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THE EFFECT OF THERAPEUTIC AND NON-THERAPEUTIC INTERVENTIONS ON THE HEALTH TRAJECTORY OF INDIVIDUALS WITH CYSTIC FIBROSIS

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“**YOU MAY HAVE INVADED MY MIND, AND MY BODY, BUT THERE’S ONE THING A SAIYAN ALWAYS KEEPS… HIS PRIDE.”**

- Vegeta

ABSTRACT

Cystic fibrosis (CF) is a lethal autosomal recessive disease caused by mutation in the cystic fibrosis transmembrane conductance regulator (CFTR), resulting in a build-up of viscous mucus and multi-organ dysfunction. Advances in treatment have decreased the burden of CF and increased survival age. However, clinicians and researchers must continue to look for areas that contribute to improved quantity and quality of life for individuals with CF.

The aim of this thesis was to explore the effects of nutritional status, aerobic capacity, and modulator therapy on clinical outcomes within CF patients. Study 1 demonstrated the minimal effective dose of exercise needed to elicit change in aerobic capacity. Safety and efficacy of this protocol was evidenced with increases in aerobic capacity akin to that seen in the general population. Study 2 observed the longitudinal effect nutritional status had on pulmonary function. Female pulmonary function evidenced an increased sensitivity to change in body mass index when compared to males. Study 3 evaluated the lived experience of CFTR treatment, highlighting despite clinically relevant benefits, benefits do not come in the absence of negative physical and psychological challenges. Study 4 demonstrated increased incidence of overweight/obesity following implementation of CFTR treatment

Introduction of CFTR treatment has rapidly changed the outlook of CF care. As landscape of the disease changes there is a need to adapt to new individual needs in what is a familiar disease with a new face. Whilst diet and exercise represented significant cornerstones of care in the past 30 years, as disease burden decreases, there is a need to view diet and exercise as means of enhancing physical and psychological health, rather than tools to manage the symptoms of the disease. Whilst this thesis is unable to quantify the effect of CFTR therapy on health, the future has never looked brighter for CF patients.

DECLERATIONS AND STATEMENTS

This work has not previously been accepted in substance for any degree and is not being concurrently submitted in candidature for any degree.

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Date: 30/03/2022

This thesis is the result of my own investigations, except where otherwise stated. Other sources are acknowledged by footnotes giving explicit references. A bibliography is appended.

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DEDICATION

I would like to dedicate this thesis to the person who brought me this far:

To the boy who wasn't supposed to live past 25

To the boy who they said would never be able to keep up

To the boy they said 'oh you don't look sick'

To the boy who hid the real him from even those closest

To the boy they took sympathy on

To the boy who got awards because he 'shouldn't be able to do what he can'

To the boy who fell asleep in class

To the boy they considered lazy

To the boy who coughed up blood of an evening

To the boy who was sick in the shower every morning

To the boy who did over 4 hours of treatment a day

To the boy who watched with his own eyes his lungs deteriorate into nothing

To the boy who cried himself to sleep at night

To the boy who lost the will to live

To the boy who shut himself off from the world

To the boy they considered a cause for concern

To the boy who never complained

To the boy who always put on a brave face

To the boy who's existence was little more than a nightmare

To the boy who still excelled when the odds were against him

To the boy with a chip on his shoulder

To the boy who wanted to prove them wrong

To the boy they did not understand

You got me this far, now is your time to rest, I will take it from here x

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ABBREVIATIONS

90% CI	90% Confidence interval
95% CI	95% Confidence interval
ASL	Airway surface liquid
ABPA	Allergic bronchopulmonary aspergillosis
BMIp	BMI percentile
BMI	Body Mass Index
CRP	C-reactive protein
CPET	Cardiopulmonary exercise test
CIS	Checklist individual strength questionnaire
Cl^-	Chloride
COPD	Chronic obstructive pulmonary disease
cAMP	Cyclic adenosine monophosphate
CF	Cystic Fibrosis
CFF	Cystic Fibrosis foundation
CFRD	Cystic Fibrosis related diabetes
CFTR	Cystic Fibrosis transmembrane regulator protein
DIOS	Distal intestinal obstruction syndrome
ELX	Elaxacaftor
ESF	European Social Fund
FFM	Fat-free mass
FEV_1	Forced expiratory volume in one second
FVC	Forced vital capacity
GET	Gas exchange threshold
GERD	Gastroesophageal reflux disease
HB	Harris-Benedict
HRQoL	Health related quality of life
HR	Heart rate
HFA	Height for age
HIIT	High-intensity interval training
IL-1	Interleukin-1

IL-10	Interleukin-10
IL-6	Interleukin-6
IV	Intravenous
IVA	Ivacaftor
KG	Kilogramme
KESS	Knowledge Economy Skills Scholarship
LUM	Lumacaftor
$\dot{V}$E	Minute ventilation
MICT	Moderate intensity continuous training
MVPA	Moderate-to-vigorous physical activity
NHS	National health service
NBS	Newborn screening
NTM	Non-tuberculous mycobacterium
NW	Normal Weight
E2	Oestradiol
OCP	Oral contraceptive pill
OW	Overweight
SpO_2	Oxygen saturation
OUES	Oxygen uptake efficiency slope
PERT	Pancreatic enzyme replacement therapy
PI	Pancreatic insufficiency
PEF	Peak expiratory flow
$\dot{V}O_{2peak}$	Peak oxygen uptake
$ppFEV_1$	Percent predicted FEV_1
PA	Physical Activity
K^+	Potassium
PSA	Pseudomonas aeruginosa
QoL	Quality of Life
RCT	Randomised controlled trial
RPD	Rate of perceived dyspnoea
RPE	Rate of perceived exertion

REHIT	Reduced exertion high intensity interval training
REC	Regional Ethics Committee
REE	Resting energy expenditure
RPM	Revolutions per minute
SACN	Scientific advisory on nutrition
Na^+	Sodium
SIT	Sprint interval training
SD	Standard deviation
TEZ	Tezacaftor
TA	Thematic Analysis
TNFα	Tumour necrosis factor alpha
UW	Underweight
UK	United Kingdom
US	United States
UHSM	University Hospital of South Manchester
$\dot{V}CO_2$	Volume of carbon dioxide output
WAP	Weight for age percentile
WFA	Weight-for-age

CHAPTER 1
INTRODUCTION

1 INTRODUCTION

1.1 Background

Cystic Fibrosis (CF) is the most common autosomal recessive disease amongst the Caucasian population. CF is caused by a mutation to the CF transmembrane regulator protein (CFTR) gene, which is responsible for the movement of chloride and sodium ions across the epithelial cell membrane in the airway, gastrointestinal system, pancreas and sweat glands (Brown, White and Tobin, 2017; Heijerman et al., 2019). Mutation in both (homozygous) or one (heterozygous) copy of the gene results in a dysfunctional, or absent, CFTR protein at the cell surface. As such, CF is characterised by impaired ion transport, a build-up of viscous mucus throughout the body (Figure 1.1) and, subsequently, multi-organ dysfunction, including airway infection and obstruction, and pancreatic insufficiency (Dalemans *et al.*, 1991; Elborn, 2016). The most common cause of death within a CF population is respiratory failure, due to progressive lung disease, accounting for 61.7% of deaths between the years 2018-2020 (Cystic Fibrosis Trust., 2020).

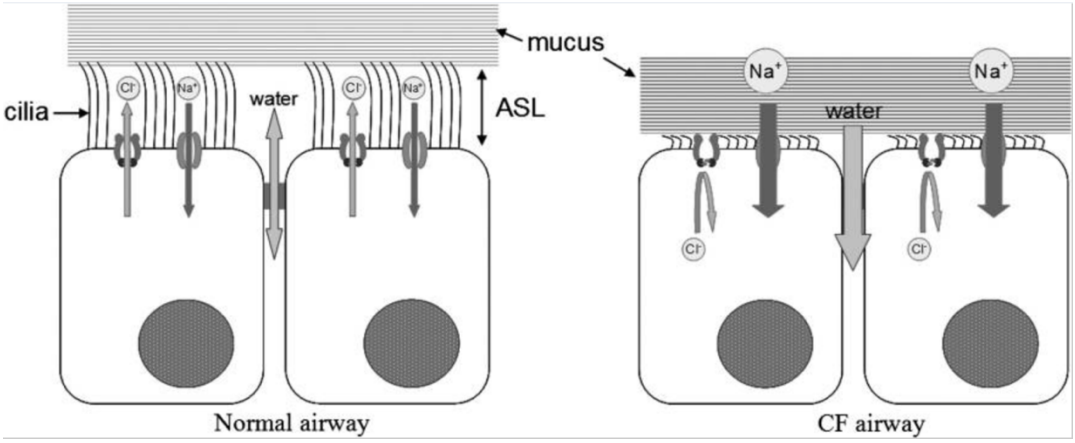


Figure 1.1. Defective chloride secretion increases the absorption of water and reduces the volume of the airway surface liquid (ASL), leading to impaired muco-ciliary clearance and increased incidence of chronic bacterial infections. Taken from Hull, (2012) with permission.

CF currently affects over 10,000 people in the United Kingdom (UK), with an incidence rate of ~1:2,500 live births (Chen, 2001; Farrell, 2008). Whilst traditionally defined as a fatal childhood disease, significant advances in clinical care mean that as of 2021 this definition is no longer considered appropriate (de Boeck, 2020; Scotet, L'hostis and Férec, 2020). When first defined in 1938 (Andersen., 1938), individuals usually died within their first year of life.

As of 2020, the mean predicted survival age is 50.6 years (Cystic Fibrosis Trust., 2020), representing a substantial improvement when compared to 8 years of age in 1974 and 29 years in 1992 (Orenstein and Higgins, 2005a). Indeed, the proportion of adult patients has more than doubled within the last 35 years, with registry data reporting 61.5% of CF patients are adults in 2018, versus 29.5% in 1984 (Scotet, L'hostis and Férec, 2020). With this growth expected to continue, it is predicted that the number of adults living with CF will increase by 75% by 2025 (Burgel *et al.*, 2015). Whilst long considered a paediatric disease, CF is rapidly becoming a disease of adulthood.

Despite well reported increases in survival, there remains a clear disparity in survival between males and females, with females considered to be at a significant disadvantage (Lam *et al.*, 2020). Indeed, reported estimated survival shows females are expected to live 7 years less than their male counterparts (Cystic Fibrosis Trust., 2020). Whilst much research focus has been placed on the effect of endogenous hormones and the subsequent effect on lung pathophysiology (Wang et al., 2010; Chotirmall et al., 2012; Harness-Brumley et al., 2014; Saint-Criq and Harvey, 2014; Sweezey and Ratjen, 2014), given the noted differences in BMI, dietary intake, and resistance to nutritional intervention between sexes (Abbott and Barber, 2010; Tierney, 2012; Stephenson et al., 2015), it is expected that variances in nutritional status will play a significant role in survival differences (Lam et al., 2020). Whilst much is known about the effects of nutritional status on health trajectories, how this differs between males and females is yet to be explored, thus making individualised nutritional prescription hard to implement within a clinical setting.

Improvements in survival irrespective of sex are multi-factorial in nature, with various breakthroughs significantly contributing to this increase in survival. Initial improvements in care involved the introduction of pancreatic enzyme replacement therapy (PERT) in combination with a high-fat, high-calorie diet in an attempt to manage malnutrition due to pancreatic insufficiency (Elborn et al., 2016). The development and advancement of both oral and nebulised antibiotic therapy, as well as the introduction of mucolytic agents, such as dornase alpha (Pulmozyme) and hypertonic saline, subsequently contributed to more effective management of the pulmonary disease (Figure 1.2; Jennings et al., 2014). More recently, the utilisation of new-born screening (NBS) has reduced the median age of diagnosis

to less than 1 month in 2020 (Cystic Fibrosis Trust., 2020), meaning that individuals gain earlier access to specialist treatment (Elborn et al., 2016).

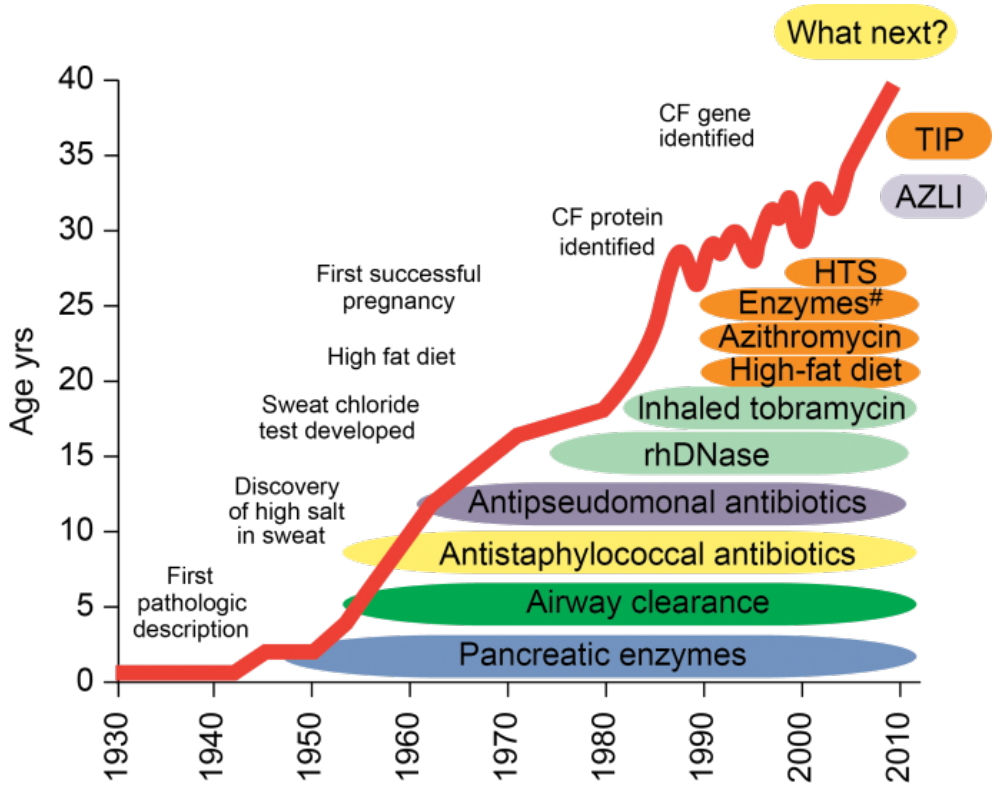


Figure 1.2 The development of treatment options for individuals with Cystic Fibrosis over the last 80 years. Taken from the Cystic Fibrosis Trust.

In the last decade, research has focused on precision therapies for individuals with CF, treating the underlying cause of the disease as opposed to the downstream complications. To date, four CFTR modulators are available for CF individuals that seek to rectify the underlying cause of the CFTR mutation (Lopes-Pacheco, 2016). These CFTR modulators are classified according to how they alter CFTR protein function, stability or trafficking. Ivacaftor (IVA), which is a potentiator, improves the CFTR channelling, ensuring the protein opens correctly and thus increases the flow of ions through the cell membrane. Tezacaftor (TEZ), Lumacaftor (LUM) and Elaxacaftor (ELX) are correctors which improve the CFTR folding and trafficking, ensuring a more mature protein reaches the cell surface (de Boeck, 2020). These therapies are mutation specific; whilst monotherapy with IVA in those with CF mutations affecting channel gating (IE. G551D) has been shown to significantly improve lung function, with an average increase in forced expiratory volume in one second (FEV_1) of 10% (Ramsey et al., 2011), the same therapy for those homozygous for F508del produced no meaningful

changes in pulmonary function. In contrast, phase 3 trials looked at combination therapy (ELX/TEZ/IVA) have evidenced a significant increase in pulmonary function for both those homozygous and heterozygous for F508del (Heijerman et al., 2019; de Boeck, 2020). Indeed, treatment with ELX/TEZ/IVA has been shown to substantially restore function to the CFTR protein, resulting in unprecented changes in sweat chloride, pulmonary function, body mass, health related quality of life and rate of exacerbation, changes which have are sustained over a significant period (Barry & Taylor-Cousar, 2021; Griese et al., 2021; Heijerman et al., 2019; Middleton et al., 2019; Ratjen et al., 2017; Taylor-Cousar et al., 2019). These collective treatments have drastically increased the predicted survival for all individuals with CF, with the introduction of modulator therapy rapidly changing the outlook for the future for those individuals eligible to take the therapy. It is pertinent to note that as of 2021, there is limited data with relation to the efficacy of treatment within everyday clinical practice. Publications with regards the effectiveness of ELX/TEZ/IVA have been completed under stringent clinical trials which led to low representativeness when considering everyday clinical practice (Gramegna et al., 2020a). Whilst these studies have evidenced the clinical usage of CFTR treatment, many questions remain as to the efficacy of this treatment when considering patients awaiting lung transplantation, receiving intravenous (IV) antibiotic therapy, recurrent haemoptysis or chronic non-tuberculous mycobacterium (NTM) infection (Gramegna et al., 2020a; Barry and Taylor-Cousar, 2021). Furthermore, it is integral to understand the key lived experience of individuals taking CFTR therapy to further inform clinical practice. Given it is not well understood how modulator treatment will affect those outside of the study populations from clinical trials, highlighting the psychological impact these changes, both positive and negative, have on an individual's mental health represents one of the many new challenges that clinical care teams must contend with.

Even with such advances in treatment, for 10% of the CF population, their CFTR mutation means such therapies will be of no effect. Further to this, it is anticipated that some patients will still suffer significantly from CF given there remains great variability in pulmonary disease progression and severity between individuals (McGarry, Williams and McColley, 2019). Aside from considerations associated with pulmonary function, it is expected that prognostic factors such as female sex, severe CFTR genotype, ethnic background, socio-economic status, lung microbiology, CF related diabetes (CFRD) and nutritional status will influence long-term

survival (Corriveau, Sykes and Stephenson, 2018). Whilst the epidemiological profile of CF continues to considerably change, there is a call for clinicians and researchers to continue to look for other areas that contribute in a significant way to overall CF health (Sweezey and Ratjen, 2014).

Within the general population, unequivocal findings demonstrate that lifestyle behaviours have an enormous impact on mortality rate, with both improving the quality of one's diet and improving the amount of physical activity and exercise, having a positive impact on all-cause mortality and overall physical and mental well-being (Haveman-Nies et al., 2002; Ford et al., 2012). Such a concept is consistent within a CF population, with nutrition, physiotherapy and exercise forming a foundation in the management of CF within a clinical setting (Villanueva *et al.*, 2017). Epidemiological studies have evidenced strong associations between poor nutritional status and less favourable clinical outcomes, such as decreased lung function (Figure 1.3) and exercise tolerance and increased morbidity and mortality (Konstan et al., 2003; Altman et al., 2019). The aetiology of malnutrition in CF individuals is multi-factorial and a combination of increased energy expenditure, energy loss (steatorrhea), inadequate energy intake and malabsorption (Wilschanski et al., 2016; van der Haak et al., 2020). Knowing that improved weight is correlated with improved pulmonary function and survival, clinical efforts have centred around achieving recommended guidelines of maintaining a body mass index (BMI) above the 50^{th} percentile for children and adolescents (Borowitz, Baker and Stallings, 2002; Borowitz et al., 2015), and above 22kg/m^2 for females and 23kg/m^2 for males (Castellani et al., 2018).

The promotion of adequate nutrition, utilising high caloric diets, supplementation with PERT and CFTR modulators has significantly reduced the prevalence of malnutrition within a CF population (Harindhanavudhi et al., 2020). However, with the introduction of CFTR modulators, comes new concerns related to increased risks of overweight and obesity. As of 2019, the US CF Foundation reported that 23.1% of CF patients were overweight and with 8.3% were obese, a doubling in the rates since 1999 (Kutney et al., 2021; Cystic Fibrosis Foundation., 2019). How long-term nutritional outcomes are impacted by CFTR modulators is currently unknown (Altman *et al.*, 2019), however, multiple phase 3 clinical trials demonstrate an increased weight versus controls (Ramsey et al., 2011; Wainwright et al.,

2015; Ratjen et al., 2017; Heijerman et al., 2019). Whilst there is currently no longitudinal evidence as to the deleterious effects of obesity within a CF population, it is likely that future nutritional management strategies may shift to a more nutrient dense, moderate energy diet as means to manage bodyweight in a post-modulator era (Engelen et al., 2014; Haak et al., 2020).

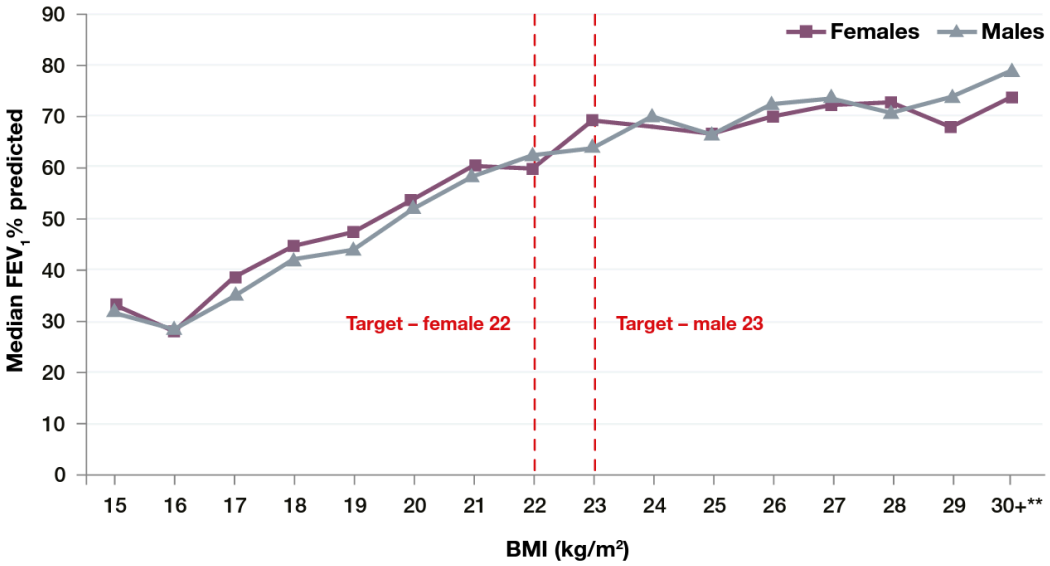


Figure 1.3 FEV_1 percent predicted values vs. BMI for adults over 20 years old in 2019. Taken from the Cystic Fibrosis Trust annual report, 2020 with permission.

