   Think back to when you're (insert example they have previously listed above), how do you feel during and after it?
   Both physically and mentally

2. **What do you think this is (show training device)?**
   Follow-Up – Can you tell me how it works?
   How did you find using the device?

   Where did you use it? (What did you like/dislike about using it there?) Places

   What did you like/not like about using the device?

3. **How did you feel before starting your 30 breaths? How did it make you feel in the middle? How did you feel at the end of your 30 breaths?**
   Follow-Up – How did your lungs feel during the training?

   How did you feel after finishing the exercise?

How did your lungs feel after finishing the 4 weeks of training?

4. **Now I'm going to ask you about the training programme. Describe to me the steps you went through to complete the training programme?**
   Follow-Up – Describe to me when in your day you completed your training?
   What made it easy/difficult to do the training programme?
   What changes, if any, did you notice if you didn't do, the training?
   How did you find the length of the training programme?
   If you could suggest something to change, what would it be?

5. **Can you describe to me how you feel the Powerbreathe has changed how you are able to exercise?**
   Follow –Up – How has the training programme effected your daily life?

6. **What are your opinions on exercise now you have finished the programme?**
   Follow-Up – How do you think the physical activity you do now has changed compared to/is different to before the programme?
   When training was completed after 4 weeks, how did this make you feel?

7. **Overall, what did you think of the training programme?**
   Follow-Up – How do you think you'd react if you were asked to do this training programme again?

8. **Any other comments?**

Applied Sports Technology Exercise and Medicine Research Centre (A-STEM)

Sport and Health Portfolio, College of Engineering

Interview Questions

25/05/2016 – Version 1.2 Study 4 & 5

N.B. child version in orange

Pre-Intervention

*What are your opinions on doing physical activity/exercise?

*Do you enjoy doing physical activity – why/why not?

*Do you enjoy exercise – why/why not?

(Physical Activity – anybody movement that works your muscles and requires more energy than resting (i.e. housework, dog walking, swimming, dancing)

(Exercise – planned, structured and repetitive with the objective of improving or maintaining fitness (i.e. gym work, cycling, running)

*What do you think about doing physical activity/exercise?

*What do you like about doing physical activity/exercise?

*What do you dislike about doing physical activity/exercise?

*Why do you/do you not exercise?

*What encourages you to exercise?

*What prevents you from exercising?

*Is exercising important to you?

*Why/Why not?

*How much physical activity do you do in a week? (active job?)

* Broken down to - Before school, during school, P.E. lessons, after school, weekends, clubs?

*Think back to when you're (insert example they have previously listed above), how do you feel during it?

*How do you feel before it? Why?

*How do you feel after it? Why?

*Is this always the same? Different? Why?

During the Intervention

< IMT Device and App >

*How did you find setting up the device with the app?

*Did you do this on your own, or did you have help?

*What are your opinions on the app?

*How did you find using the app (easy/hard)?

*What are your opinions on the design/layout?

*What did you like/dislike about the colours and graphs on the app?

*What do you think about the feedback that the app provided?

*How well did you understand the information you got?

*How useful did you find it?

*How did it make you feel?

*How did it make you behave?

<IMT Device>

*What are your opinions on the IMT device

*What did you like about using it? Why?

*What did you dislike about using it? Why?

*How did you find its usability?

*How did you find using it, was it easy/hard? Why?

*Where did you use it?

*What did you like about using it there?

*What did you dislike about using it there?

* What are your pros and cons of using it?

<Exercise Programme>

*How did you feel (physically, emotionally, mentally) before you began the training?

*How did you feel (body, describe feelings, what were you thinking) before you began training

*How did you feel (physically, emotionally, mentally) during the training?

*How did you feel (body, describe feelings, what were you thinking) during the training?

*How did you feel (physically, emotionally, mentally) finishing the exercise session?

* How did you feel (body, describe feelings, what were you thinking) finishing the

exercise?

*Was it all of the exercise programme/ Just part of it/ which part?

* Was there any changes in these feelings across time/ across the exercise? Why?