As with nutritional status, exercise training is linked to numerous health benefits in individuals with CF, including increased exercise capacity, health related quality of life (HRQoL) and sputum expectoration and reduced breathlessness (Radtke et al., 2017). In addition to the benefits associated with exercise, aerobic fitness is considered a key marker of prognosis and survival in a CF population (Hebestreit et al., 2015; Nixon et al., 1992; Pianosi et al., 2005). Given that a lower aerobic capacity has been associated with increased hospitalisation (Pérez *et al.*, 2014a), a lower quality of life (Hebestreit *et al.*, 2014) and a higher 5- to 8-year mortality rate (Nixon et al., 1992), it is imperative that an individual is able to maintain aerobic fitness. Whilst CFTR therapy has had pronounced effects on many clinically relevant outcomes, limited evidence would suggest that despite large improvements in pulmonary function, aerobic capacity is still significantly reduced (Edgeworth et al., 2017; Oelberg et al., 1998; Wilson et al., 2021).

With the known benefits associated with exercise on overall health, the promotion and facilitation of appropriate, regular exercise remains a priority within the multi-disciplinary care of individuals with CF. In the dawn of CFTR treatment, given many individuals will present with a normal lung function, it is unlikely that exercise will be applied as a means to prevent or delay pulmonary disease progression (Gruet *et al.*, 2021). Indeed, with an ageing CF population, the development of new training modalities is expected to address the extra pulmonary complications associated with the ageing process (Gruet *et al.*, 2021). As noted in the general population, exercise has a significant effect in the prevention of cardiovascular disease and cancer (Lee, 2003; Lee et al., 2003), with active individuals demonstrating a 72% lower risk of premature all-cause mortality when compared to inactive peers (Ekelund *et al.*, 2019). Furthermore, given the increased incidence of overweight/obesity within a CF population, exercise prescription is likely to represent a significant tool to aid in the management of obesity related co-morbidities (Harindhanavudhi et al., 2020; Bellicha et al., 2021; Gruet et al., 2021).

Given the relative importance of exercise to maintaining overall health, understanding facilitators and barriers to regular exercise is key. Prior to the implementation of modulator therapy, many individuals felt incapable to exercise due to the deleterious effects of CF as a disease (Moola, Faulkner and Schneiderman, 2012). However, with an expected decrease in disease burden it is likely that many may look to become more active, post the implementation of CFTR therapy (Savi et al., 2019). As CFTR therapy is expected to have a varied response at an individual level, it is suggested that future exercise prescription must be individualised to facilitate adherence and the desired physiological adaptation over a long-term period. For instance, whilst aerobic exercise is regularly used as an effective modality, the recent study into the utilisation of telemedicine has highlighted a preference for high-intensity interval training (HIIT) in this population (McCrea et al., 2021). Understanding the efficacy of HIIT modalities within a CF population is therefore a timely challenge. Whilst many may have positive intention to increase physical activity with an increase in health status, it is expected that those with a previously negative interpretation of exercise may be more reluctant to engage (Gruet *et al.*, 2021). In the absence of a clearly 'optimal' exercise modality (Radtke et al., 2017) the ultimate aim must be to move towards a fully individualised training prescription, taking into consideration the effectiveness of CFTR treatment, as well as factors

such as biological and training age (Gruet *et al.*, 2021). Whilst the physiological and psychological barriers to exercise have been characterised prior to the implementation of CFTR therapy, it is imperative to understand whether these barriers remain, whether barriers to exercise now mirror those of the general population or whether new barriers to activity and exercise arise, understanding that these may vary greatly across an individual's lifespan (Denford et al., 2020; Denford, van Beurden, et al., 2020; Gruet et al., 2021).

1.2 Aims and objective of this thesis

The overall aim of this thesis is to extend the current literature with relation to therapeutic and non-therapeutic interventions in individuals with CF and their effect on clinically significant outcomes. Specifically, this thesis will:

- Chapter 2 – Provide a comprehensive literature review addressing the effect of CFTR modulator therapy and prognostic factors on an individual's health trajectory
- Chapter 3 – Provide an overview of the general methods used within the experimental chapters within this thesis
- Chapter 4 – Assess the effectiveness of the reduced exertion high intensity interval training (REHIT) protocol in an individual with CF, its effects on pulmonary function and aerobic capacity and the suitability of REHIT within this population, beyond its physiological efficacy.
- Chapter 5 – Demonstrate current trends with relation to BMI and long-term health outcomes in children and adolescents with CF according to sex.
- Chapter 6 – Explore individual, real-world, lived experience of treatment with ELX/TEZ/IVA in an adult CF population and its effects on quality of life and disease narrative
- Chapter 7 – Determine the effect of treatment with ELX/TEZ/IVA on nutritional status and whether this has a pronounced effect on the incidence of overweight/obesity within a CF population

All relevant hypothesis for experimental studies will be presented within their respective chapters. Finally, Chapter 8 will provide a summary of all research findings, with discussion around its contribution to the literature and highlighting remaining gaps in the evidence base.

CHAPTER 2
LITERATURE REVEIW

2 LITERATURE REVIEW

2.1 Pathophysiology of Cystic Fibrosis

CF is regarded as the most common and severe autosomal, recessive genetic disorder in the Caucasian population, caused by a single gene defect (Rommens *et al.*, 1990). The defective gene was localised to chromosome 7 in 1985 (Wainwright et al., 1985) and identified through genetic sequencing in 1989 (Kerem, 1989). The CF genetic defect leads to an alteration of the CFTR protein, affecting the transport of chloride, sodium and water at the apical membrane of the epithelial cell (Frizzell and Hanrahan, 2012).

To date, over 2,000 different CFTR mutations have been identified (www.genet.sickkids.on.ca), however, whether all these mutations contribute to the development of CF is still unknown. These mutations are classified according to their effect on the protein (Wang et al., 2014), with CFTR mutations classified as I-III generally considered more severe than those classified as IV-VI which retain some element of CFTR function. The more severe class I-III mutations are also typically associated with pancreatic insufficiency whereas class IV-VI are generally pancreatic sufficient (Terlizzi et al., 2017). The most common mutation is the Phe508del for which 90% of UK CF patients are homozygous (Cystic Fibrosis Trust., 2020). The missense mutations G551D and R117H represent the next largest proportion of CF individuals within the UK, accounting for 5.9% and 5.5%, respectively. ΔF508 is a class II mutation, characterised by a defective processing of the CFTR protein, whilst G551D a class III mutation characterised by defective chloride gating and R117H is a class IV mutation leading to defective channel conductance. However, there is considerable variation in the severity of lung disease even within classifications (Figure 2.1). Although the majority of individuals with CF will experience some 'classic' CF-related issues (respiratory and gastrointestinal symptoms), some mutations which retain some residual CFTR function can lead to milder symptoms or mild variant cystic fibrosis

The primary function of the CFTR protein is a cAMP-activated ion channel that transports substances across the apical membrane of the epithelial cell, maintaining the 'hydration' status of the airway surface through chloride secretion and inhibition of sodium absorption (Davies et al., 2007). Abnormalities of the CFTR channel within CF individuals alter ion transport and thus the function of the pancreas, respiratory and digestive tract, in which the

epithelial cells are largely expressed (Sheppard and Welsh, 1999). CF therefore affects multiple organs and is consequently characterised by the accumulation of viscous mucus in the lungs, malabsorption and pancreatic insufficiency leading to malnutrition, failure to thrive in infants and young children and skeletal muscle weakness (Davies et al., 2007; Troosters et al., 2009).

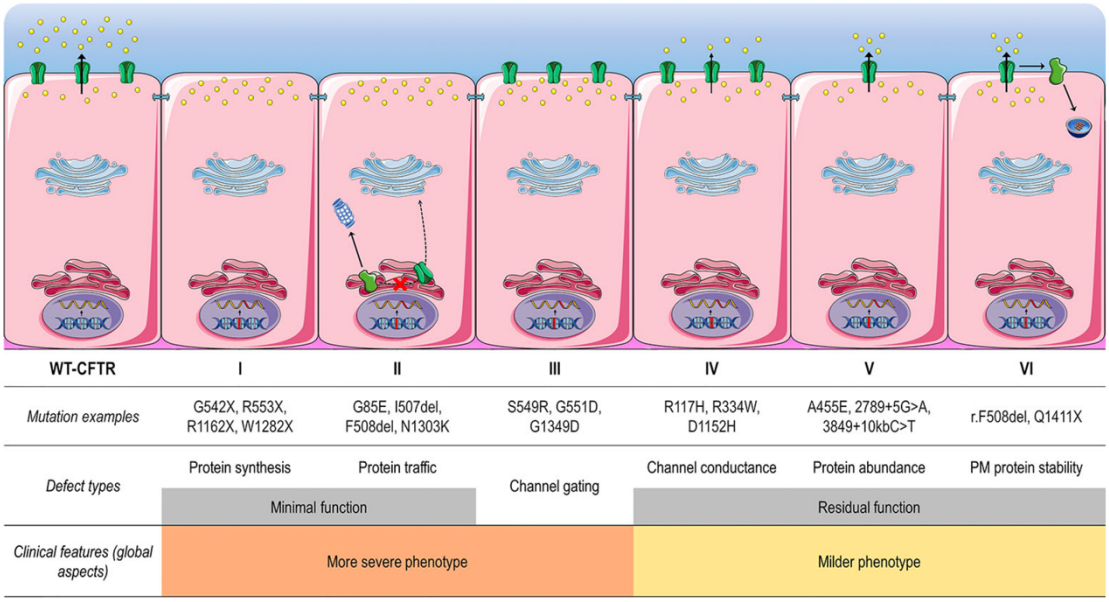


Figure 2.1. Classification of CFTR mutations. Taken from Lopes-Pacheco (2020) with permission.

Due to the abnormality of CFTR function in the lung epithelial cell, there is an alteration in the composition of the airway surface liquid (ASL). It has been hypothesised that the dysfunction in the CFTR protein produces a dehydrated airway surface, due to the over absorption of sodium (Na^+) and failure to secrete chloride (Cl^-) (Boucher, 2007). This reduced volume of ASL results in a highly viscous mucus layer, a reduced mucociliary clearance and mucus stasis (Davies et al., 2007; Matsui et al., 1998), leading to recurrent infections, inflammation, airway obstruction and, ultimately, leading to a progressive decline in pulmonary function (Cantin, 1995; Penketh et al., 1987).

Chronic inflammation, in response to persistent infection, is largely responsible for the damage of the respiratory tract in individuals with CF. The inflammatory profile of an individual with CF is characterised by persistently elevated pro-inflammatory cytokines (Interleukin-6 (IL-6), Interleukin-1 (IL-1), tumour necrosis factor alpha (TNFα)) as well as

systemic markers of inflammation such as C-reactive protein (CRP) (Ionescu *et al.*, 2002). Comparably, anti-inflammatory cytokines (Interleukin-10 (L-10)) are observed to be lower, thus further contributing to the pro-inflammatory state (Osika et al., 1999). The presence of these elevated levels of pro-inflammatory cytokines are a primary contributor towards the development of bronchiectasis. Bronchiectasis refers to the anatomical alteration of the airway, characterised by irreversible changes such as thickening, herniation or dilation of the airways (Morrissey, 2007). Bronchiectasis further compromises the impaired clearance mechanisms of the airway, resulting in mucus retention and mucus plugging. The inability to clear the airway impairs the ability to resolve respiratory tract infection, thus contributing towards a vicious cycle of persistent infection and increased inflammation leading to further structural damage and ultimately progressive pulmonary decline (Cole, 1986; Morrissey, 2007).

Whilst the main burden of the disease is primarily related to the pulmonary system, CF is a multi-system condition also affecting the pancreas, gastrointestinal tract, kidneys and the hepatobiliary system. As lung function and life expectancy increase within the CF population, it is expected that these extrapulmonary complications will increasingly contribute to morbidity and mortality within individuals with CF (Lavelle *et al.*, 2015). Indeed, 85-90% of individuals with CF are pancreatic insufficient whereby thick secretions in the pancreas cause obstruction of the ducts, leading to deficient pancreatic enzyme production and subsequent fat malabsorption (Lavelle et al., 2015; Li and Somerset, 2014). Given that individuals with CF have an increased metabolic demand to maintain homeostasis, this, coupled with intestinal malabsorption often lead to malnutrition and nutritional deficiencies due to challenges achieving adequate nutritional intake (Ratchford et al., 2018). Poor nutritional status and malnutrition are established risk factors associated with greater declines in pulmonary function and increased morbidity and mortality (Kerem et al., 2014). As such, nutritional management has conventionally focused on high-fat, high calorie diets in an attempt to maintain weight and thus a more favourable pulmonary function (Michel et al., 2009).

2.2 Predicted Survival

Individuals with CF have a reduced life expectancy compared to the general population. However, what once was considered a fatal childhood disease in the 1960's now requires

long-term management as many individuals reach adulthood in 2021 (Chiron et al., 2016). Furthermore, life expectancy continues to improve due to significant advances in clinical care, with specialist centres putting greater emphasis on nutritional status and physiotherapy. During the last decade, the introduction of CFTR modulator therapies has further increased this life expectancy. One of the most poignant markers of this improvement in prognosis is that, as of 2020, 60.6% of individuals with CF in the UK were aged 16 years or above, resulting in CF being recategorised as an adult disease. Subsequently, as of 2022, it is expected that the mean predicted age of survival is 50.6 years (48.2-53.1), an increase of seven years from 2007. In the same regard, the median age of death increased from 29 to 36 years across the same period. Despite an improved prognosis, data highlights 97 individuals died in 2020, of which respiratory/cardiovascular issues accounted for 61.6% of overall deaths (Cystic Fibrosis Trust., 2020).

Regardless of this increase in survival, there remains a significant disparity in estimated survival between males and females with CF. Although magnitude of increase in survival is similar between sexes, overall life expectancy remains significantly lower in females (47.0 years, 95% CI: 44.0-56.0) when compared to their male counterparts (53.1 years, 95% CI: 50.6-55.3).

2.3 Advancements in Medical Treatment

Advances in the understanding of CF across the last 30 years has enabled early diagnosis and early intervention, resulting in a more positive outlook for CF individuals at birth and an increased life expectancy. Indeed, the implementation of new-born blood spot screening (NBS) has emerged as a valid strategy to help promote increased quality of life and survival in individuals with CF (Castellani *et al.*, 2016). Long-term follow up data has shown that those diagnosed after the introduction of NBS have improved survival compared to those diagnosed clinically (Castellani *et al.*, 2016). The use of NBS screening has rapidly increased in Europe from 2000 to 2015 and as of 2018, 66% of individuals within the UK were diagnosed using NBS (Carr et al., 2019). Earlier diagnosis has meant that individuals have access to advanced therapies from an earlier age. Therapeutical improvements since the 1960's have focused on addressing both pulmonary and weight-related clinical outcomes. Pancreatic enzyme replacement therapy, coupled with high calorie, high fat diets have helped raise the body

mass index (BMI) of many individuals above 50th percentile in children, ≥ 22 kg/m^2 in adult women; and ≥ 23 kg/m^2 in adult men, figures identified as a significant milestone for long-term health (Castellani et al., 2018; Harindhanavudhi et al., 2020). Similarly, the introduction of mucolytics such as dornase alpha (pulmozyme), hypertonic saline and effective airway clearance techniques have contributed to the management of lung function deterioration (Elborn et al., 2016; Jennings et al., 2014).

Until the last decade, the only treatments available for CF individuals were those that addressed the downstream complications of the disease rather than the underlying cause of the disease itself (Heijerman *et al.*, 2019). However, the introduction of modulation therapy in 2012 has paved the way for improved clinical outcomes in addressing the molecular defects caused by the dysfunctional CFTR gene (Riordan et al., 1989; Rommens et al., 1990). Modulator therapies aim to enhance or restore the expression, function, and stability of the defective CFTR protein, thus reducing the quantity of abnormal mucus secretion and its impact on multi-organ dysfunction (Lopes-Pacheco, 2020).

Potentiators are CFTR modulators that facilitate ion transport across the epithelial cell membrane by increasing CFTR open channel probability (Kramer and Clancy, 2016; van Goor et al., 2009). Ivacaftor (IVA) (VX-770, Kalydeco, Vertex Pharmaceutical) is a potentiator which has been shown to partially restore CFTR function in those with impaired channel gating and missense mutations (G551D, R117H, S549N, R347P) (van Goor et al., 2014). IVA has set the standard for CFTR modulators, with randomised controlled trials showing potentiation sufficient to improve airway surface liquid (ASL) composition, mucucilliary clearance and ciliary beat frequency to levels comparable with non-CF individuals (Clancy, 2018). Such changes have been reported to translate to clinically significant findings, including a: 17.2% increase in pulmonary function, a 60% reduction in exacerbations and an increase in body weight of 3.1 kg across a 48-week period (Figure 2.2) (Ramsey et al., 2011). IVA also evidenced substantial improvements in sweat chloride and respiratory-related quality of life. Furthermore, whilst CF pancreatic damage starts in utero, early treatment with IVA in those with suitable mutations has been shown to alter the progression of pancreatic dysfunction, with improvements in fecal elastase suggesting some level of pancreatic sufficiency in individuals aged over 12-months (Rosenfeld et al., 2018). As such, it is hypothesised that early

intervention with modulator therapy is not only tolerable, but also may help minimise both pulmonary and pancreatic damage in CF individuals.

Despite its efficacy, IVA is only eligible for use in those with Class III mutations which account for only 5% of the total CF population. Monotherapy with IVA for those homozygous for the *F508del* genetic mutation does not demonstrate the same benefits for those with gating channel mutations. As such, there is a need for a stabilised CFTR protein to reach the cell surface prior to potentiation.

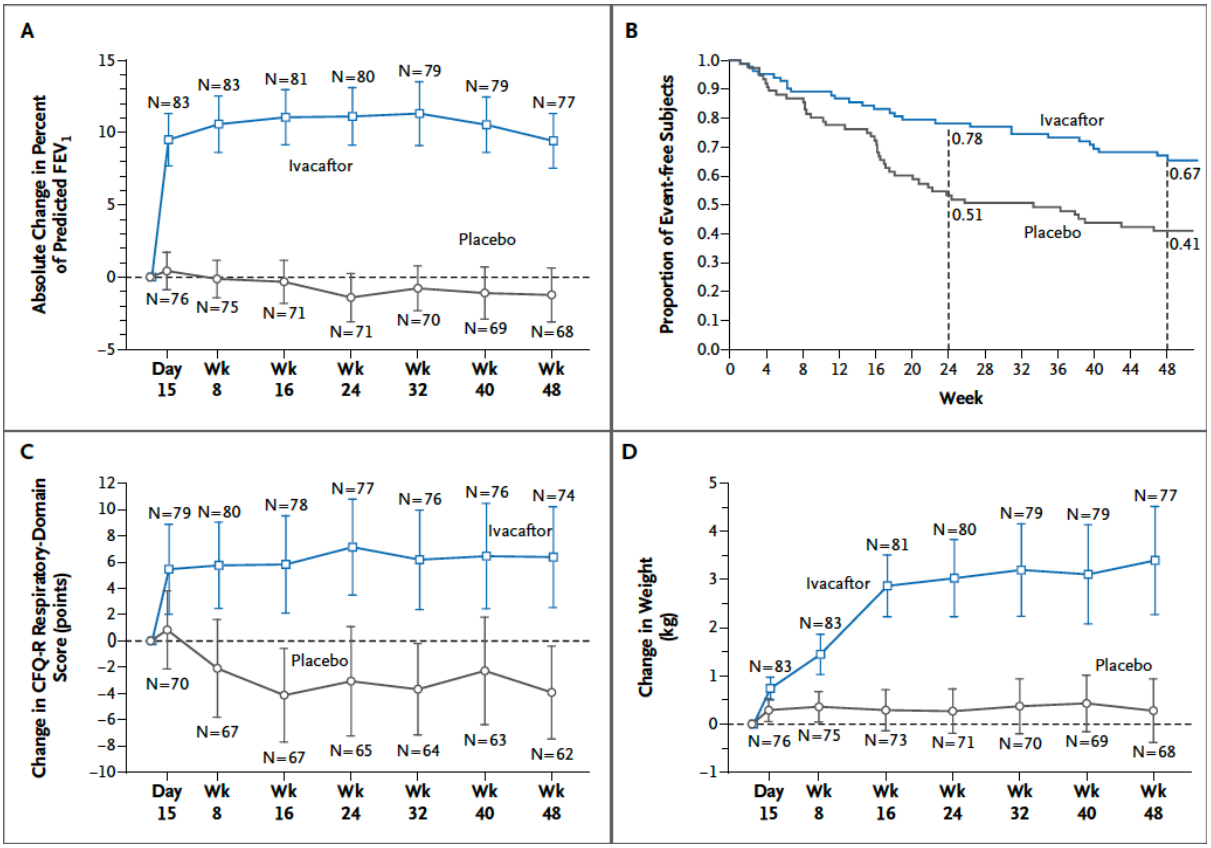


Figure 2.2. Changes in clinical outcomes in response to therapy with IVA. Taken from Ramsey et al., (2011) with permission.

The *F508del* mutation impairs CFTR processing, preventing the unfolding of the protein, causing it to be retained in the endoplasmic reticulum and resulting in little or no protein reaching the cell surface (Denning et al., 1992; Kartner et al., 1992). Further to this, the CFTR protein that reaches the cell surface exhibits a similar impaired channel gating as those with *G551D* and *R117H* mutations (Denning et al., 1992). Correctors are agents that aim to increase

the delivery of *functional* CFTR protein to the cell surface (van Goor et al., 2006). *VX-809* (Lumacaftor [LUM], Vertex Pharmaceutical) and *VX-661* (Tezacaftor [TEZ], Vertex Pharmaceutical) are CFTR correctors demonstrated to elicit clinical benefits. Specifically, in vitro, *VX-809* and *VX-661* have demonstrated the ability to improve the maturation of the CFTR protein. However, monotherapy with compounds has been shown to be insufficient to produce meaning clinical efficacy in those with two copies of the *F508del* gene, or those with one *F508del* variant and one minimal function variant (Rowe et al., 2017). Although monotherapy with either IVA or LUM produce no significant clinical changes, a combination of therapies have shown modest improvements in FEV_1, as well as decreased rates of hospitalisation, pulmonary exacerbations and significant improvements in BMI (Wainwright et al., 2015)**.** Nonetheless, whilst findings from IVA-LUM combinations were significant, the magnitude of increase falls below that of IVA in *G551D* mutations in adults (Davies et al., 2013; Ramsey et al., 2011)**.** Interestingly, treatment with IVA-LUM in those aged 6-11 years has shown more profound changes in sweat chloride and lung function compared to older populations (Ratjen et al., 2017)**,** suggesting dual combination therapy may play a preventative role in the development of CF-related damage in young individuals. For residual function genotypes, for those with at least one copy of *F508del* and a residual function mutation, the phase 3 study EXPAND evidenced an increase in FEV_1 of 6.8 percentage points after therapy with TEZ/IVA (Rowe et al., 2017). Further to this, LUM was also able to aid in other CF variations which cause protein misfolding, namely *E92K, L1077P* and *M1101K* (Avramescu et al., 2017; Awatade et al., 2019; Lopes-Pacheco, 2016)

To further enhance the modulation of the CFTR protein, it was theorised that a new corrector was needed to further facilitate a mature protein to the cell surface. *VX-445* (Elaxacaftor [ELA], Vertex Pharmaceutical), a new generation corrector, evidenced a significant increase in mature CFTR protein when combined with TEZ/IVA in vitro (Keating et al., 2018)**.** Importantly, treatment with triple modulator therapy has shown efficacious in patients with at least one F508del mutation, making modulator therapy accessible for around 90% of individuals with CF (Taylor-Cousar et al., 2019). Phase III clinical trials of treatment with ELX/TEZ/IVA achieved a 10.6 percentage point increase in FEV_1 versus placebo (Figure 2.3) in those homozygous for *F508del* and a 14.3 percentage increase in those with only one copy of

the *F508del* gene, alongside meaningful alterations in sweat chloride, weight, BMI and respiratory related quality of life (Heijerman et al., 2019; Middleton et al., 2019).

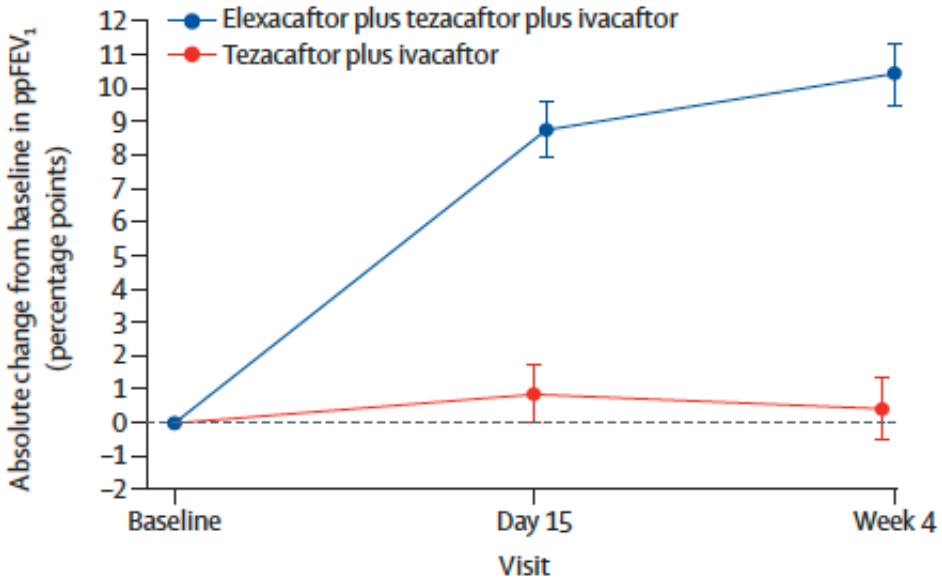


Figure 2.3. Absolute changes over time in pulmonary function from baseline after therapy with ELX/TEZ/IVA, taken from Heijerman et al., 2019 with permission.

More recently, an open label study found such changes in clinical outcomes were maintained or improved over a 36-week period (Griese et al., 2021). Further to this, where individuals were excluded from clinical trials on the basis of disease severity ($ppFEV_1$ <40%), case series have found similar increases in FEV_1 (+15.1%) alongside additional improvements in BMI, long term oxygen use and a reduced need for lung transplantation (Burgel et al., 2021; Djavid et al., 2021). Whilst such a subgroup represents the most challenging to treat given relative disease burden, early findings with regards efficacy in the most severe cases are promising, however how efficacious triple therapy is in those living with lung transplantation, continuous IV antibiotic therapy, recurrent haemoptysis and NTM pulmonary disease is still yet to be established (Gramegna et al., 2020). Although as of yet there is limited data to the efficacy of these compounds within everyday clinical practice, 96-week open label studies (Clinical trials.gov NCT03525574) are expected to provide a realistic safety and efficacy over a long-term period (Taylor-Cousar *et al.*, 2019), with a patient registry report from the US Cystic Fibrosis foundation expected to evidence real-world efficacy for individuals aged 12years+ (Barry and Taylor-Cousar, 2021). Given such studies fail to understand the lived experience of

such treatment, it is encouraged that observational studies further explore the effects of CFTR modulators on psychological and physiological health (Gramegna et al., 2020; Havermans & Duff, 2020).

2.4 Predictors of mortality in Cystic Fibrosis

2.4.1 Aerobic Exercise Capacity

As lung function is better maintained and the average age of patients increase in response to advancements in diagnosis and treatment, there is a need to manage the other comorbidities associated with the disease, such as aerobic fitness and exercise intolerance. Whilst pulmonary function (expressed as forced expiratory volume in one second (FEV_1)), remains the gold standard for determining disease severity and predicting survival in CF individuals, aerobic capacity, expressed as peak oxygen uptake ($\dot{V}O_2$peak), has been identified as an important predictor of mortality and prognosis in individuals with CF (Vendrusculo et al., 2019). Improvements in aerobic capacity in CF individuals have been associated with improvements in clinically significant markers, such as quality of life (Selvadurai *et al.*, 2002; Troosters *et al.*, 2009), an attenuated rate of decline in pulmonary function (Schneiderman-Walker et al., 2000) and a reduced risk of being hospitalized with a pulmonary exacerbation (Pérez et al., 2014). Indeed, a large international sample (N = 433) conducted over a 10-year period confirmed that over this period, individuals with the highest $\dot{V}O_2$peak (>82% predicted) had a 72% lower risk of dying and a 49% lower risk of receiving a lung transplant when compared with patients <81% predicted $\dot{V}O_2$peak (Hebestreit et al., 2019).

The gold standard assessment of aerobic fitness involves a voluntary exhaustive cardio-pulmonary exercise test (CPET) to ascertain the maximal rate at which the pulmonary, cardiovascular, and peripheral muscle can take up and utilise oxygen (Poole and Jones, 2017). For those with CF, a comprehensive analysis of aerobic capacity must also consider ventilatory limitation ($\dot{V}E/\dot{V}O_2$peak) and ventilatory efficiency ($\dot{V}E/\dot{V}CO_2$) as they represent important factors when predicting mortality and lung transplantation in individuals with CF (Hebestreit et al., 2019). The use of CPET also allows clinicians to follow the evolution of the disease and correctly inform the prescription of exercise at an individual level (Ferrazza et al., 2009; Pianosi et al., 2005). Indeed, the consensus is now that for all individuals ≥10 years, CPET

should be an established part of the annual review process (Hebestreit et al., 2015), with future research considerations centring around the most suitable and feasible CPET protocol for those with more severe lung disease (Hebestreit et al., 2016). Whilst FEV_1 remains the gold standard for following disease progression, for those who are considered in 'early disease' and pulmonary 'stable', abnormalities within aerobic fitness may reflect the effect of the condition on other organ systems that would have not been identified through spirometry alone (Vendrusculo et al., 2019).

2.4.1.1 Exercise and Aerobic Capacity

Given the indisputable link between aerobic capacity and mortality, preserving fitness remains important for individuals with CF. As the effects of detraining and being physically inactive have been suggested to contribute to the functional decline in individuals with CF (Schneiderman et al., 2014), strategies utilising exercise to slow the deterioration in lung function have received considerable attention. Regular exercise is now routinely recommended as a significant component of standard CF care (Carr et al., 2019). Physical exercise is defined as, "*…physical activity that is planned, structured, repetitive and purposive in the sense that improvement or maintenance of one or more components of physical fitness is an objective"* (Caspersen et al., 1985).

A recent systematic review concluded that currently there was only low-quality evidence to support that aerobic or anaerobic physical exercise training (or a combination of both) has a positive effect on aerobic exercise capacity, pulmonary function, and health related quality of life (Radtke et al., 2017). Much of the available data on exercise and CF suffers from low methodological quality, with the variable effect of exercise on aerobic capacity likely linked to inadequate sample sizes, varied interventions and differing intervention duration and intensity (Radtke et al., 2017). Although current studies do not allow for a consensus regarding the optimal dosage of exercise to elicit positive change, it is deemed *unlikely* that short periods of training (< 1 month) would achieve physiological benefit (Casaburi, 1992). Indeed, to have any significant benefit on exercise capacity, any intervention should be performed for at least 6-weeks in duration, with exercises progressing to an intensity of 55-64% of maximum heart rate, for three to five days a week (Gruet *et al.*, 2021). As of yet, there

is no data available on the minimal important dose of exercise to elicit a clinically significant benefit on aerobic capacity in individuals with CF.

One consistent finding within the exercise literature is that exercise intolerance remains an issue amongst CF individuals, especially those with severe lung impairment (Orenstein and Higgins, 2005). The precise mechanism(s) which underpins this intolerance is unclear, however it is known that pulmonary factors are *not* limiting in individuals with moderate CF (Dodd et al., 2006), with ventilatory limitations and bronchial obstruction playing a significant role only in those with severe disease status (Pastre et al., 2014). In contrast, several factors have been suggested to contribute, including impaired lung function, genotype, poor nutritional status, low muscle power, cardiac dysfunction, peripheral muscle dysfunction, ventilatory limitation and inflammatory status (Hulzebos et al., 2015; Pastre et al., 2014; Vendrusculo et al., 2019). Data from 102 adult patients did not observe one single exercise profile common to all patients, reflecting the complexity of the mechanisms involved in exercise intolerance (Pastre et al., 2014).

Although current data provides some consensus that participating in regular exercise increases exercise capacity, any potential increase relies on the individuals' capability to complete the specified protocol. Indeed, to guide future patient care, understanding CF-related exercise intolerance is of utmost importance when considering maximising training responses. Given the multi-factorial nature of exercise intolerance, it is imperative to consider that although exercise in CF may promote health, one, or a multitude of, these factors may need to be taken into consideration before an effective exercise intervention can be prescribed. Indeed, away from more conventional postulations around exercise intolerance, exercise is known to activate the same inflammatory pathways that have been associated with reduced exercise capacity (van de Weert-Van Leeuwen et al., 2014) and skeletal muscle weakness (Troosters et al., 2009) in individuals with CF. As such, it is possible that some forms of exercise should be avoided by individuals with CF (Nguyen et al., 2012). Whilst research is limited, findings suggest that HIIT may elicit a smaller inflammatory response when compared to aerobic training in CF adults (Nguyen et al., 2012) and could therefore offer a preferable alternative to aerobic exercise in terms of managing inflammation. However, further research is needed into both the longer-term inflammatory response to exercise and whether HIIT is

an effective alternative to increase aerobic capacity before recommendations should be given.

For those with severe disease progression, there is growing interest in the safety and effectiveness of time efficient exercise modalities such as HIIT or sprint interval training (SIT). HIIT involves performing repeated bouts of submaximal exercise, interspersed with periods of low intensity exercise/rest. There is wide scope for variations within HIIT protocols, with intensity of work and duration of work/rest varied to produce a different exercise stimulus (Gibala et al., 2012). To date most HIIT protocols can be grouped as either *submaximal* or *supramaximal* intensity. For example, a standardised submaximal HIIT protocol would be 10 x 1 minute efforts at 90% of heart rate max, whilst a supramaximal bout (intensity above $\dot{V}O_2$peak) would be 4-6 x 30 second maximal Wingate sprints (such supramaximal protocols are termed as classical 'SIT') (Vollaard and Metcalfe, 2017).

As ventilatory limitations and bronchial obstruction are major determinants of a decreased exercise capacity within the CF population, it is believed that HIIT/SIT may represent an appropriate training method, inducing skeletal muscle remodelling and without maximally taxing the ventilatory system (Hulzebos et al., 2011). Furthermore, as Erickson *et al.* (2015) identified a deficit in skeletal muscle oxidative capacity in individuals with CF, HIIT may offer a time-efficient alternative to moderate-intensity continuous training (MICT) to potentially ameliorate this deficit. Indeed, findings from healthy individuals suggest that, despite large differences in training volume, low-dose HIIT increased skeletal muscle oxidative capacity and cardiovascular adaptations compared to MICT (Burgomaster et al., 2005; Gibala, 2007; Gibala et al., 2006). Similarly, although a single session of HIIT or MICT activates signalling pathways associated with mitochondrial biogenesis (Gibala et al., 2009), findings suggest that HIIT elicited a greater increase in mitochondrial content compared to MICT (MacInnis and Gibala, 2017). Though this concept has not been explored in a CF population, findings from Gruber *et al.* (2011) suggest that HIIT may increase $\dot{V}O_2$peak through peripheral muscle adaptation. Despite a diminishing potential for pulmonary improvement, there is suggestion that an increase in $\dot{V}O_2$peak in response to HIIT may facilitate an enhanced level of physical activity and a subsequent improvement in factors related to quality of life, when compared to MICT.

However, further long-term HIIT study is needed to clarify the magnitude of change in skeletal muscle capacity and whether this directly correlates with an increase in physical activity levels and quality of life in CF individuals.

Surprisingly, despite CF being characterised by a progressive decline in lung function, studies exploring the benefits of exercise in relation to disease severity are limited. Findings from Gruber *et al.* (2011) demonstrated that a 6-week intervention increased exercise capacity in CF individuals with a wide range of pulmonary function. While increases in FEV_1 were reported in those with low baseline fitness levels, it is unclear as to whether the exercise programme per se or the extra physiotherapy or nutritional supplementations were primarily responsible for these increases in pulmonary function (Gruber, Orenstein, and Braumann, 2011). Furthermore, although CF-related exercise intolerance may be explained by a reduction in pulmonary function, increases in $\dot{V}O_2$peak appear to depend more on baseline fitness than lung function, with less fit individuals experiencing greater relative benefit to aerobic capacity than their fitter counterpart of any given intervention, irrespective of sex (Gruber, Orenstein, and Braumann, 2011; Orenstein & Nixon, 1991). Such findings may provide motivation for less fit individuals if they are aware that they may positively benefit. Although these results are congruent with research in healthy populations, showing an inverse relationship between baseline aerobic capacity and the magnitude of improvement (Skinner et al., 2001), further research is needed into the efficacy of exercise interventions, especially in females.

Whilst the benefits of exercise within a CF population are evident throughout literature, the detrimental impact of CF on the ability to be physically active strongly influences participation and adherence (Moola et al., 2012). Unpleasant physical symptoms, such as coughing and breathlessness, coupled with a potential inability to keep up with able-bodied peers, means many people with CF become physically inactive, thereby further exacerbating CF symptoms, known as the 'vicious cycle of inactivity' (Nixon et al., 2001). As such, any attempt to increase activity within this population must focus on an individualised, progressive programme to minimise physical discomfort whilst overcoming any further barriers to exercise. There is a suggestion that at least some degree of supervision is needed for some individuals to maintain training adherence and thus maximise training responses (Moorcroft et al., 2004;

Schneiderman-Walker et al., 2000). Indeed, adherence to all sessions during supervised training in Kriemler *et al.* (2013) was reported to be 80% over a 6-month period, with improvements ameliorated when sessions were no longer supervised.

Given that both HIIT and aerobic interventions are associated with an improved $\dot{V}O_2$peak, it could be postulated that a HIIT programme may represent a more time-efficient modality to produce similar physiological adaptations to aerobic exercise. Indeed, such findings have been consistently reported within healthy populations and as well as those with chronic obstructive pulmonary disease (Arnardóttir et al., 2007; Meyer et al., 1996). Within a CF population, findings, at least in part, support this notion, with $\dot{V}O_2$peak increased by 18% and ~5% in response to a HIIT (Hulzebos et al., 2011) and aerobic exercise (Gruber et al., 2011a) intervention, respectively. Despite the potential of HIIT as a suitable modality for CF individuals, there is a suggestion that when PA is increased or decreased in one domain, there may be a compensatory effect in another domain (Gomersall et al., 2013; Mackintosh et al., 2017). Therefore, whilst HIIT initially appears to be both suitable and effective for individuals with CF, it is important to determine whether introducing brief HIIT sessions to their daily schedule alters their typical PA levels.

While HIIT appears to be an effective, time-efficient strategy to increase aerobic capacity in CF individuals, due to the scarcity of research, fundamental questions still need to be addressed to elucidate optimal and sustainable training interventions. Similarly, further exploration into SIT is needed within this population to address questions such as the optimal volume and intensity of exercise required to elicit benefits and whether these benefits can be maintained over the long-term remain to be resolved. Indeed, findings from research within the general population suggest that SIT protocols mimic the benefits seen within HIIT (Metcalfe et al., 2012, 2016; Songsorn et al., 2020), with a significantly reduced time commitment. Furthermore, the interpretation of previous studies is limited as the magnitude of change that is 'clinically relevant' remains to be clarified; further research is needed to determine whether these exercise-induced increases translate to an improved prognosis in the long-term (Williams and Stevens, 2013).

2.4.1.2 Exercise and Pulmonary Function

Collectively, current literature suggests absolute improvements in lung function are unlikely in response to an exercise intervention. However, evidence from long-term (6-36 months) exercise interventions suggest that although interventions may not elicit significant increases in FEV_1, they may prevent, or at least slow, the rate of decline in FEV_1 typically associated with disease progression. Studies conducted over a 12-month period reported declines in FEV_1 no greater than 1.46% (Moorcroft et al., 2004; Orenstein et al., 2004a; Schneiderman-Walker et al., 2000) compared to an average 3.94% in the respective control groups (Harun et al., 2016; Moorcroft et al., 2004; Schneiderman-Walker et al., 2000). The prolonged preservation of FEV_1 is complex in those with CF, with risk factors such as infection with *Pseudomonas aeruginosa* and pancreatic insufficiency that may elicit a more rapid decline in FEV_1 (Harun *et al.*, 2016). Preservation is likely to involve a complex inter-play of pharmacological and non-pharmacological interventions; further research is required to elucidate the long-term role exercise plays. Indeed, such findings would help prioritise exercise as a treatment for both children and adults with CF (Moorcroft et al., 2004). As FEV_1 is still considered the best predictor of mortality in CF individuals (Breuer et al., 2018), this evidence may help alter the perceptions of exercise in parents of children with CF who restrict youth from being active due to negative perceptions of illness and adverse views toward exercise (Moola et al., 2012).

There is a paucity of studies that have considered the influence of a HIIT/SIT intervention on lung function in those with CF. From those that have, only Hulzebos *et al.* (2011) reported increases in FEV_1, in response to a 6-week HIIT intervention with a single 16-year-old individual. Such findings contrast with those from Gruber *et al.* (2014) and Klijn *et al.* (2004). With limited, short-term research available, it is impossible to conclude as to the effect HIIT may have on pulmonary function and whether it has the capacity to slow the rate of decline on FEV_1. However, it could be speculated that due to HIIT/SIT eliciting a reduced toll on the respiratory system (Burgomaster et al., 2005), the capacity for improvement in pulmonary function could be limited. As such, further research is warranted into the long-term effects of HIIT/SIT on pulmonary function and exploration of the benefits that a combination of both types of training (HIIT/SIT & Aerobic) may have on individuals with CF.