*How did your lungs feel after finishing the 8 weeks of training, compared to the first week?

*What was the highest level you got to?

*What did you think about the different levels? Why?

*What did you think about the decreasing rest times?

* How did you react? How did they make you feel? – Were there any changes?

*When did you complete your training?

*What made it easy/difficult to do the training?

*What changes, if any, did you notice if you didn't do the training? Good? Bad? Why?

*How did you find the length of the exercise session?

<Top Up>

*Why did you decide to continue training?

More effect further tests effect

*Did anyone influence your decision to continue?

*What did they say/do that influenced you?

*What changes (physically) if any, did you notice when training decreased to once a week?

*What changes, if any, did you observe from ending the first 8 weeks to the end of the top-up period?

<Detraining>

*Why did you decide to stop training?

*Did anyone influence your decision to stop?

*What they say/do that influence you?

*What changes (physically), if any, did you notice from the end of the 8 week of training to the 8 weeks of no training?

*If you were given the option again, would you take the top-up period or would you stick with the detraining? Why?

Post Intervention Reflections and Recommendations

< Intervention >

*What changes, if any, would you make to the design/layout of the app. Why?

*What other feedback, if any, would you like to receive?

*What changes, if any, would you make to the IMT device? Why?

*What changes, if any, would you make to the IMT programme? Why?

*What would have made you complete more of the exercise sessions? (If adherence was poor). What were the specific reasons for not completing the exercise on those days?

*What would have made you do more training?

*How has the training changed the way you are able to exercise? In what way?

*How the training effected your daily life? If so, can you explain how?

*What are your opinions on the exercise now you have finished the programme?

*Has the amount of exercise you do now changed compared to before the programme? In what way. Why? If not any reason?

*How did you feel when training was completed? Why?

*How would you feel if you were asked to do this training programme again?

*Would you like IMT to integrated into your treatment regime and why?

*Would you like to continue doing more IMT and why?

*Do you have any other comments or suggestions about the programme?

Appendix C

Physical Activity and Sleep Logs

Physical Activity Log - Child

Activity – Tell us what type of activity you did on that day e.g. walking the dog, PE lesson, football practice.

Length – Tell us how long you spent doing the activity e.g. 30 minutes

Monitor – If you had to remove your monitor for anything e.g. water based activities, contact sports, please record how long you had your monitor off for.

Sleep - Tell us time you went to bed, time you woke up and how long you slept for

*Don't forget to fill it in everyday and every week *

Please Return Monitors To:
Jessica McCreery
Swansea University Bay Campus

School of Sport and Exercise Science
A-STEM Hub
Fabien Way
Swansea

SA1 8EN

	Mon	Tue	Wed	Thur	Fri	Sat	Sun
Week 1 Activity (Type, how long for)							

Monitor Removal (Why? How long For?							

Sleep Log - Child (Week 1 Only)

	Mon	Tues	Wed	Thur	Fri	Sat	Sun
Last night I went to bed at…							
I woke up this morning at…							
I slept for _ hours							

Physical Activity Log - Adults

Activity – Tell us what type of activity you did on that day e.g. walking the dog, gym work (strength, cardio) football practice.

Length – Tell us how long you spent doing the activity e.g. 30 minutes

Monitor – If you had to remove your monitor for anything e.g. water-based activities, contact sports, please record how long you had your monitor off for.

Sleep - Tell us time you went to bed, time you woke up and how long you slept for

*Don't forget to fill it in everyday and every week *

Please Return Monitors To:
Jessica McCreery
Swansea University Bay Campus

School of Sport and Exercise Science
A-STEM Hub
Fabien Way
Swansea

SA1 8EN

Swansea University
Prifysgol Abertawe

	Mon	Tue	Wed	Thur	Fri	Sat	Sun
Week 1 Activity (Type, how long for)							

Monitor Removal (Why? How long For?							

Sleep Log-Adults (Week 1 Only)

	Mon	Tues	Wed	Thur	Fri	Sat	Sun
Last night I went to bed at…							
I woke up this morning at…							
I slept for _ hours							