2.4.2 BMI, Nutritional Status and Mortality

Correctly assessing nutritional status is vital to accurately determine those at risk of nutritional failure. Within routine clinical practice, BMI (body mass(kg)/height(m)^2) is widely accepted as the most appropriate measure of nutritional status for those over 2 years old (Stallings et al., 2008). However, as BMI may fail to identify a substantial proportion of children with stunting or poor nutritional status (Konstan et al., 2017a), recommendations for clinical care specify that BMI should be used in conjunction with other tools, such as weight-for-age (WFA) and height-for-age (HFA)**.** In the UK, it is recommended that UK world health organisation age-specific growth charts should be used in line with common clinical practice (WHO., 2020)

Although pulmonary failure is considered the main cause of death within a CF population, individuals are classically at risk of malnutrition and low bodyweight due to a combination of nutrient malabsorption, increased work of breathing, chronic inflammation, and recurrent pulmonary infections (Bailey et al., 2021). Importantly, malnutrition and low bodyweight are associated with a decline in pulmonary function and increased incidence of morbidity and mortality (Bonhoure et al., 2020; Hauschild et al., 2018; Kerem et al., 2014; Konstan et al., 2007; Steinkamp and Wiedemann, 2002). Figure 2.4 depicts the relationship between pulmonary function and BMI, with achieving a BMI in line with recommended guidelines (≥ 22 kg/m^2 in adult women; and ≥ 23 kg/m^2 in adult men) associated with a more favourable FEV_1.

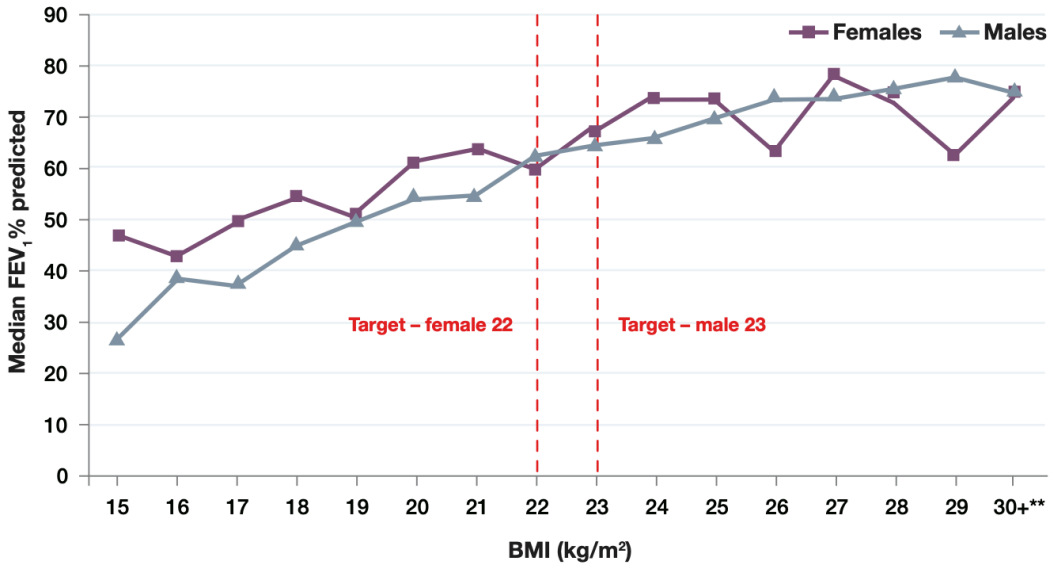


Figure 2.4. Association between FEV_1 and BMI. Cystic Fibrosis Patient registry (2020). Taken with permission.

With the positive association with BMI and pulmonary function, dietetic intervention is considered one of the cornerstones of regular CF care. Given the history of malnutrition, interventions have focused on increasing BMI through the implementation of a high-fat, high-energy diet, supplemented with pancreatic enzyme replacement therapy. Such has become the standard of care for CF individuals worldwide given its association with a 9-year survival advantage compared to those prescribed fat restriction (Corey et al., 1988). Aggressive nutritional support is also recommended in paediatric care in an attempt to prevent malnutrition and promote catch up growth (Shepherd et al., 1988).

Nutritional status has a direct impact on prognosis of the pulmonary disease in individuals and is seen as part of the evolution of the severity of the disease (Pencharz and Durie, 1993). Malnutrition, subsequent protein catabolism and muscle loss have cascading effects on force and resistance of the respiratory muscles, compromising diaphragm function, and impairing immune function (Hart et al., 2004). Positive association has been established between better nutritional status and a higher pulmonary function, with an inverse relationship on morbidity and mortality (Boëlle et al., 2012; Dodge and Turck, 2006; Harindhanavudhi et al., 2020; Kastner-Cole et al., 2005; Konstan et al., 2017; Michel et al., 2009; Stephenson et al., 2013). Acute instances of weight gain have been positively associated with increases in FEV_1 (+9.31%), whilst weight loss is associated with a negative impact on lung function (Cano Megías et al., 2015). Furthermore, those who were considered overweight (OW) had significantly better lung function than those who were categorised as underweight (UW), with no significant difference between OW and those who were 'normal' weight (NW) (González Jiménez *et al.*, 2017). Thus, means to improve nutrient intake and absorption have been central to patient care and have significantly contributed to an observed increase in pulmonary function and survival.

However, whilst the consensus is that a higher BMI translates to a more favourable pulmonary function and mortality risk, to what extent this weight gain translates to cardiometabolic risk is currently unknown (Bonhoure et al., 2020). Specifically, those who are obese, or experience short-term rapid weight gain, may have positive improvements in key clinical outcomes but both populations exhibit worse cardiometabolic profiles (Bonhoure et

al., 2020). Whilst intensive efforts to promote adequate nutrition have resulted in a significant decline in the incidence of malnutrition over the last decade (Harindhanavudhi et al., 2020), the prevalence of overweight/obesity has now emerged as an important consideration in the management of CF. In 2005, an analysis of the UK CF registry found that 9% of children and adults were overweight with 1% classified as obese (Kastner-Cole et al., 2005). As of 2021, overweight and obese status are thought to be four times as prevalent as underweight status in some CF populations (McDonald et al., 2021; Petersen et al., 2022). Indeed, recent reports cite the incidence of obesity ranging between 10-30% (Hanna and Weiner, 2015; Litvin et al., 2019). A longitudinal analysis of the US CF registry over the past 20 years found the percentage of overweight has increased from 7% to 16% and the incidence of obesity had raised by 345% across the same period (Flume et al., 2019). A recent single centre-analysis at the University of Minnesota adult CF centre found that over 30% of individuals treated at the centre between 2015 and 2017 were classified as overweight/obese (Harindhanavudhi et al., 2020). Likewise, a multi-centre study from Italy found the incidence of overweight/obesity to be 22% within this cohort (Gramegna *et al.*, 2022).

The aetiology of this increase in overnutrition is multifactorial, with advancements in treatment, increased predicted survival and the introduction of CFTR treatment all having significant contributions to the increased incidence (Litvin et al., 2019). A recent systematic review reported the efficacy of CFTR compounds on nutritional status is highly dependent on therapy formulation and CFTR mutation (Bailey *et al.*, 2021). Whilst conclusions are limited to the efficacy of treatment with ELX/TEZ/IVA on long-term incidence of obesity, long-term follow up of chronic treatment with the potentiator IVA demonstrated the incidence of overweight/obesity increased from 16 to 25% over a 5.5-year period (Guimbellot *et al.*, 2021). However, given that early data on weight gain in response to treatment with the highly effective ELX/TEZ/IVA has reported changes in BMI of up to 1.28 kg/m^2 (Griese et al., 2021; Heijerman et al., 2019; Middleton et al., 2019), it is expected that such treatment will significantly contribute to the acceleration of this trend in overweight/obesity within a CF population (Petersen *et al.*, 2022).

Whilst there is evidence to suggest that individuals with CF may benefit from achieving a higher BMI threshold (~25 kg/m^2) with relation to quality of life and pulmonary function, such

must be balanced with balanced with potential adverse cardiometabolic effects later in life. Research identifies overweight/obesity as a global health concern of which is associated with increased incidence of hyperlipidaemia, hypertension, cardiovascular disease (Berrington de Gonzalez *et al.*, 2010). Whilst there is currently limited data available on the long-term effects of obesity on mortality in CF individuals, recent studies associate overweight/obesity with insulin resistance, hormonal disturbance, worse transplant outcomes, dyslipidemia and increased central fat storage within a CF population (Bailey et al., 2021; González Jiménez et al., 2012; Harindhanavudhi et al., 2020; Petersen et al., 2022). Furthermore, despite a lack of longitudinal data, it cannot be ruled out that persistent cardiometabolic risk over time would develop into cardiovascular disease, as seen within the general population (Harindhanavudhi et al., 2020).

Currently no guidelines exist with regards treatment of overweight/obesity within this population. Further to this, since the implementation of CFTR therapy there has been no formally updated guidance with regards dietary intake for individuals with CF (Bailey et al., 2022). In an attempt to previously manage malnutrition, individuals with CF have been conditioned to consume an unrestricted, high-calorie, high-fat diet. Despite the evident links to excessive weight gain following the implementation of CFTR therapy, studies show considerable issues around quality of the diet, with considerably high intake of saturated fat, trans fat and total calories, coupled with low intake of nutrient dense food (McDonald et al., 2021). Following the implementation of CFTR treatment there is suggestion from the Academy of Nutrition and Dietetics that there is no evidence to support that individuals with CF have any benefit from consuming a diet outside of what is recommended to the general population (McDonald et al., 2021). As such, suggestion is that nutritional considerations must shift away from the traditional CF legacy diet towards a more nutrient dense, moderate energy diet for most individuals. Further to this, there is considerable emphasis on taking a more individualised approach to nutritional treatment and thus accounting more closely for resting metabolic rate, genetic mutation, modulator treatment, body composition goals and nutritional status at regular clinic visits (McDonald et al., 2021; van der Haak et al., 2020). Given that many individuals with CF have been conditioned to follow a high-calorie diet since early childhood, it is imperative that this transition is treated with empathy and understanding that such a shift in dietary intake will take considerable time and follow up. As

the lived experience of treatment with ELX/TEZ/IVA is still to be explored, understanding barriers and facilitators of food, knowledge on nutrition and confidence in managing diet is something that warrants further investigation to further find a consensus around what works best for the individual.

2.4.2.1 Intervention from an early age

With the conclusive link between FEV_1, BMI and positive clinical outcomes, optimisation of growth and nutritional status is essential. Early studies noted an association between lipid absorption and pulmonary function with children who have normal fat absorption presenting with milder symptoms, lower sweat chloride and overall better prognosis compared to children with steatorrhea (Gaskin et al., 1982). A more recent systematic review of nutritional related management of CF (Stallings et al., 2008) concluded that normal ranges for values such as weight-for-age, height-for-age and weight-for-height percentiles, were associated with more favourable clinical markers later in life in both children and adults. For those in early life, the recommendations of energy intakes ranging from 110-200% of that of general population is maintained in order to achieve weight gain at an age-appropriate rate in children (Stallings et al., 2008).

Early intervention and maintaining an ideal weight in infancy is crucial to long term development and reducing the likelihood that individuals present with other CF-related co-morbidities. Data from over 3,000 CF individuals between the years of 1982-1999 concluded that FEV_1 predicted during childhood and adolescence was lower in individuals with a weight-for-age percentile (WAP) below 10% at 4 years of age (Yen et al., 2013), with none of the population achieving a standard of >80% FEV_1 predicted. Higher WAP groups had incrementally better results, with those >50^{th} percentile having the highest figures at >90% FEV_1 predicted. Rate of decline was similar amongst all groups. Aside from improved lung function, those at a higher WAP also presented with increased glucose metabolism, fewer pulmonary exacerbations, less time as an inpatient, better survival and better timing and velocity of pubertal height growth (Yen et al., 2013). Furthering this, data analysed on 931 children found that those with a WAP less <50^{th} percentile at age 3 years had an FEV_1 of 86 ± 20% predicted at age 6 years, compared to 102 ± 18% predicted in those at the same age who

were >75th percentile (Konstan et al., 2003). As such, the recommendation is that gains are greatest when nutritional intervention and therapy is initiated in infancy (Sproul and Huang, 1964).

Given that infants who regain their z-score within 2 years of diagnosis have better lung function at age 6 years (Lai et al., 2009), and better pulmonary function later in life, guidelines strongly recommend that children are able to reach and *sustain* the 50th percentile for WAP by this age (Brownell et al., 2019). With this being the case, early diagnosis is key so therapy can begin earlier. Since 2007, an ongoing longitudinal study identified children diagnosed through NBS had higher stature, weight and head circumference versus those diagnosed later in life, differences which persisted beyond 16 years of age (Farrell et al., 1997, 2005). Further to this, a systematic review on NBS found that mortality risk was lower in the population who were diagnosed via NBS as opposed to presenting with CF related symptoms (Grosse *et al.*, 2006). Such highlights show the importance of NBS and how it allows for early intervention to ensure that growth milestones are achieved in early life to maximise short- and long-term clinical outcomes. Indeed, the focus allows for achieving optimal nutritional status to support growth and development with the aim then to maintain this through adolescence and into adult life (Brownell et al., 2019).

2.4.3 The CF Gender Gap

Despite significant improvements in life expectancy within a CF population, there still remains a gap in clinical outcomes and survival between men and women (Lam et al., 2020). Even when accounting for differences in BMI, pulmonary function and bacterial infections, the female sex is considered an independent risk factor for increased morbidity and mortality within this population (Harness-Brumley et al., 2014). As of 2020, data from the UK CF registry indicates that despite a 7-year increase in survival between 2011 and 2020, females are expected to live 4 years fewer than their male counterparts (47.0 vs 53.1 years). Such a trend is in opposition to that seen in the general population. Life expectancy at birth between the years of 2018-2020 was 79.0 years for males and 82.9 years for females (ONS., 2020) – however, within the CF population over the same period, there still remains a significant difference between the life expectancy when comparing males to females in the UK (Cystic

Fibrosis Trust., 2020). Whilst a gender gap in clinical outcomes is well documented in CF registry data worldwide (Harness-Brumley et al., 2014; Olesen et al., 2010; Rosenfeld et al., 1997) and other respiratory diseases (Celli et al., 2011; Farha et al., 2009; Morrissey and Harper, 2004), the underlying cause for this gender gap is still not understood and most likely multifactorial in nature.

Anatomically, women on average have a smaller airway diameter and a smaller lung volume, even when adjusted for height. It has been suggested that such anatomical differences may further inhibit mucus clearance (Raghavan and Jain, 2016). Additionally, women have a higher predisposition to bronchoconstriction as smaller airways may result in more frequent inflammation, leading to more mucus production, impaction, and subsequent infection (Lam *et al.*, 2020). Several co-morbidities have been suggested to contribute to the difference. Specifically, In CFRD, females are diagnosed at an earlier age and have a considerably poorer survival after diagnosis (Konstan *et al.*, 2007) and chronic infection with mucoid *Pseudomonas aeruginosa* at an earlier age (Levy et al., 2008). However, whilst these factors contribute to the increased mortality of CF females, they do not identify the underlying cause (Olesen *et al.*, 2010). Given the lack of evidence of a precise molecular mechanistic cause of this gender gap, studies addressing this issue have narrowed the focus to both psychosocial and hormonal differences.

2.4.3.1 Hormonal effects

As the rate of lung exacerbations increases around the time that females reach puberty, it is hypothesised that endogenous oestrogen production plays a role in this discrepancy. Whilst both dominant female sex hormones, oestrogen and progesterone, are endogenously produced in both sexes, they are higher in females and fluctuate with monthly menstrual cycles. At the beginning of the cycle, both oestrogen and progesterone remain low before oestrogen subsequently rises and peaks during the follicular phase (pre-ovulation). In contrast, post-ovulation, both oestrogen and progesterone rise before falling back to low levels in line with the start of a new cycle (Figure 2.5; Lam *et al.*, 2020). Clinical observation indicates that lung exacerbation rates occur more frequently in women once they reach puberty, suggesting that the worsening of airway inflammation and infection corresponds to

the increased in endogenous levels of oestrogen and progesterone (Holtrop *et al.*, 2021). Furthermore, data suggests that midway through a female's menstrual cycle, when oestrogen levels peak, lung exacerbations are at their highest (Saint-Criq and Harvey, 2014), thus implying a significant contribution of endogenous hormones on lung pathophysiology.

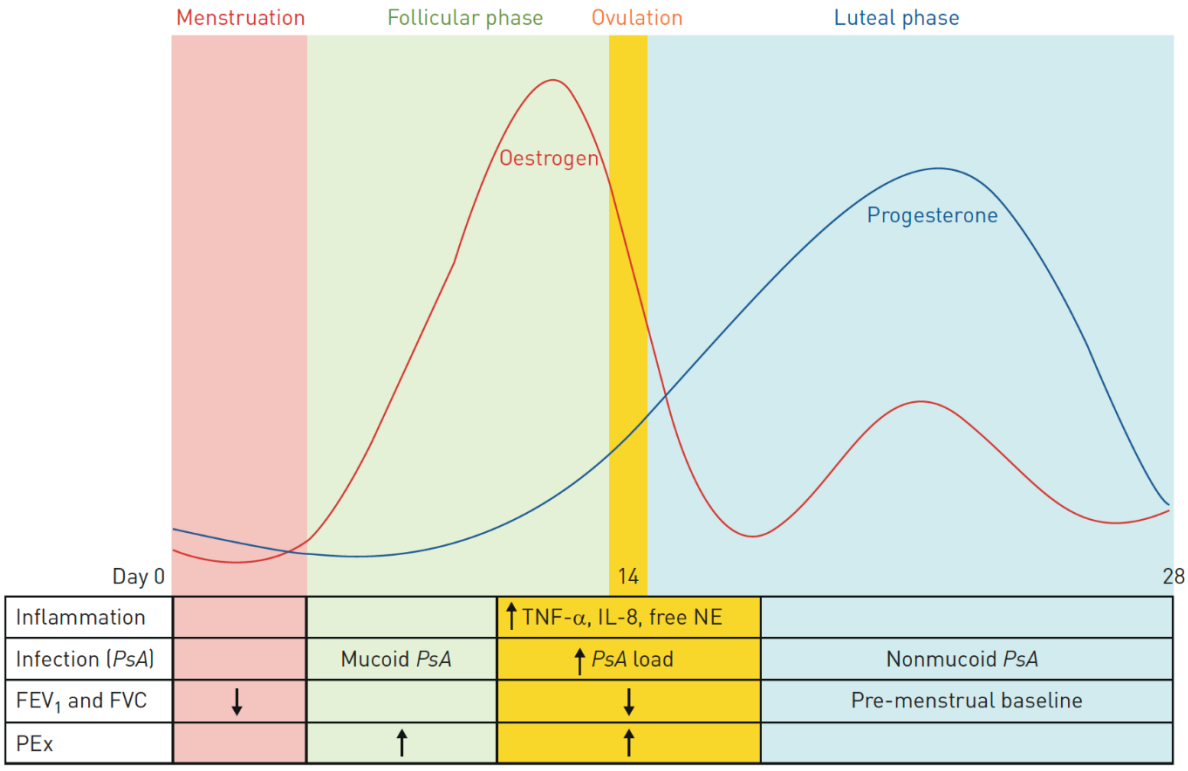


Figure 2.5. Changes in oestrogen and progesterone throughout the menstrual cycle in the context of clinical, infections and inflammatory findings, taken from Lam et al. 2020 with permission.

Despite individuals with CF having an already compromised ASL, oestrogen appears to have an additional negative effect on CFTR chloride channel activity, further reducing chloride ion secretion and thus producing more viscous mucus production (Kroncke et al., 2016). Adequate levels of ASL are needed to ensure effective mucocilliary clearance, suboptimal levels of which result in mucus impaction and an inability to remove secretions from the airway, leading to further inflammation and infection. Oestrogen appears to reduce the intensity of the ciliary beat in the airway epithelial cells, further compromising the ability to clear these thickened secretions (Jain et al., 2012). Despite expression of the CFTR protein potentially being enhanced in response to higher oestrogen levels (Ajonuma et al., 2005), the deleterious effect oestrogen has on ASL and mucocilliary clearance may play a significant role in a compromised female CF airway.

The effects of oestrogen are not limited to the composition of the mucosal fluid, however, as they may also play a significant role in the development of more severe bacterial infections. Pulmonary function remains the main predictor of mortality in individuals with CF, a decline in which is propogated by the colonisation of bacteria such as *Burkholderia Cepacia* and *Pseudomonas aeruginosa (PSA)* (Ledson et al., 2002; Saint-Criq and Harvey, 2014). PSA is a gram-negative, opportunistic environmental bacteria, capable of causing acute and chronic infection, particularly in immunocompromised patients (Moradali et al., 2017). Studies have demonstrated that CF females acquired *chronic* PSA infection at an earlier median age when compared to males, with females demonstrating a more rapid decline in lung function after infection with PSA (Demko et al., 1995; Levy et al., 2008; Pittman et al., 2011; Rosenfeld et al., 1997). Oestrogen has been shown to have a direct effect on the modulate of the immune system in response to these pathogens. Data from (Chotirmall et al., 2010) highlighted the cascading effects of oestrogen and oestradiol (E2) which reduced IL-8 production and compromised the protective inflammatory effect, thus leading to a rise in both PSA infection and colonisation. Further to this, Wang et al, (2010) found oestrogen promoted the conversion of PSA from the nonmucoid to the mucoid form in individuals with CF, which represents a more drug resistant form of the bacteria. Of further significance, mucoid strains of PSA were significantly more prevalent *following* the onset of puberty and predominately isolated during phases of the menstrual cycle in which E2 was highest (Figure 2.6; Chotirmall et al., 2012; Coakley et al., 2008; Z. Li et al., 2005). As such, females tend to have significantly higher doses (1.5x higher) of IV antibiotics when compared to their male counterparts, irrespective of $FEV_{1,}$ and to spend more days in hospital (Olesen *et al.*, 2010). Importantly, this increase in hospital days is not solely explained by IV therapy and suggests that females are in higher need for hospitalisation, even when matched for disease severity. Furthermore, low dose macrolides, such as *azithromycin,* are found to be of higher use in females, even before chronic infection with PA. As such, it appears that females are treated more aggressively, but whether that is due to severity of disease, increased presence of symptoms or whether the prior knowledge of such a gender gap influences the way in which clinical teams treat females remains to be elucidated (Olesen *et al.*, 2010).

Interestingly, women who are receiving oral contraceptives showed lower rates of lung exacerbations compared to those without, with registry data suggesting that these individuals require fewer courses of antibiotics to manage infection and exacerbation (Chotirmall et al., 2012). A recent study demonstrated a favourable increase of 2.5% in FEV_1 for those women taking oral contraceptive pills (OCP), when compared to their lung function pre-OCP therapy**.** Moreover, bacterial load and sputum inflammatory markers were significantly reduced during ovulation following OCP therapy (Lam *et al.*, 2020). When considering QoL, individuals attending clinic completed the CFQ-R questionnaire pre- and post- commencing OCP therapy, with a significant improvement in QoL once OCP was initiated (Kernan et al., 2013). Whilst suggestions are that OCP may have a positive effect of the prevalence and severity of mucoid PSA, the long-term effects of these drugs in this population is currently unknown. Side effects within the general population are well evidenced with hot flushes, mood variability, insomnia and potentially premature menopause could further exacerbate other CF related co-morbidities (Liao and Dollin, 2012). Whilst there appears to be a protective effect on pulmonary health, further study is needed to ascertain whether the longitudinal benefits of hormone replacement therapy outweigh the potential risks within a CF population.

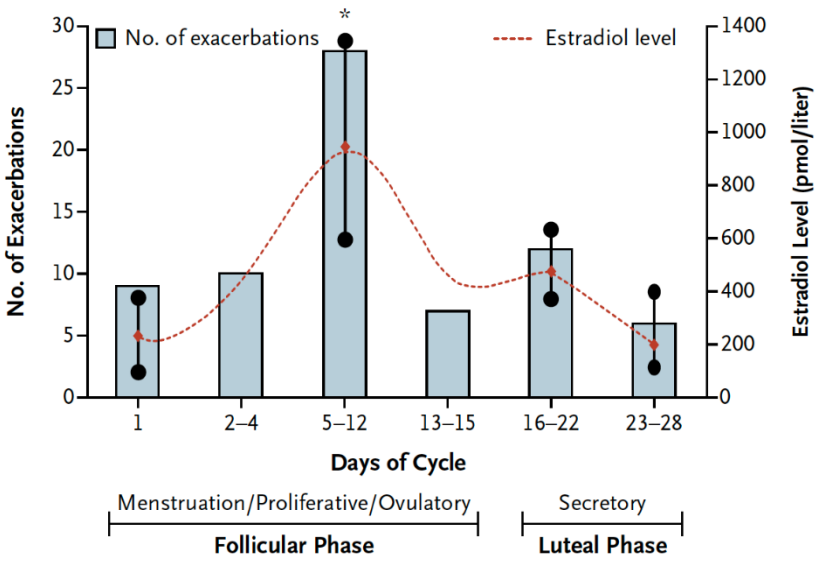


Figure 2.6. Exacerbations according to the time within the menstrual cycle. The asterisk represents the significant differences in oestradiol between the proliferative phase in the menstrual cycle and the menstrual and ovulatory phase. Figure taken from Chotirmall et al., 2012 with permission.

2.4.3.2 Psychosocial effects

Despite significant improvements in treatment and survival, the reality remains that individuals living with CF face significant psychosocial challenges of which some are unique to CF, with others mirroring that of other chronic disease (Muther et al., 2018). The realisation for a need to hit CF related 'milestones' early in life can adversely impact the mental health of the individual. Events such as; initiation of new therapy, onset of CF related infection, aggressive antibiotic therapy, hospitalisation and surgery, have all been linked to stress, depression and anxiety (Muther et al., 2018). These challenges are often amplified through adolescence at a time when lung function begins to decline and the need for hospitalisation becomes more frequent (Vandenbranden *et al.*, 2012). Further to this, increased treatment load (>2hrs daily) and complexity results in many individuals reporting low adherence to treatment, especially in adolescence and early adulthood (Quittner et al., 2014; Sawicki et al., 2009; Shakkottai et al., 2015). The downstream effects of these psychosocial factors on mental health mean that many individuals present with decreased lung function, lower BMI, poorer adherence to treatment, a worse HRQoL and more frequent hospitalisations (Hilliard et al., 2015; Muther et al., 2018; Ploessl et al., 2014; Riekert et al., 2007; Smith et al., 2010; Snell et al., 2014). All of this being particularly prominent for females given they have a notoriously higher mortality rate and poorer HRQoL than males (Arias Llorente et al., 2008).

Current research suggests an important positive correlation between dietary intake, lung function and mortality rate (Collins et al., 1998; Stallings et al., 2008). Indeed, individuals with a better nutritional status and higher BMI demonstrate more favourable clinical status in terms of FEV_1 (Cano Megías *et al.*, 2015). However, despite this it appears that females had a smaller relative energy intake when compared to males (Collins et al., 1998), of which has been linked to self-esteem and poor body image. Body image is important to CF individuals of all ages with a negative perception of self, related to depression and anxiety which can influence self-management and adherence to treatment (Truby and Paxton, 2001; Wenninger et al., 2003). Differing socio-cultural messages between sexes are prevalent, with females judged more on their aesthetics, with male focus being placed on functional capacity (Abbott and Barber, 2010). As such, the result is that women's desires are placed on aspirations of being thin, with females reporting discomfort with being too large (Gray and Ginsberg, 2008;

Grogan, 2016). However, when compared to healthy peers and males, females report having a better body image, given that their low weight, fits the socio-cultural models for perceived 'attractiveness' for women (Tierney, 2012). However, when we consider the detrimental effect of a lower body weight and BMI on clinical outcomes (Stallings *et al.*, 2008), values placed on this slender physique may play a role in the gender gap and poorer survival in females, given their poor motivation to work towards a body weight linked to more favourable weight related outcomes (Rosenfeld et al., 1997). Further to this, in terms of a health belief model, it is postulated that given CF females are aware of their shortened life-expectancy, this may further push them to disregard their additional risk of pursing a physique in line with social 'norms' (Rosenstock, 1974).

With the introduction of modulator therapy, which has been shown to make weight gain easier (Heijerman et al., 2019)**,** whilst females may start to meet criteria associated with positive clinical outcomes, understanding the effects this has on self-perception, body image and adherence to this treatment is imperative. Data from our own qualitative research highlights weight gain as a significant negative to modulator therapy, with individuals adopting risky behaviours such as uneducated dieting and avoidance of treatment all together. As the message to all CF individuals' counters that of the traditional 'norms', in that they are encouraged to eat a higher calorie, high fat diet – as the landscape of CF changes, there needs to be a shift in nutritional consideration, away from these norms, towards a more nutrient dense, moderate energy intake diet. As whilst previous advice was to switch the focus away from aesthetics (Tamburrino., 2003), to do so in an age of Kaftrio may come at a detriment to adherence. Whilst screening for poor body image is not part of current clinical care, the use of the Body Image Quality of Life Inventory (Cash and Fleming, 2002) may help identify those individuals who may benefit from help to alter their perception of self and shift the self-narrative towards being individuals' content within their own bodies. Highlighting those most vulnerable, acknowledging and managing perceived imperfections and what the body can *do,* as opposed to its image may help reduce risky behaviours (Tierney, 2012).

2.5 Summary

Improvements in the management and treatment of CF has been associated with a significant change in CF survival. Between its first description in 1935 and the 1970's, CF was a universally fatal childhood disease. As of 2020, an individual with CF is expected to live into their 5th decade, with projections estimating a 38% increase in the number of adults with CF in the UK (Keogh et al., 2020). The combination of a rapidly increasing adult population and the associated complications associated with an ageing population offers a substantial challenge to health care professionals for optimising the delivery of care (Plant et al., 2013). However, whilst the classical challenges are very well recognised, whether these will play as significant a role in adult care in the era of CFTR modulator therapy is yet to be known. For those who are born today, there is potential for CFTR modulation to reverse complications such as pancreatic insufficiency and hope that these drugs also limit the development of CF related bronchiectasis, diabetes, and other CF related complications (de Boeck, 2020). As the standards of living in CF individuals increases, identification of other possible determinants of human longevity should now be at the forefront of CF care, with special attention to be taken to the effects of lifestyle aspects on health and survival. As such, the aim of this thesis is to:

1. Extend current understanding as to the effect's lifestyle factors, namely nutrition and exercise, have on significant clinical outcomes such as BMI, aerobic capacity and survival.
2. Explore whether a gender disparity in these lifestyle factors exists within a UK CF population, and how that translates to long term clinical outcomes.
3. Analyse the patient perspective of Kaftrio and how individuals now perceive their condition and implications that has for clinical care was investigated.

CHAPTER 3
GENERAL METHODS

3 GENERAL METHODS

This chapter outlines the general methods utilised in all experimental chapters. Further detail, where necessary, is provided in the specific research chapters (Chapters 4 to 7).

3.1 Study Designs

Throughout this thesis, differing study designs were utilised. Chapter 4 represents an individual participant case study; Chapters 5 and 7 are retrospective data analyses utilising registry (Chapter 5) and single centre (Chapter 7) data; Chapter 6 is a qualitative analysis of a cohort of individuals with CF.

3.2 Scientific Review and Ethics Approval

Due to differing experimental designs within this thesis, alternative ethics approval processes were required based on the specific nature of the studies.

For experimental chapters utilising NHS data, ethical approval was obtained from the local NHS Research Ethics Service Committee with subsequent approval from the Research Ethics Committee at the College of Engineering at Swansea University. Ethical approval for Chapter 4 and 6 was obtained directly from the Research Ethics Committee at the College of Engineering at Swansea University.

Throughout all studies, access to all personal data associated to research participants was restricted to members of the research team only.

3.3 Funding

All studies were funded through the Knowledge Economy Skills Scholarship (KESS). KESS is a pan-Wales higher level skills initiative led by Bangor University on behalf of the HE sector in Wales. It is part funded by the Welsh Government's European Social Fund (ESF) convergence programme for West Wales and the Valleys.

Ysgoloriaeth Sgiliau Economi Gwybodaeth (KESS) yn Gymru gyfan sgiliau lefel uwch yn fenter a arweinir gan Brifysgol Bangor ar ran y sector AU yng Nghymru. Fe'i cyllidir yn rhannol gan Gronfeydd Cymdeithasol Ewropeaidd (ESF) cydgyfeirio ar gyfer Gorllewin Cymru a'r Cymoedd.

3.4 Study Participants and Inclusion/Exclusion Criteria

Throughout the thesis, only individuals with CF were included. Dependant on the study design and primary outcomes, differing inclusion/exclusion criteria were applied prior to study enrolment.

Chapter 4

The participant for the case study was recruited from Swansea University. The method of recruitment was voluntary participation. The participant for this study was the main researcher as disclosed in Chapter 4. The individual was approved to participate in the study based on pre-approved inclusion criteria:

- CF diagnosis based on consensus guidelines (Farrell *et al.*, 2017), presenting with a sweat chloride of ≥60mmol/L and the identification of known CF causing mutations in the CFTR gene.
- Disease state considered stable, on the basis that their pulmonary function (FEV_1) is stable (classified as within 10% of that from the last two clinic visits and no exacerbations within 12-weeks of the commencement of the study
- No acute exacerbation or treatment with Oral or IV antibiotics in the preceding 2-weeks before study commencement.

- No other co-morbidities that may impair exercise ability.

Chapter 5

All participant data within this study was obtained from the UK CF registry. The registry has NHS research approval and consent for each individual for whom data is collected. To be included in the registry individuals must meet the CF diagnosis criteria as outlined above. Individuals were excluded from this study on the basis of:

- Individuals aged <6 years and >17 years of age
- Individuals received lung transplantation during the study years analysed as it is likely this would alter an individual's pulmonary function and body mass

Chapter 6

Adolescents and Adults (16-18+ years) with CF were recruited through the social media channels of the primary researcher. The lower age limit (16 years) was set to ensure that participants could adhere, felt comfortable and could provide *quality* answers during the interview schedule. The method of recruitment was voluntary participation. Individuals who expressed a desire to participate received written information (Appendix E) detailing the exact procedure, schedule and study details via email. Prior to interview, individuals were explained the process by the main researcher to ensure that they read and understood everything. All participants were informed that they could voluntarily withdraw at any stage of the interview and their clinical care would not be compromised for doing so. Verbal consent was taken and recorded via Zoom (Zoom Video Communications, Inc. 2020). Patients aged <18 years were required to provide an email from their parent or guardian of which written and verbal assent was needed prior to the commencement of the interview.

Chapter 7

All participant data within this study was obtained from annual review data between the years of 2019 and 2021 from individuals receiving clinical care from University Hospital

Llandough, Wales. In addition to inclusion criteria with regards diagnosis, the following inclusion criteria was also utilised at the onset of the study:

- Hetrozygous/Homozygous for F508del mutation
- At least 2-years worth of data from annual review clinics
- Receiving modulator treatment as of 2020/2021
- Currently receiving treatment at the adult centre for CF at Llandough University Hospital

In addition to this, CF individuals were excluded from analysis on the basis of:

- Received or due to receive transplantation
- <18 years of age
- No presentation of F508del mutation
- No data for 2+ years at annual review

3.5 Participant information and consent/assent

For the respective studies (Chapter 4 and 6), all participants were provided with research ethics committee approved written information sheets outlining the purpose of the study, as well as all the procedures involved, expected time commitment and information with regard to withdrawal. Verbal consent was obtained and recorded for Chapter 6, with written consent attained for the individual within Chapter 4. Examples of all information sheets alongside study specific consent forms for Chapters 4 and 6 are provided in the appendices.

3.6 Age

Decimal age was calculated to the nearest 0.1 year. This age was calculated on the basis of the difference between date of birth and age at the commencement of the study protocol. For registry data, age was determined as the years and months since the relevant annual review clinical visit. Age in this scenario was rounded to the nearest whole year. Age within Chapter 7 was recorded as an individual's age on the 31/12 of the respective year.

3.7 Anthropometry

Anthropometric data was collected at the participant's first testing session for each individual study. All measurements were taken by the same researcher to ensure repeatability. For secondary data, all anthropometric data were taken as part of the individual's annual review by a member of the patient's clinical team.

3.7.1 Body Mass

Body mass was measured as kilogrammes (kg). Body mass in Chapter 4 was taken using electronic weighing scales (Seca 876, Hamburg, Germany) and rounded to the nearest 0.1 kg**.** Equipment used to collect data for the Chapter 5 and 7 is not available and subject to the individual centres discretion.

3.7.2 Height

Height was measured to the nearest centimetre (cm) using a stadiometer (Seca 213, Hamburg, Germany). Individuals were asked to remove their footwear and position their back to the measuring rod on the stadiometer, ensuring feet were together with heels touching heel plate or back of the stadiometer. The participant was instructed to look straight ahead, and the head plate is brought down until it touches the top of the head with gentle pressure.

3.7.3 Body Mass Index (BMI)

Body mass index was calculated for each individual using the following equation:

$$\text{Body Mass Index} = \text{Weight (kg)} / \text{Height (m)}^2$$

All experimental studies using BMI were in adult populations. For registry data where individuals were under the age of 18 years, BMI scores were grouped using age and sex specific percentiles based on growth charts. The National Institute of Health (NIH) now uses BMI to define a person as underweight, normal weight, overweight or obese with classifications listed below:

Table 3.1. BMI classifications, adapted from Weir and Jan, (2020).

Adult Populations	
Severely Underweight	BMI less than 16.5 kg/m^2
Underweight	BMI under 18.5 kg/m^2
Normal Weight	BMI greater than or equal to 18.5 to 24.9 kg/m^2
Overweight	BMI greater than or equal to 25 to 29.9 kg/m^2
Obese	BMI Greater than or equal to 30 kg/m^2 - Obesity class I – BMI 30 to 34.9 kg/m^2 - Obesity class II – BMI 35 to 39.9 kg/m^2 - Obesity class III – BMI greater than or equal to 40 kg/m^2
Children/Adolescent Population	
Underweight	<5th Percentile
Obese	>95th Percentile

3.8 Pulmonary Function

Forced Expiratory Volume in one second (FEV_1), Forced Vital Capacity (FVC), FEV_1/FVC ratio, Peak Expiratory Flow (PEF), and Forced Expiratory Flow between 25-75% of vital capacity (FEF_{25-75}) were assessed using a flow-volume loop spirometer (EasyOne, ndd Medizintechnik AC, Zurich), following guidelines from the British Thoracic Society (British Thoracic Society, 1994). Patients were seated comfortably and a minimum of three acceptable tests were obtained. Individuals were instructed to place their lips around the mouthpiece with a tight seal. They were verbally encouraged to produce a maximal effort at the beginning of the blow and continue to exhale until no further air could be exhaled to achieve a maximal test. Repeatability criteria were satisfied when values did not differ by more than 100ml-150ml between tests. The largest FEV_1 and FVC from the three acceptable tests were then used to determine the severity of lung function impairment. In Chapter 7, equations from Quanjer et al. (1993) were utilised to calculate FEV_1 as a percent of predicted. Pulmonary function was split into categories of 'mild' ($\geq$ 70%), 'moderate' (40-70%) and 'severe' lung disease (< 40%) (Tomlinson *et al.*, 2020). For registry data, all pulmonary function data were collected by the individual's clinical team under the guidance of trained professionals.

3.9 Exercise Testing

All exercise testing was completed in a designated laboratory at Swansea University Bay Campus. All testing across visits was performed at the same time of the day, with individuals required to arrive for testing after 24 hours of rest from exercise, hydrated and 120-minutes postprandial. For consistency, the same ergometers and gas analysers were used.

3.9.1 Familiarisation

Prior to undertaking the CPET and exercise protocol within Chapter 4, the participant was familiarised to all experimental procedures in order to ensure that they understood what was involved. Appropriate, individualised adjustments were made to the cycle ergometer seat, handlebars and pedals and recorded for the subsequent testing/intervention sessions. Scales of rating of perceived exertion (RPE) and dyspnoea (RPD) were thoroughly explained prior to initiation of the research. Participants were also further informed of their right to withdraw at any time.

3.9.2 Equipment

For the CPET's utilised within this thesis, all exercise was performed on an electronically braked cycle ergometer (Lode Excalibur Sport, Lode, The Netherlands). This ergometer was fitted with a digital screen which displayed revolutions per minute (RPM). Individuals were advised to keep the cadence between 60-80 rpm for all testing procedures. To observe outcomes of the CPET, participants wore an oro-nasal facemask (Hans Rudolph, Shawnee, KS, USA), connected to a turbine and metabolic cart (Vyntus CPX metabolic cart, Vyaire Medical, Illinois, USA).

3.9.3 Incremental Ramp Test

All incremental ramp tests were preceded by a 3-minute warm up consisting of unloaded pedalling (20 W) during which participants were asked to practise maintaining a steady cadence. The warmup immediately transitioned into the test protocol. Pedal resistance was increased at a pre-determined rate (20 $W \cdot min^{-1}$) until volitional exhaustion (Buchfuhrer et al., 1983; Day et al., 2003). Participants were asked to maintain a cadence of 60-80 rpm and

instructed to continue this pace until volitional exhaustion, defined as a drop in cadence > 10 rpm for five consecutive seconds. Strong verbal encouragement was given consistently throughout the test protocol by the researcher.

3.9.4 Criteria for maximal oxygen uptake

A maximal CPET assessment was accepted if the participant achieved a plateau in $\dot{V}O_2$peak despite an increase in work rate. A linear regression was plotted over the *linear* portion of the $\dot{V}O_2$ response, with the residuals from the final 60-seconds isolated and examined. A negative residual indicated a deceleration in $\dot{V}O_2$ against power output and was considered a plateau when the magnitude of the residual was $\geq$ 5% of the projected $\dot{V}O_2$ (Barker et al., 2011). Verification of a maximal effort was further confirmed utilising a supramaximal verification bout. After a seated 15-minute rest, the participant completed a 3 minute warm up against 20 W followed by a step transition to 110% of peak power achieved during the ramp protocol. As within the ramp protocol, the test was terminated if cadence fell below 60rpm for over 5 consecutive seconds. This supramaximal bout is considered a valid and reliable protocol to confirm a maximal $\dot{V}O_{2peak}$ has been achieved within a CF population (Saynor et al., 2013).

3.9.5 Measurement of gas exchange parameters

For the incremental ramp test, gas exchange variables were measured on a breath-by-breath basis (Vyntus CPX metabolic cart, Vyaire Medical, Illinois, USA). Prior to each test, the gas analyser was calibrated using gases of known concentrations (15.0% O_2 and 5.0% CO_2) and the turbine volume transducer calibrated using a 3L syringe (Hans Rudolph, Kansas City, MO). The same gas anlayser was used for all exercise studies to ensure that no equipment variance could affect the results of the CPET.

3.9.6 Measurement of heart rate and oxygen saturation

Heart rate (HR) was measured continuously during exercise using a Bluetooth heart rate monitor (Polar Electro; Polar, Kempele, Finalnd). Blood oxygen saturation (SpO_2) was estimated using a non-invasive fingertip pulse oximetry and was measured prior to and during

the CPET. Measures of SpO_2 provided an objective measure of termination within the CPET, as it is suggested that exercise testing should be terminated at SpO_2 < 80% (Hebestreit et al., 2015).

3.9.7 Determination of gas exchange threshold

The gas exchange threshold (GET) was determined using the V-slope method as in Beaver, Wasserman and Whipp, (1986). The utilisation of GET represents a non-invasive method of determining the lactate threshold, with an earlier occurrence indicative of poorer fitness (Urquhart and Vendrusculo, 2017). Specifically, $\dot{V}CO_2$ was plotted against $\dot{V}O_2$, excluding the initial warm-up period. GET was identified as the breakpoint at which $\dot{V}CO_2$ (in L·min^{-1}) production increased disproportionately to $\dot{V}O_2$ (in L·min^{-1}) (Figure 3.1). The GET was then displayed graphically and visually verified by other members of the research team. If there was disagreement, then a third researcher was invited to assess the data. Such a method has been deemed appropriate for use within a CF population (Visschers et al., 2015).

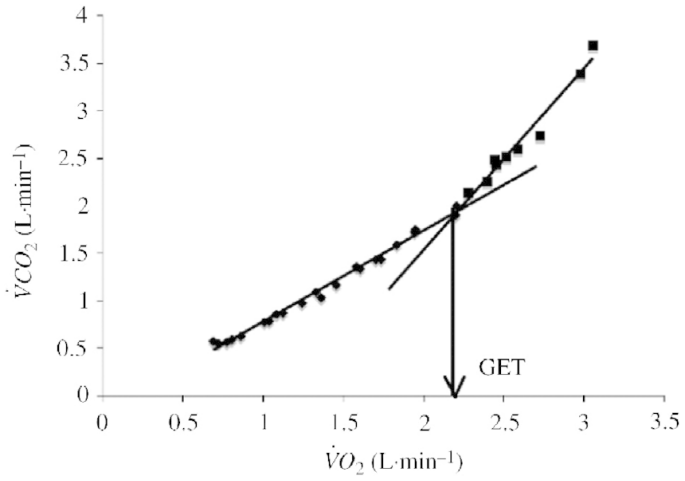


FIGURE 3.1. The determination of GET using the V-Slope method (Beaver et al., 1986).

3.9.8 Determination of oxygen uptake efficiency slope

The oxygen uptake efficiency slope (OUES) was determined using the following equation: $\dot{V}O_2 = a\ (\log \dot{V}E) + b$ (Baba *et al.*, 1996). Where an individual is unable or willing to reach volitional exhaustion, OUES represents a reliable and effort independent measure of ventilatory

efficiency of which may represent a suitable submaximal measure of $\dot{V}O_{2max}$ within a CF population (Saynor et al., 2013). Within Chapter 4, OUES was calculated at several points during the CPET, utilising the following thresholds: 50% $\dot{V}O_{2peak,}$ 75% $\dot{V}O_{2peak,}$ and 100% $\dot{V}O_{2peak.}$ More recently the validity of OUES as a surrogate to $\dot{V}O_{2peak}$ has been questioned, with clinical teams advised, where possible, to utilise CPET as a means of measuring aerobic fitness (Tomlinson et al., 2018; Williams et al., 2018).

3.9.9 Measurement of effort and dyspnoea

The Borg Scale (Borg, 1982) was used to assess subjective ratings of perceived exertion (RPE), with a modified Borg Scale used to measure ratings of perceived dyspnoea (RPD) (Pianosi et al., 2016). For Chapter 4, RPE and RPD were taken at the end of the first training session and then subsequently at the end of each training session, immediately after the cessation of exercise. Individuals were familiarised with both RPE and RPD before commencing in the respective exercise protocol.

3.9.10 Questionnaires

Individuals were asked to complete the revised version on the CF questionnaire (CFQ-R). The CFQ-R was devised to measure impact of CF on overall health, daily-life, perceived well-being and symptoms was developed specifically for use within CF patients. It is considered the best validated and most widely used method of patient reported outcomes for CF. Individuals in Chapter 4 completed the CFQ-R at the beginning and cessation of the research protocol. If queries arose around the questionnaire, then individuals were able to ask for help from a member of the research team.

3.10 Reduced Exertion High Intensity Interval Training (REHIT)

3.10.1 Equipment & Protocol

All REHIT sessions were completed as in Metcalfe *et al.* (2012) (Figure 3.2). All sessions were completed on a mechanically braked cycle ergometer (Ergomedic 874e, Monark, Vansbro, Sweden). Individuals completed the REHIT protocol three time per week, interspersed with 24-hr rest periods, for a six-week period. Individual sessions across the six-week period lasted a total of 10-minutes, including warm up and cool down. Participants completed two maximal sprints per session, ranging from 10 seconds (Week 1), 15 Seconds (Week 2-3) and 20 seconds (Week 4-6). Prior to each sprint individuals were asked to increase pedal cadence against no resistance before a weight/breaking force of 7.5% bodyweight was applied to the ergometer for the required sprint duration. Individuals were given verbal encouragement throughout to ensure maximal effort on each sprint.

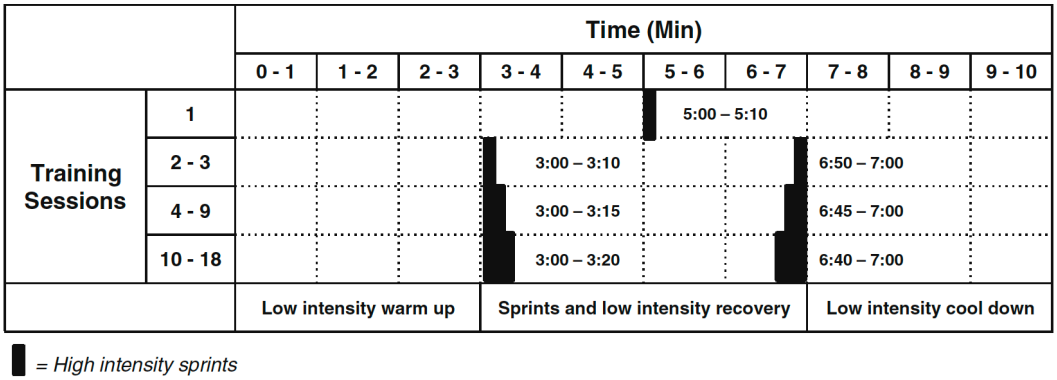


Figure 3.2. REHIT protocol, taken from Metcalfe *et al*. (2012) with permission.

3.11 Qualitative Measurement

3.11.1 Semi-Structured Interviews

Semi-structured interviews were conducted on adults with CF to ascertain individual experiences of Kaftrio. Specifically, individuals were asked about any changes associated with Kaftrio (positive or negative) in relation to their life pre-modulator therapy. A semi-structured interview schedule was developed with a secondary qualitative researcher, consulting the existing literature and draft schedules were discussed by the research team to ascertain suitability of all questions. Questions were delivered by the interviewing researcher (Sean Aspinall) in a logical order, with initial questions being open ended to invite discussion and important points developed as the interview proceeded to explore experiences of Kaftrio in more detail (Kvale and Brinkmann., 2009). In addition, the researcher ensured that questions were worded in a manner that developed an element of trust and were not leading.

Individuals were given enough information to fully understand the topic of interest, with participants free to respond however they felt appropriate (Clarke and Braun., 2014). During interview, probes and prompts were used to encourage elaboration on certain points, for example:

"How did that make you feel?" and "Tell me more about that"

The semi-structured interviews investigated an individual's experiences of life with CF pre-commencement of modulator therapy. The research focused on the impact modulator therapy had had on: physical health, psychological wellbeing, relationships with family and friends, relationships with clinical teams, hopes for the future and a reflection on the past, as well as elaborating on areas of interest (Gill *et al.*, 2008). Research questions were not fixed and used as a guide, tailored to the individual conversation. Given the researchers personal understanding with CF, he was able to exchange experiences with individuals, making participants feel comfortable about contributing honestly whilst at the same time balancing an empathetic and professional standpoint (Ashton., 2014). In line with (Rubin and Rubin., 2012), the interview was concluded by asking participants to give a message to the 10% of people who were not eligible for Kafrtrio, reflecting on what they would have done differently in the past, knowing what they know now. Such a final question allowed participants to summarise their experiences, which (Rubin and Rubin., 2012) state allows an individual to feel in control through providing a final statement of their narrative.

Given the retrospective nature of the interview, it was reliant on the researcher's ability to reconstruct the past using the information available. The logical progression of the interview aided in ensuring that things were discussed in a manner that explored life pre- and then post-Kaftrio. Interviews were recorded, in which the recordings were listened to by the researcher and the supervisory team to confirm the effectiveness of the interview schedule.

3.11.1.1 Conducting the interview

Individuals took part in the study voluntarily in response to an advert on the main researcher's social media channels. Eligibility was discussed via messenger in which once eligible participants were identified, individuals were sent an email containing an information sheet.

Individuals were then asked to provide a time and date of their preference to schedule a video call via Zoom (Zoom Video Communications, Inc. 2020). Data collection was completed by the same researcher for all interviews to ensure continuity.

Prior to the interview, the researcher ensured that the participant had read and understood the information sheet before the study was verbally explained to them. Once individuals expressed an understanding for the study, they were presented with the opportunity to ask any questions. Individuals were then asked to provide verbal consent, which was recorded. Participants were at no time asked to disclose data on their address or telephone number. Individuals provided their email address so the researcher could contact them at the end of the research to share their findings. All confidential information was available to no one other than the researcher.

Once the interview was finished, individuals had a de-brief with the researcher and had the opportunity to reflect on the interview and ask any questions. Once the research had been analysed, the researcher contacted all individuals and shared a copy of the manuscript with them.

3.11.2 Self Report Interview

To explore the personal experience of the REHIT protocol (Chapter 4), the participant was asked to complete a self-report narrative diary throughout the duration of the REHIT intervention. The participant completed a diary entry pre-, post- and 12-hours post completing the exercise protocol. For the purpose of repeatability, a semi-structured interview schedule was developed with a secondary qualitative researcher. Questions were open ended in nature, exploring thoughts, feelings, motivation and challenges associated with each specific session. In line with (Teddlie and Tashakkori, 2009), all questions included written prompts to encourage further exploration of specific points where necessary. All diary entries were completed using the 'voice-note' feature in Whatsapp. All recorded diary entries were transcribed verbatim and analysed using thematic analysis (Braun and Clarke, 2006).

3.11.3 Thematic Analysis

Analysis of narrative data from both Chapter 4 and 6 was completed utilising thematic analysis. Braun and Clarke (2006) present thematic analysis as an analytic method which involves the generation of codes and themes from interactive (interviews and focus groups) qualitative data. For the initial topic of identifying data relevant to the respective research question, content analysis was used to examine frequency of responses in order to generate specific codes. Coding of the narrative data captures interesting and relevant aspects of the narrative with relation to the overarching research question. For all subsequent anlayses within Chapters 4 and 6, thematic analysis was utilised to construct themes from the codes within the data where there was commonality between participant responses. Construction of such themes allows for further exploration of both semantic (surface) and latent (underlying) meaning within a topic, ensuring analysis captures a broader pattern of meaning and individual perspective from the available data (Clarke and Braun, 2014). Themes were checked by members of the research team to ensure the validity of the respective themes.

One unique strength within this methodology is the researcher's personal experience with CF. The researcher had personal insight into CF after being diagnosed with the disease aged 2 years. The researcher also had experience of modulator therapy after being granted access to both dual and triple therapy modulators prior to commencing the research studies. The supervisory team believed that this insight would enable him to empathise with participants given he had a clear understanding of the day to day physical and psychological demands on CF individuals. When considering Langdridge's (2007) proposal of analytical rigor in phenomenological research, the attitude of the researcher is considered key when undertaking collection and analysis of the data. Langdridge affirms that the researcher is required to pay attention to everything that confirms or disconfirms the theme, with a taken for granted attitude not permitted when analysing the data. Personal experience allowed the researcher to engage in an empathetic and meaningful interview but also produce a truthful and credible depiction of each participant's lived experience. The researcher acknowledged the variability of individual differences in CF and individual responses to modulator therapy, with the researcher aiming to investigate deeper into each individual's CF experience. Triangulation and transparency of the collected data were achieved through discussions with another qualitative researcher within the research team to determine appropriate interpretation of all phases of the analysis.

CHAPTER 4
REDUCED EXERTION HIGH-INTENISTY INTERVAL TRAINING (REHIT) IN AN ADULT WITH CYSTIC FIBROSIS: A MIXED METHODS CASE STUDY

4 REDUCED EXERTION HIGH-INTENISTY INTERVAL TRAINING (REHIT) IN AN ADULT WITH CYSTIC FIBROISIS: A MIXED METHODS CASE STUDY

4.1 Introduction

Cystic Fibrosis (CF) is one of the most common, life threatening genetic disorders, affecting more than 10,000 people, in the UK (Cystic Fibrosis Trust., 2020). Due to a defect in the CF trans membrane conductance regulator (CFTR), CF is associated with a range of systemic disorders but is primarily characterised by a build-up of abnormally thick mucus in the gastrointestinal tract and lungs leading to nutritional deficiencies, exercise intolerance, recurrent and chronic respiratory infections, and finally, respiratory failure (Cystic Fibrosis Trust., 2020). Peak aerobic capacity ($\dot{V}O_{2peak}$) is one of the strongest predictors of prognosis and mortality in individuals with CF (Vendrusculo et al., 2019). The growing body of evidence suggesting that exercise interventions can elicit improvements in aerobic capacity, as well as strength, quality of life and pulmonary function (Gruber, Orenstein and Braumann, 2011) is therefore of major clinical importance.

Despite the benefits associated with exercise, there is a tendency for individuals with CF to accumulate less moderate-to-vigorous physical activity (MVPA) than their healthy peers, with significantly fewer females achieving more than 30minutes of daily MVPA (Cox and Holland, 2017). As individuals with CF have to accommodate extensive daily treatment regimes alongside professional and personal commitments, many report a *lack of time* as a significant barrier to exercise (Moola, Faulkner and Schneiderman, 2012). As such, sprint interval training (SIT) and high-intensity interval training (HIIT) has been proposed as a time-efficient alternative to traditional moderate-intensity continuous exercise. Although research investigating the potential efficacy of HIIT/SIT in a CF population is limited, it appears that these exercise modalities are able to elicit increases in peak oxygen uptake ($\dot{V}O_2peak$) across a range of disease severities (Gruber et al., 2014). However, the time efficiency of many of these protocols is highly questionable, with a total time commitment exceeding 30-minutes per session towards the end of the training programme (Hulzebos et al., 2011). As such, total time commitment over a weekly period may ultimately fail to overcome barriers to exercise associated with a lack of time, leaving a need to identify whether current HIIT/SIT protocols can be modified to elicit positive exercise adaptations with a lower time commitment.

In healthy adults, Metcalfe *et al.* (2012) demonstrated that reduced-exertion high-intensity interval training (REHIT), involving two 20s Wingate sprints within a 10-minute exercise session, three times a week for six weeks, provides a sufficient stimulus to elicit a 14% increase in $\dot{V}O_2$peak. These findings suggest that the efficacy of interval training may not be related to the number of sprints *per se*, but rather the intensity associated with these sprints. Furthermore, although there is debate as to whether such intense exercise programmes are appropriate for use by the general population (Hardcastle *et al.*, 2014), REHIT only becomes associated with more negative affect, compared to moderate intensity continuous training (MICT), when sprint repetitions are increased (Stork et al., 2018). Given the substantially reduced time-commitment of the REHIT protocol, overall exposure to negative affect is brief when compared to a longer duration MICT protocol. Taken together with the suggestion that HIIT/SIT may elicit favourable physiological adaptations whilst placing a lower toll on the respiratory system (Burgomaster et al., 2005), REHIT may therefore represent a more preferable, and sustainable, exercise option for those with CF.

As individuals' perceptions of exercise are influenced by their baseline fitness levels and physical activity status (Frazão et al., 2017), it could be suggested that many within the CF population may feel physically 'incapable' and insufficiently motivated to adhere to the intense REHIT protocol, especially those who are largely sedentary. Moreover, in addition to capability and motivation, enjoyment plays a key role in exercise adherence. Whilst there is growing evidence to suggest that REHIT may be more enjoyable when compared to MICT in inactive individuals (Metcalfe et al., 2012), there remains a need for a better understanding of individual's phenomenological experience of high-intensity exercise. Although quantitative measures may provide an indicative value of 'enjoyment', this gives limited information regarding how the exercise experience can be manipulated to improve positive affect, enjoyment and long-term adherence. Given that the barriers to exercise within a CF population are multi-faceted, there is a need for researchers to adopt qualitative methods in order to explore in greater detail, whether high-intensity exercise can be suitable for a CF population.

If the results of the REHIT protocol in sedentary individuals can be replicated within a CF population, it may offer a novel, and truly time-effective exercise modality that can help

improve markers of cardiorespiratory health. Therefore, the aim of this case study was to understand the viability and sustainability of REHIT within a CF population. Qualitative methods were used to identify CF-specific exercise enablers and barriers that may need to be taken into account before the protocol can be delivered to a larger population.

4.2 Case Report

Participant

A 25-year old male, diagnosed with Cystic Fibrosis (homozygous F508del) at the age of two years, and currently being treated at the Manchester Adults Cystic Fibrosis Centre at the University Hospital of South Manchester (UHSM), was recruited for this case study in September 2018. His disease was characterised by pancreatic insufficiency and chronic infections with Pseudomonas aeruginosa, non-tuberculous mycobacterium abscesses (NTM) and allergic bronchopulmonary aspergillosis (ABPA) for over five years. Since January 2018, his FEV_1 had remained stable at around 2.34 L and he has had no inpatient admissions or intravenous antibiotics since June 2016. He is currently physically active and participates in Olympic weightlifting 3-4 times per week. As the participant experienced an acute exacerbation in December 2018, he was required to complete two-weeks of oral antibiotics and, subsequently, was unable to complete the intended six-week follow-up.

4.3 Experimental Design

A mixed-methods case study design was adopted to address the aims of the study, where conclusions were drawn from the collection and analysis of both quantitative and qualitative data. The participant underwent pre- and post-intervention testing for $\dot{V}O_2$peak and pulmonary function. Measures of pulmonary function were completed at UHSM, during clinic appointments booked in line with the study requirements. All other measurements, along with the training protocol, were completed at Swansea University. Ethical approval for data collection was approved by the College of Engineering Research Ethics Committee at Swansea University (July 2018, No: 2018-071).

4.3.1 Pulmonary Function

Forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) were measured at rest using a spirometer (EasyOne, ndd Medizintechnik AC, Zurich), following the British Thoracic Society guidelines (British Thoracic Society, 1994). The highest FEV_1 and FVC values were chosen from at least three efforts.

4.3.2 Cardiopulmonary Exercise Test (CPET)

Peak $\dot{V}O_2$ was determined by an incremental ramp test on an electronically braked cycle ergometer (Lode excalibur sport, Lode, The Netherlands). The participant completed a warm-up, pedaling at between 60-80 revolutions per minute (rpm) against a 20 W load for 3 minutes. The workload was subsequently increased by 20 $W \cdot min^{-1}$ until volitional exhaustion at which point a cadence of 60-80 rpm could no longer be maintained, despite strong verbal encouragement. To validate that it was a true maximal effort, the participant completed a supramaximal verification test to exhaustion (S_{max}), following at least 15 minutes of recovery. Specifically, a 3-minute warm-up at 20 W was followed by a 'step transition' to 110% of the peak power achieved during the incremental test, which the participant was asked to maintain for as long as tolerable. During both the incremental test and S_{max} test, the participant breathed through a low-dead space facemask and breath-by-breath gas exchange was measured (Vyntus CPX metabolic cart, Vyaire Medical, Illinois, USA). $\dot{V}O_2$peak, peak carbon dioxide output ($\dot{V}CO_2$) and peak minute ventilation ($\dot{V}E$) were determined using the highest value from a 15-second moving average. The gas exchange threshold (GET) was identified using the V-slope method and the oxygen uptake efficiency slope (OUES) was determined according to the following equation:

$$\dot{V}O_2 = a\ (log \dot{V}E) + b$$

where the constant *a* is defined as the OUES and *b* is the intercept with the y-axis. OUES was calculated using data up to and including three different thresholds (50%, 75%, 100% of $\dot{V}O_2$peak).

4.3.3 Quality of Life and Fatigue Index

During both pre- and post-testing visits, the participant completed a quality-of-life questionnaire (Cystic Fibrosis Questionnaire – CFK-UK; Alton et al., 2016). This validated questionnaire consists of twelve scales with scores ranging from 0 to 100, where higher scores represent a reduced frequency of symptoms and a higher QoL. The participant also completed the Checklist Individual Strength Questionnaire (CIS). This validated questionnaire has been used in both CF and chronic obstructive pulmonary disease (COPD) to assess fatigue (Nap-van der Vlist *et al.*, 2018). Higher scores indicate a higher degree of fatigue, greater problems with concentration, reduced motivation and less physical activity. A score of 35 or higher is used to define severe fatigue in adults.

4.3.4 Training Protocol

Akin to Metcalfe *et al.* (2012), the participant completed a modified version of the REHIT protocol, three times per-week, with at least 24-hours recovery between sessions, for a six-week period. All sessions were completed on a mechanically braked cycle ergometer (Ergomedic 874e, Monark, Vansrbo, Sweden) and lasted 10-minutes in total, including warm-up and cool down. Prior to each sprint, the participant was asked to increase pedal cadence against no resistance before a breaking force of 7.5% body weight was applied to the cycle ergometer for the specified sprint duration. Rate of perceived exertion (RPE) was collected immediately after each session using the 15-point Borg scale. At the same time-point, a subjective measure of dyspnoea was collected using the modified Borg dyspnoea scale.

4.4 Case Study

The case study approach offers an in-depth exploration of the REHIT protocol in an individual with CF. Though generalisability is limited, the case study allows for a detailed understanding of an individual's perception towards the REHIT protocol and identifies enablers and barriers which may encourage and inhibit the implementation of REHIT in future research or as an exercise prescription. Indeed, future research, informed by this case study, should endeavour to proactively promote any exercise enablers, and directly address the negative aspects of REHIT, in order to minimise attrition rates and ultimately gain an understanding of the

potential physiological and psycho-social benefits that REHIT can provide the wider CF population.

4.5 Self-report Narrative

To explore in detail the personal experience of the training intervention, the participant was asked to complete a self-report narrative over the six-week period. This was conducted pre-, post- and 12-hours post-exercise. The participant answered a series of open-ended, 'interview style' questions, relating to their feelings, expectations, motivation and challenges they associated with each specific session. The first and second author developed the series of questions, examples of which are shown in Table 4.1.

Table 4.1. Example interview questions. Full question schedule available in appendix.

Pre	Post	12-hours post
What are your thoughts on today's session?	What were the most enjoyable aspects of the session [if any]?	Are you thinking/feeling differently towards today's session?
	What were the most enjoyable aspects of the session [if any]?	
What are your expectations regarding today's session?	What factors enabled you to complete the session?	Was the exercise easy to fit in with your day?

Pre – Completed before the exercise session, Post – Completed following the exercise session, 12-hours post, Completed at least 12-hours post completing the exercise session

In line with Teddlie and Tashakkori (2009), all questions included written probes to remind the participant to elaborate on points where necessary. The participant's narrative was analysed through qualitative content analysis (Schreier, 2012). All forms of recorded communication were transcribed verbatim and read several times to ensure familiaristion. The transcripts were examined and quotations/phrases extracted, providing pertinent

examples of the participant's thoughts, feelings, expectations and behaviours before, during and after a REHIT session, in order to assess the suitability of, and challenges presented by, the protocol and how the individual was able to overcome these. All quotations/phrases with a similar meaning were categorised into the main themes, which in turn were collated further into sub-themes to provide a detailed narrative. Two of the research team independently analysed the data and reached a consensus on the themes and sub-themes.

4.6 Results

The participant characteristics pre- and post-intervention are shown in Table 4.2. At the end of the six-week intervention, there was no change in body mass or BMI. The adherence to the training programme was good, with an attendance rate of 94% (17/18 sessions). The reason for absence was exhaustion from an unsettled night due to persistent coughing.

Table 4.2 Participant characteristic data.

	Baseline	**Post-Training**
Age	25	25
Height (cm)	171.5	171.5
Weight (kg)	66.8	66.9
BMI (kg/m^2)	22.7	22.7
FEV_1 (L)	2.34	2.32
FEV_1 (% predicted)	54	53
FVC (L)	3.46	3.45
FVC (% predicted)	66	66
$\dot{V}O_2$peak ($L \cdot min^{-1}$)	2.54	2.70
$\dot{V}O_2$peak ($ml \cdot kg \cdot min^{-1}$)	38.0	40.4
V_E ($L \cdot min^{-1}$)	122.1	121.4
GET (%$\dot{V}O_2$peak)	55	59
OUES (50% $\dot{V}O_2$peak)	1,249.0	1,229.4
OUES (75% $\dot{V}O_2$peak)	1,909.2	1,953.6
OUES (100% $\dot{V}O_2$peak)	2,592.6	2,655.6

4.6.1 Physiological Measures

At the end of the six-week intervention, there was no difference in pulmonary function. In contrast, the REHIT protocol resulted in an increase in $\dot{V}O_2$peak of 6.3% and 6.1% when expressed in absolute terms or relative to body mass. Furthermore, the GET increased by 7% and OUES increased at both 75% and 100% of $\dot{V}O_2$peak.

4.6.2 Subjective Measures (RPE, Dyspnoea, HRQoL, CIS)

Overall, the training intervention was well-tolerated by the participant, with a mean six-week RPE score of 14, corresponding to 'somewhat hard'. Mean weekly RPE values peaked in Week 4. The mean dyspnoea score for the 6-week intervention was 4, corresponding to 'somewhat severe'. Mean weekly dyspnoea scores peaked in weeks 4 and 6, with a score of 5, corresponding to 'severe'. Following the six-week intervention, higher scores in the HRQoL questionnaire were found in the Physical (+33%) and Digestive (+13%) domains, whereas decreases were identified in the Emotional (9.08%), Treatment (50%), Body Image (20%) and Respiratory (27%) domains. There were no changes in the remaining domains. All measures from the CIS fatigue index showed decreases following the six-week intervention with the total score decreasing from 70 to 56 (20%). The largest decrease (44%) was the physical activity domain.

4.6.3 Qualitative findings

Three over-arching dimensions were identified: *motives towards taking part in the protocol; maintaining exercise protocol involvement; and barriers to adhering to the exercise protocol.* Please note that a pseudonym has been used throughout the following narrative.

Motives towards taking part in the protocol

The main motives for taking part in the protocol were: i) history of Physical activity (PA) and exercise for health management; and ii) not being defined by CF.

i) History of PA and exercise for health management

Ben had always been an active individual, with the pre-conceived notion that *"exercise will keep me well"* based on his mother's influence and beliefs. He has (until 2016) been active within martial arts since the age of 10 years, and as an adult was training up to 10 times per-week. After experiencing a significant knee injury, Ben's inactivity over a period of over 12-months led to him becoming underweight and experiencing a significant decrease in lung function and capacity to complete daily tasks. Therefore, to improve his day-to-day functioning and quality of life, he joined an Olympic weightlifting gym and has been an active member for the last two years, which, "*helped improve my health and helped me gain weight*". As a result, his lung function over the last year has been stable, although significantly lower than the previous few years. Therefore, for Ben, the key motive to exercise and engage within the protocol was to help maintain his overall health and "*make day-to-day life easier*". Specifically, he wished to undertake the protocol to "*test*" himself, see whether he could "*still do what I used to be able to do"* and ascertain if he could improve his health any further.

ii) Not being defined by CF

While Ben stated that he was more symptomatic as he aged (due to multiple chronic infections), he believed that engaging in this exercise protocol and improving his fitness may help him maintain his goal of not being defined by his CF; *"…whilst CF is a part of me; I never want to be defined by it".* For Ben, exercise represented an "*escape from reality"*, a place where he was able to be *"normal"* and not have to think about treatment or the daily routine that comes with CF: *"I can be a different person [when exercising]…where my only thoughts are to do with the exercise and the social environment that goes with that. At home I have CF. In the gym, I am Ben who lifts weights".* Accordingly, taking part in the exercise protocol provided Ben with an opportunity to "escape" CF, but also try and maintain control over his condition (rather than vice versa): *"I have CF, but that doesn't mean CF should stop me doing things. It makes things difficult but if I can keep well and keep fighting then I can avoid CF's control for as long as possible".*

Maintaining exercise protocol involvement (enablers)

The key reasons for sustained protocol involvement were: i) initial positive feedback; ii) short-term exercise commitment; iii) visualization; iv) management and planning of exercise; and v) social support.

i) Initial positive feedback

Ben's performance in the baseline test provided him with reassurance that his fitness was "*better than I thought*", and led to the belief that he was capable of completing the REHIT protocol "*I used to think that I would be less fit as my lung function declined. I have now learned this isn't necessarily the case."* Thus, this initial positive feedback not only enhanced Ben's perceived capability (self-efficacy) to exercise and complete the protocol, but also raised his desire to improve his fitness further: *"I came into this [protocol] happy with my* $\dot{V}O_2$ *if it was at 20. So, 38 is crazy! But I still want to see if I can improve"* Furthermore, Ben identified that the baseline score had reinforced his belief that the effort directed towards his exercise regime over the last two years had been worthwhile, and it provided further motivation to explore whether the additional cardio-based exercise would continue to improve his fitness capacity.

Of note, the increased self-efficacy gained from the baseline testing, prompted Ben's desire to exert more effort during the exercise protocol: *"…not that I would have gone less than 100%, but these results gave me the knowledge that I can complete this to a decent standard".*

ii) Low time-commitment

The structure of the REHIT protocol, with its low time-commitment and limited amount of high-intensity work, was a main contributing factor to taking part and then adhering to the exercise programme: "*the whole 10 minutes thing is a massive motivational factor. If the session was 30-45 minutes I would have found it very hard to justify to myself that it would be worth doing when I was so tired".* Given the large time-commitment to treatment and increased fatigue amongst most individuals with CF, Ben proposed that REHIT may represent a time-efficient strategy that may help implement exercise into their daily lives. He felt it represented a low-volume alternative to "*traditional*" endurance training, which may appeal

to those who want to improve their fitness, and/or prefer a low-volume exercise option. Similarly, given that improved health was one of Ben's main motives to begin the protocol, the potential to achieve this goal in such a short space of time was an important driver for adherence, *"I mean it's pretty hard to argue that only 10 minutes of your day is needed to potentially make your life a little easier".*

iii) Visualization

The use of psychological skills played an important role in continued adherence to the protocol**,** particularly during the tough sessions, and on days where Ben did not want to attend. This mainly included visualization, where he would imagine the consequences of non-compliance and successful completion: "*I visualized how I would feel if I missed a session…then visualizing myself after the session and the good feeling I have of completing a session… and then visualizing the end of the programme when it has all been worth the effort".* He had learnt this strategy through his treatment programme; *"I do the same with my treatment, as at times when I can't be bothered, I have to sit down and rationalize how I'm going to feel afterwards and how is it going to affect me long-term… normally I feel guilty and end up doing it"*.

iv) Management and planning of exercise

Ben did find that the intensity required for each session of the protocol was difficult, and after experiencing fatigue at the end of week 2, he chose to re-structure his current physical activity and daily schedule: "…*managing your week is very important to avoid both mental and physical exhaustion".* For him, this planning enabled him to recover and feel physically *"less exhausted"*, thereby giving him the opportunity to sustain involvement. Ben stated that *"…once I planned things properly, I knew I could manage the workload and my worries went away. It gave me the boost to know that I could still do this despite going through a tough period".*

v) Social support

Ben consistently referenced the support of a peer (i.e., researcher overseeing each exercise session) as a critical factor in enabling him to sustain involvement in the protocol. He believed that this person was, "*in it with me",* and so was invested in his successful completion of the protocol. Ben was also able to discuss his experiences and feelings (whether positive or negative) with a researcher, and such a sounding board helped rationalize his own feelings. Moreover, feedback from someone who was witnessing the exercise first-hand was considered highly motivating: "*My training partner today though said my sprints were much faster and my recovery was a lot better than Friday. This feedback is great, I think even if you feel you have had a bad session it may look a lot easier on the eye, and that changes your perception of the training session all together… having someone with you does give you that extra 1% you need just to going out the last few seconds".* Accordingly, social support (informational and emotional) enabled Ben to perceive a bad session more positively and notice the fitness improvements that were occurring through the testing: *"It [social support] helps because it [the protocol] never…feels easier, and I didn't notice I was getting better. So the feedback helped me know that I am getting fitter…and knowing that kept me coming back".*

Ben emphasised that the support provided by the peer/researcher also helped his motivation during each session, by offering encouragement and the exercise goal of counting down the remaining time: *"…we went with a 10 second count down so I knew how long I needed to keep pushing for"*. He also stated that this strategy was only effective during the last part of the sprints, and when the supporting peer verbalized the countdown: *"I have tried things like this in the past and if I watch the clock myself everything seems to go so much slower and then I slow down before the end because I know I am almost done. So, if you have someone helping you get through that last 10 seconds it keeps you going".* Overall, Ben concluded:*"…this protocol definitely needs someone to oversee it… because without them, and their encouragement, and their investment, it would have been very easy to slack off when it got tough".*

Barriers to adhering to the exercise protocol

The following barriers to exercise protocol adherence were identified and overcome by Ben: i) aggravating symptoms; ii) lack of enjoyment; and iii) fatigue.

i) Aggravating symptoms

Prior to the exercise protocol, Ben discussed how adverse physical reactions had prevented him participating in certain types of exercise and had created concerns regarding the current protocol: "*…obviously physical symptoms after doing cardio are never nice. Being sick, breathless, wheezing and a tight chest is something people with CF know is going to be part of their day-to-day life anyway. So why exacerbate it further with this exercise?".*

Indeed, due to past negative experience of aerobic activity, in a period when his health was declining, Ben had chosen to undertake exercise that did not exacerbate his symptoms. Thus, given his understanding of this particular type of protocol, Ben hoped it would present an opportunity to overcome the perceived barriers associated with exertion (i.e., breathlessness): *"If this was a long duration, continuous exercise protocol I would have 100% avoided it. I know I cough doing stuff like that so what's the point*". Moreover, as it was completed in an environment where his condition was understood, his symptoms could have been managed without any explanation, which was considered important.

Thus, Ben reinforced the importance of experiencing a positive physical response, and gaining confidence, early in the exercise programme: *"Once I got the first few sessions out the way and realized, you know what, I'm not actually coughing, then my confidence just doubled… it was nice to be able to push myself again without coughing or throwing up".* Moreover, by the time Ben had experienced any symptoms (Week 3), the fact that he was able to continue, gave him further belief in being able to overcome such barriers; *"Today I actually had a little cough during the rest after the first sprint. Nothing major but I am sure in the past that would have put me off doing another sprint just in case it got worse…I think the fact that it passed so quickly and I recovered in time to give 100% in the second sprint; just helped me believe I can do this".*

ii) Lack of enjoyment

Though the sessions were perceived as manageable and Ben overcame many of the barriers to partaking in PA, he stated that he didn't particularly enjoy the protocol due to its level of intensity: *"On paper, two 20's sprints looks easy, but the resistance is so much that it completely alters how the session feels!"* Ben noted that whilst he eventually got used to the intensity of each session, when time increases were implemented, these were the sessions he least looked forward to: *"You spend weeks getting used to 15s sprints and can just about manage them, then they increase and it feels like two steps back…20s almost seems impossible before you do it"*.

However, Ben believed that his background in high-intensity sports played a significant role in maintaining adherence: *"I have experience in grinding through sessions and looking at the bigger picture, even though at the time things don't feel pleasant…Maybe for those who don't have this experience, they may find things more difficult".* Ben explained that as not every session was unpleasant, he tried to rationalize afterwards, why that particular session may have been more difficult or less enjoyable. Taking into consideration sleep, nutrition, daily activity and stress, Ben stated that he was able to account for his lack of enjoyment and look to correct that for future sessions. Similarly, Ben identified that he would try to remember why he was taking part in this process, and revisited his belief that this programme would be beneficial in the long-term: *"I know every session can't be enjoyable, that's the case in every sport. But with this, I know it is only short-term and whilst not always enjoyable, I can see my goal at the end and that's what keeps me going. I want to be fitter and one bad session will not deter me from achieving that".*

iii) Fatigue

Whilst Ben was able to complete the protocol, fatigue was a major barrier to adherence, especially during the first 3 weeks. An inability to manage the programme alongside his own physical activity left Ben, *"mentally and physically exhausted…"* and increasingly amotivated*, "I don't know how I'm going to do six-weeks of this".* His main concern was that the feeling of exhaustion had the potential to manifest itself as an infection or period of illness: *"as I kid I ran myself into the ground exercising without knowing it and got an infection which I have*

never got rid of since…Whilst I love to push myself, I am far more aware of my boundaries these days". Therefore, Ben reiterated the importance of "*knowing your body*" as a main factor in adhering to the protocol. *"…at the end of the day, this [exercise] is supposed to be beneficial. I think my advice to anyone would be 'if you need a rest, take one'. Having a few days off is going to be more beneficial if you complete the protocol rather than make yourself ill pushing too hard".* Accordingly, Ben missed one session when he was feeling particularly fatigued and reduced any additional PA until his fatigue was managed. Such management of his training was the key mechanism to overcome this barrier.

Therefore, while the protocol appears to be difficult, with periods in which the participant may need to be monitored, managed and encouraged to continue, Ben concluded that: "*Those with CF go through far worse experiences on a day-to-day basis, and this protocol should be seen as something they can conquer as opposed to something negative…In the grand scheme of things this [the protocol] is easy".*

4.7. Discussion

The aim of the present study was to investigate the viability of a low-volume HIIT protocol in an individual with CF and therefore extend the limited literature regarding the potential beneficial effects of HIIT/SIT in individuals with CF. Overall, the findings indicate that the number of sprints and overall exercise duration may be reduced substantially when compared to both MICT and traditional HIIT/SIT, whilst still retaining the positive physiological effects seen in previous exercise research (Gruber *et al.,* 2014a; Hulzebos *et al.,* 2011). The narrative data also provides a holistic insight into the experience of completing REHIT, highlighting specific factors that need to be considered to encourage adherence and enable successful future exercise prescription. Specifically, this case study demonstrates the importance of the low time-commitment, highlights the imperative role that social support plays in enhancing motivation and self-efficacy, and identifies the collective impact that both factors have on sustaining adherence. Hence, REHIT may represent a potentially highly appropriate and effective exercise modality for a variety of CF individuals, if such factors are considered.

Despite the low time-commitment and training volume, the current six-week REHIT protocol was associated with a 6.3% and 7.0% increase in $\dot{V}O_2$peak and GET, respectively. Such increases in aerobic capacity are of considerable clinical significance, given that a higher aerobic capacity is associated with improved HRQoL, a reduced risk of hospitalistion and improved survival (Vendrusculo et al., 2019). It is interesting to note that the magnitude of change observed in this case study is in accord with those typically reported in those with CF following conventional MICT (Gruber et al., 2011b) or HIIT protocols (Gruber et al., 2014a) despite the time commitment being significantly less. This is pertinent for those with CF; many of whom have to accommodate ≥2 hours of daily treatment alongside the usual demand of 'regular' daily life (Boyle, 2003).

Indeed, for any exercise prescription to be effective, adherence is imperative. Therefore, the potential health improvements must be balanced with the accessibility and the ability to overcome individual barriers to exercise. As such, exploring the minimum dose of exercise required to elicit enhanced aerobic fitness and HRQoL is crucial to identifying long-term, effective strategies. The current findings suggest that the *intensity* of work, as opposed to the total *volume*, may be the key factor when considering the training stimulus (Metcalfe *et al.*, 2012). Although the mechanisms which underpin the adaptation to REHIT remain uncertain, it is widely suggested that peripheral adaptations involving the rate of glycogen depletion and activation of glycogen-bound protein kinases during initial sprint efforts play a significant role (Metcalfe *et al.*, 2015). For those whose pathological pulmonary constraints limit daily PA to short intermittent efforts, peripheral muscular adaptation may represent an opportunity to improve exercise capacity despite a diminished ability for pulmonary improvement. In accord with findings in severely affected adults with CF in response to HIIT (Gruber et al., 2014a), the improvement in exercise capacity at the GET may reflect these muscular adaptations. Congruent with Metcalfe *et al.,* (2012) the present study questions whether conventional HIIT/SIT protocols may be longer and more strenuous than necessary.

The current case study identifies key psycho-social elements that may underpin the success of this specific protocol, furthering our understanding of how individuals with CF may experience and perceive the REHIT protocol. Indeed, by understanding the influence of perceptions such as *short-term exercise commitment, peer support* and *management of*

fatigue, participant's experience of the protocol can be optimised, and thereby facilitate adherence. Given typical attrition rates associated with general exercise interventions, an in depth understanding of individual facilitators to exercise is vital. That is, for REHIT to be considered effective, retention of participants in future, larger studies is key to elucidating the true viability and validity of REHIT, before it can be considered for use more broadly, as an exercise prescription. Similarly, for a population that may experience feelings of low competence, self-esteem and motivation to exercise (Moola, Faulkner and Schneiderman, 2012), understanding the motives and facilitators/enablers of exercise, as well as ensuring that exercise is perceived as 'fun' and not a 'treatment' (Radtke et al., 2015) will underpin the development of effective therapeutic strategies in the future.

The short-term exercise commitment associated with REHIT was cited as a key element in maintaining adherence over the six-week period. Specifically, the limited weekly time-commitment, coupled with the brief nature of the individual sessions, ensured REHIT was perceived as 'manageable', despite the high-intensity bouts. Although it is suggested that high-intensity exercise may be perceived as too arduous, evoking lower levels of self-esteem (Hein and Hagger, 2007), the manageability of each REHIT session induced increased levels of motivation in the current study, through enhanced self-efficacy; with the individual also noting that completing each session adding to a sense of achievement. As opposed to MICT, HIIT enabled the individual to experience multiple mastery experiences per session, thus enhancing the participant's self-efficacy towards the interval training (Jung, Little and Batterham, 2016). Such increases in self-efficacy and motivation are important for the development of sustainable, long-term health behaviour patterns (Teixeira *et al.*, 2012). Furthermore, Segar *et al.* (2016) reported that individuals are unlikely to be motivated towards exercise for health reasons alone, highlighting the need to utilise protocols that promote differing motives to exercise.

A widely purported limitation to the utility of HIIT/SIT is that it is not enjoyable, and as a result, the majority of people will not engage in this type long-term (Hardcastle *et al.*, 2014). However, recent studies suggest that the affective response to REHIT is similar to that experienced in MICT (Schneiderman-Walker *et al.*, 2000), although the applicability of these findings to those with CF may be limited. Specifically, whilst the total session RPE reported in

the current case study is in accord with Metcalfe *et al.* (2012), it is important to account for factors such as CF-related fatigue and muscle weakness, which may mean that individuals with CF experience higher levels of negative affect during each sprint compared to healthy counterparts. One potential strategy to avoid such issues would be to reduce the resistance to 5% as utilised elsewhere (Gillen and Gibala, 2014) as the high resistance contributed to the presently reported negative perception of the protocol. However, any such reduction in intensity would need to be balanced with the potentially reduced potency of this protocol to elicit clinically significant physiological benefits. Conversely, 5% resistance may still be perceived as strenuous for those who are sedentary or those with moderate-to-severe disease progression. As such implementing effective strategies identified within the narrative, such as positive feedback, encouragement and promoting optimism towards the next session through visualisation and goal setting, may contribute to enhancing enjoyment and decreasing negative affect.

The present study also highlighted the pivotal role of social support in the implementation of, and adherence to, this protocol. Social support has been demonstrated as a positive predictor of health behaviours and associated with increased PA participation in CF populations (Moola, Faulkner and Schneiderman, 2012). The current findings support the tenets of the social cognitive theory (SCT; Bandura, 1998), whereby increased informational and emotional social support is proposed to enhance individual's levels of self-efficacy and motivation. Support and feedback on a session-by-session basis were noted as promoting a positive perception of the REHIT protocol and was a major contributing factor in ensuring that each session was perceived as manageable. Incorporating motivational goal-setting tools, such as a 'countdown' for the final seconds of the sprint helped maintain effort and increase a sense of mastery / accomplishment at the end of each sprint. Given the socially-isolated nature of CF, with some individuals feeling they are unable to exercise with their 'able-bodied peers', support from family, friends or a member of the individual's care team is evidently essential to help individuals engage with the REHIT protocol, and future physical activity (Moola, Faulkner and Schneiderman, 2012). With the importance placed on parental support, especially for younger individuals, implementation of the protocol in a home environment may facilitate the active engagement of parents with their child's exercise and PA (Moola, Faulkner and Schneiderman, 2012).

When considering barriers to exercise, it was highlighted that fatigue negatively influenced enjoyment and self-efficacy, whilst also being the only factor linked to potential withdrawal from the study. Interestingly, CIS data suggests that the individual presented with severe fatigue prior to starting the protocol. Given that a higher fatigue score is associated with a decrease in the individuals perception of physical functioning (Nap-van der Vlist *et al.*, 2018), the individual's baseline level of fatigue may have negatively altered the perception of the protocol, as opposed to the protocol itself being overly strenuous. As 26% experience severe fatigue (Nap-van der Vlist *et al.*, 2018), addressing the underlying physiological and psychosocial factors that underpin this fatigue is key to maintaining REHIT adherence. Accordingly, implementation of the CIS into both a research and medical setting may aid in identifying individuals with a higher probability of experiencing fatigue, enabling strategies to be put in place to manage this and potentially reduce attrition rates.

Whilst fatigue was raised as a concern, REHIT was not associated with negative physical experiences, such as breathlessness and coughing, which have been consistently associated with early termination, or complete avoidance, of exercise (Moola, Faulkner and Schneiderman, 2012). Both narrative and physiological data highlighted the limited impact REHIT had on levels of dyspnoea, with the individual noting how a lack of symptoms enhanced their positive perception of REHIT and willingness to adhere. Whilst there is likely to be a large variance in dyspnea severity in response to REHIT between individuals, muscular fatigue and dynamic hyperinflation have been identified as the two greatest predictors of dyspnoea in those with mild-to-moderate disease severity (Stevens and Neyedli., 2017). Given that the REHIT model encompasses large rest periods and a low-volume of high-intensity work, it may represent an exercise mode that could promote a positive association with exercise for those with CF, by placing limited strain on the respiratory system and promoting an increased sense of mastery.

4.8 Limitations

Although there are numerous strengths of the present study, it is pertinent to note that the generalistion of the results from a case study must be considered with caution. Specifically, the individual in the current case study presented with a positive perception of exercise prior

to partaking in the exercise protocol, with exercise viewed as an instrument to demonstrate that CF had not 'defined him' (see Moola *et al.,* (Moola, Faulkner and Schneiderman, 2012). Given that exercise is part of the individual's identity (Duncan *et al.*, 2010), the ability to self-generate motivation towards exercise may have played a key role in his willingness to adhere to the programme, despite adversity over the six-week period. Whether such ability to overcome adverse periods would be the case for other individuals, or those with a negative perception of exercise needs to be explored with the aim of ensuring that REHIT is accessible to every CF individual in the future. It is also important to highlight that the participant chose to continue with regular physical activity (weightlifting) throughout the six-week intervention, which may have had an additional training and fatigue effect that cannot be quantified within the case study. However, it is also pertinent to note the participant's high baseline fitness, according to CF-specific fitness levels (Gruber, Orenstein and Braumann, 2011). It could therefore be postulated that REHIT may be able to elicit considerably greater improvements in those with low baseline fitness, given its inverse relationship with the magnitude of change in response to an exercise intervention (Gruber, Orenstein and Braumann, 2011).

4.9 Conclusion

The present case study identifies REHIT as a feasible and potentially effective alternative to HIIT/SIT and MICT. Given that current HIIT/SIT and MICT exercise modes have been suggested to be unnecessarily strenuous, REHIT could represent a time-effective alternative that may be more accessible for a wider CF population. The current study identifies key facilitators and barriers to REHIT, which should be considered in future studies seeking to implement HIIT. Specifically, the pivotal role of self-efficacy and social support for long-term adherence was highlighted, with adherence facilitated by the short duration of each sprint and overall session. Whilst initial findings are promising, further research is needed to fully elucidate the applicability and effectiveness of REHIT within the CF population.

CHAPTER 5
THE EFFECT OF NUTRITIONAL STATUS ON TRAJECTORY OF PULMONARY FUNCTION DURING ADOLESCENCE IN INDIVIDUALS WITH CYSTIC FIBROSIS

5 THE EFFECT OF NUTRITIONAL STATUS ON TRAJECTORY OF PULMONARY FUNCTION DURING ADOLESCENCE IN INDIVIDUALS WITH CYSTIC FIBROSIS

5.1 Introduction

Cystic Fibrosis (CF) is the most common genetic disorder in Caucasian populations caused by a single genetic defect (Rommens et al., 1990). Abnormalities of the cystic fibrosis transmembrane conductance regulator gene (CFTR) lead to defective ion transport and altered function of organs, such as the pancreas, respiratory and digestive tract in which epithelial cells are largely expressed (Sheppard and Welsh, 1999). As such, CF is characterised by nutritional deficiency and frequent respiratory infections, with the foremost cause of morbidity and mortality being lung pathophysiology (Stephenson *et al.*, 2015).

Over recent decades, there has been a significant improvement in the life expectancy of those with CF. Specifically, advancements in nutritional and pulmonary therapy have improved the median life expectancy from 31.3 years in 1998 (Orenstein et al., 2004) to 49 years in 2019 (Cystic Fibrosis Trust, 2019). Despite these advances, females with CF continue to have worse outcomes in comparison to their male counterparts, even when controlling for modulator therapy (Harness-Brumley et al., 2014; Sweezey and Ratjen, 2014). Indeed, a 1997 analysis of over 21,000 individuals with CF found a three-year difference in life expectancy, with males and females, on average, living 28.4 and 25.3 years, respectively (Cystic Fibrosis Trust, 2019). This disparity still exists despite aggressive treatment, with registry studies worldwide consistently showing poorer outcomes in females with relation to morbidity and mortality (Harness-Brumley et al., 2014; Olesen et al., 2010; Rosenfeld et al., 1997)**.** Although life expectancy has increased almost linearly over the past decade, female life expectancy in the UK as of 2019 is significantly shorter than that of males (45.7 vs. 51.6 years, $P<0.001$; Cystic Fibrosis Trust, 2019). It is also pertinent to note that poorer disease outcomes in females compared to males are congruent with the findings of multiple epidemiological studies in various respiratory diseases (Celli et al., 2011; Farha et al., 2009; Morrissey and Harper, 2004). This sex disparity is of particular concern given it is in direct contrast to that observed in the general population, in which females have a four-year survival benefit (Public Health Matters, 2020). Whilst the mechanisms underpinning this sex disparity remain contentious, and are likely disease-specific, the rate of exacerbation has been shown to increase in girls with

Asthma (Suruki et al., 2017) and CF (Saint-Criq and Harvey, 2014) at the onset of puberty, suggesting that endogenous oestrogen production may play a significant role. Indeed, oestrogen has been implicated in a greater viscosity of airway mucus through its effects on airway surface liquid (Saint-Criq and Harvey, 2014) and in the development of bacterial infections, with females with CF characterised by an earlier acquisition of chronic mucoid *Pseudomonas Aeruginosa* infection (Chotirmall et al., 2010; Levy et al., 2008).

The cause of this sex disparity is likely to be multi-factorial, encompassing the fundamental physiological differences (i.e. hormonal status), in addition to nutritional and behaviour differences between sexes (Lam et al., 2020; Stephenson et al., 2015). The effects of nutritional status and body mass index (BMI) on clinical outcomes are well established in CF, with poorer weight management identified as a significant influencing factor when considering sex disparities (Marshall et al., 2005; Saint-Criq and Harvey, 2014). There is consensus that malnutrition and low BMI within a CF population is associated with a decline in pulmonary function and increased risk of mortality (Harindhanavudhi et al., 2020; Hauschild et al., 2018), with a positive association between better nutritional status, BMI and high pulmonary function frequently reported (Boëlle et al., 2012; Konstan et al., 2017). However, despite this, females with CF are documented to have smaller relative energy intake and lower BMI than their male counterparts and 'healthy' age-matched females (Collins, O'Loughlin and Henry, 1998; Stephenson et al., 2015). Congruent with Wenninger et al. (2003), females with CF are reported to be more satisfied with their body image than males and non-CF peers, despite low BMI and bodyweight (Abbott et al., 2000; Tierney, 2012). Furthermore, the desirability of females to attain a lower bodyweight is believed to play a role in the sex disparity, with females more resistant to adhere to nutritional interventions (Simon et al., 2011), of which may have substantial complications when considering long-term prognosis.

Whilst early treatment intervention appears to be reducing the discrepancy in survival between sex (Stephenson et al., 2015), female sex is still considered to be an independent risk factor of death (Harness-Brumley *et al.*, 2014). Although much emphasis is placed on the effects of endogenous hormones, given the association between BMI and survival, it is likely that nutritional status contributes to the disparity in pulmonary function and survival (Lam et

al., 2020). Therefore, the aim of this study was to further understand the influence of BMI and sex on pulmonary function trajectories through childhood and adolescence, and to identify whether female BMI has a significantly greater impact on clinical outcomes when compared to their male counterparts.

5.2 Methods

5.2.1 Ethics

The study received NHS research ethics approval (07/Q0104/2 UK Cystic Fibrosis Registry, AB/AM04/1) for the use of anonymised data.

5.2.2 Study Design and Participants

This longitudinal study used annual data across an eight-year period, between 2007 and 2015, from the United Kingdom (UK) CF Registry. The UK CF Registry contains detailed clinical data of people with CF under clinical care within UK hospitals and is estimated to capture around 99% of the UK CF population (Schlüter et al., 2019). All UK-based CF centres routinely collect data in a standardised manner. All data included in the registry is collated from a comprehensive annual review clinic, including pulmonary function and nutritional status. The registry has National Health Service (NHS) research ethics approval; all individuals within the registry provide informed consent for their data to be used for research purposes.

Participant's data were included between the ages of 6 and 17 years to ascertain trajectories across childhood and adolescence. All demographic (age [years], sex [male, female]), BMI percentile [BMIp], and pulmonary function (percent predicted forced expiratory volume in one second [ppFEV$_1$]) data was obtained from the registry database. Specifically, pulmonary function values were collected in accord with the British Thoracic Society (1994) guidelines. Congruent with other studies examining the sex disparity in clinical outcomes in individuals with CF (Rosenfeld et al., 1997; Taylor-Robinson et al., 2020), the primary outcome was ppFEV$_1$.

The definition of 'puberty' is based on a data from Goldsweig et al. (2019). Although it was believed that individuals with CF experience a delayed pubertal onset, newer data shows a

normalisation of pubertal timing within a CF population (Goldsweig et al., 2019). As such, puberty for females is defined as 9-12 years and 10-13 years in males (Bordini and Rosenfield, 2011). Adolescence is defined as 10-24 years as outlined Sawyer et al, (2018), for the purpose of this study, adolescence specifically relates to 10-17 years.

5.2.3 Statistical Analyses

Descriptive data are reported as means $\pm$ standard deviation (SD), unless otherwise stated. Welch's t-tests were used to determine sex differences in $ppFEV_1$ for a given BMI percentile. A linear mixed model was used to analyse the effect of multiple confounders [sex, BMIp] on FEV_1 for each participant, across time. First, a compact model was developed using only linear terms of age, BMI and the interaction between the two covariates. Specifically, each term was also an interaction with sex to identify significant between-group differences. This model was then extended (full model) by progressively adding quadratic or cubic terms for age, BMI, and their interaction. For both models, terms were retained if there was a significant improvement in the log-likelihood. Categorical differences in $ppFEV_1$ in response to BMIp were explored in an independent model in which pairwise comparisons were adjusted using Tukey-Kramer.

The random effects, grouped by participant, were the intercept and age using on autoregressive heterogeneous covariance matrix to account for correlations within participants as they aged. Statistical analyses were performed in SAS Studio using the MIXED procedure (Version 9.4; SAS Institute Inc., Cary, NC, USA).

5.3 Results

5.3.1 Population

A summary of pulmonary function and nutritional status parameters is presented in Table 5.1. The data set contained 15,755 values of $ppFEV_1$ and BMIp from 4,137 CF patients between 2007 and 2015 in the UK. The model excluded 6,670 values due to missing data. Of these individuals, 49.7% were female. The median number of observations for an individual was 4 with a maximum of 9.0.

Table 5.1 Participant characteristics and pulmonary function data, stratified by BMI percentile.

Characteristics	BMI Percentile	Male *n = 2,084 (50.3%)*		Female *n = 2,057 (49.7%)*		*P* value
		Mean	SD	Mean	SD	
FEV_1 (% predicted)						
	5^{th}	72.71	5.51	66.66	8.42	<0.001*
	10^{th}	74.77	5.12	69.13	7.70	<0.001*
	25^{th}	79.50	4.18	74.86	5.90	<0.001*
	50^{th}	84.22	3.40	80.70	4.20	0.006**
	75^{th}	87.89	3.11	85.41	3.10	0.879
	90^{th}	91.00	3.01	89.36	2.70	0.116
	95^{th}	92.35	2.99	91.06	2.72	0.179

All values represented as means and standard deviation. FEV_1 – forced expiratory volume in one second * - significance (P<0.001) ** - significance (P<0.05)

The results of the compact and full mixed models are presented in Figure 5.1 and Table 5.2. The multivariate analysis noted an interaction effect of; age x sex, BMIp x sex, and age x BMIp x sex, of which were significantly associated with $ppFEV_1$ (P<0.001). Significant findings from the fixed effects enabled the creation of clinically relevant prediction equations, represented in Equation 5.1. The strongest interaction within the compact model was age x sex, with females' pulmonary function declining at a slightly faster rate (-2.27% $\pm$ 0.1) in comparison to males (-1.75% $\pm$ 0.1). Conversely, when addressing trajectory over time in the full model, BMIp x sex was the biggest predictor of $ppFEV_1$ (Table 5.2). The interactions between age x sex x BMIp highlights that for every percentage change in BMIp, females see a significant decrease (P<0.0001) in $\%FEV_1$, whereas males do not. As a function of age, $ppFEV_1$ demonstrated a cubic relationship, with $ppFEV_1$ declining around from age 7-8 years, with some evidence of recovery from the ages of 14-17 years. Nonetheless, such a recovery was weak when BMIp was below the 50^{th} percentile (Figure 5.1). Random effects revealed a large between-participant variance in $ppFEV_1$ (95% CI = 437.1, 533.6 [SE = 21.9]), for a given age (95% CI = 3.08, 3.87 [SE = 1.9]), even when accounting for BMIp. Root mean square error (RMSE) of the residual shows a small within-participant variation (SE = 8). The auto regressive correlation highlights a weak correlation for every subsequent year of age (-0.76 per year).

Male: $ppFEV_1$ = 94.54 – (1.747*age) + (0.074*BMIp) + (0.006*age*BMIp) $\pm$ 8 (SE)

Female: $ppFEV_1 = 94.537 – (2.267*age) + (0.037*BMIp) + (0.014*age*BMIp) \pm 8$ (SE)

Equation 5.1 Solution for fixed effects from the 'compact model' – represented as a prediction equation for percent predicted of pulmonary function

Table 5.2. Solution of fixed effects from the 'full model' – comparisons between male and female

	t-statistic		
Effect	**Male**	**Female**	**Effect Size**
Age*Sex	40.74*	42.13*	0.01
Age*Age*Sex	-22.82*	-23.93*	-0.01
Age*Age*Age*Sex	14.4*	14.84*	0.00
BMIp*Sex	7.82*	11.12*	0.11
BMIp*BMIp*Sex	-5.59*	-9.45*	0.00
BMIp*BMIp*BMIp*Sex	4.34*	4.99*	0.00
Age*BMIp*Sex	-6.07*	-9.64*	-0.02
Age*Age*BMIp*Sex	6.12*	10.03*	0.00
Age*BMIp*BMIp*Sex	3.93*	8.33*	0.00
Age*Age*BMIp*BMIp*Sex	-4.15*	-8.42*	0.00

*BMIp – Body mass index as a percentile; * - P<0.001*

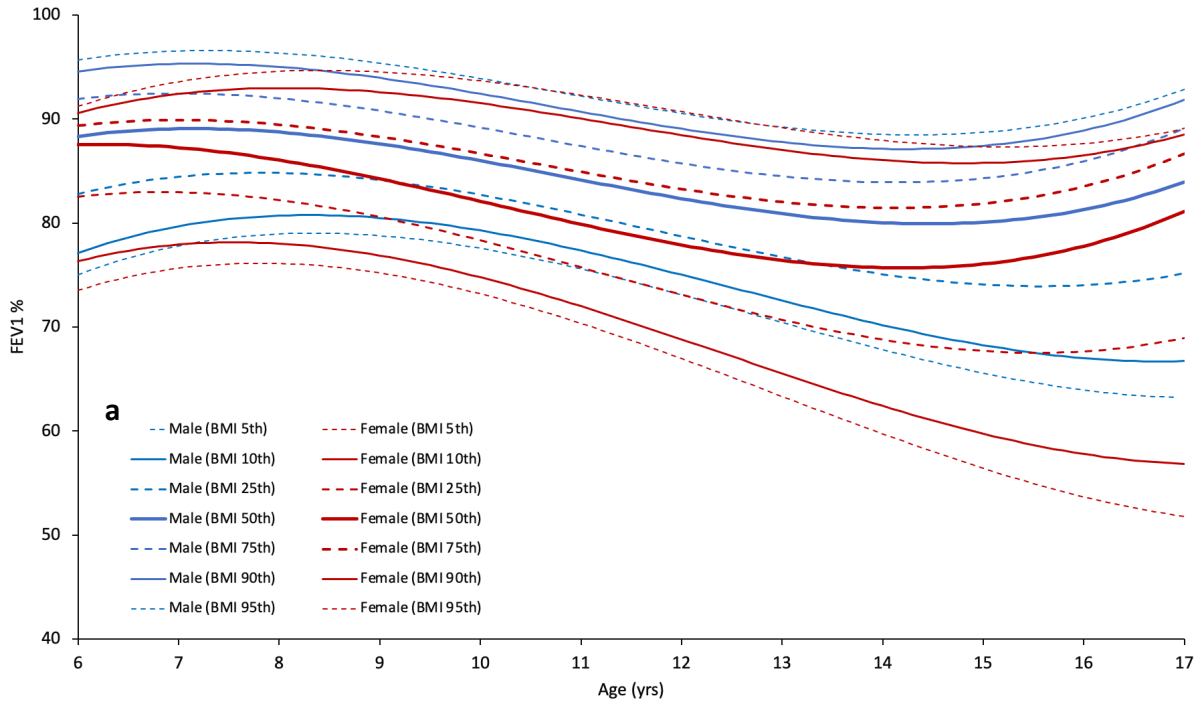
The categorical BMIp model shows a significantly reduced $ppFEV_1$ for participants below the 25th percentile, irrespective of sex (Table 5.3). Incremental decreases in pulmonary function were demonstrated for participants in each BMI percentile below the 50th. Each lower BMIp was associated with poorer $ppFEV_1$ over time, with the greatest declines in $ppFEV_1$ found in those $\leq$10th percentile. In females, there were significant declines ($P < 0.001$) in $ppFEV_1$ for every percentile below the 50th, whilst this significance was only evident below the 25th percentile for males. Regardless of sex, BMIp above the 75th percentile was associated with a larger $ppFEV_1$, although such increases were not statistically significant. However, the continuous model shows achieving a BMIp $\geq$75th percentile was associated with the most favourable $ppFEV_1$ values over time, with lower declines in $ppFEV_1$ between the ages of 7-14 years and a stronger recovery by age 17 years. Irrespective of sex or BMIp, declines in $ppFEV_1$ were predominately between the ages of 7-14 years, in which a BMIp below the 50th

percentile were associated with the largest declines and poorest recovery in pulmonary function (Figure 5.1).

Table 5.3 Categorical differences in pulmonary function with relation to body mass index.

Characteristics	BMI Percentile	Sex			
		Male		Female	
		Estimate	P	Estimate	P
FEV_1 (% predicted)*					
	01-05th	-4.12	<0.0001	-4.89	<0.0001
	05-10th	-4.88	<0.0001	-5.43	<0.0001
	10-25th	-2.73	<0.0001	-5.17	<0.0001
	25-50th	-1.18	0.0871	-2.88	<0.0001
	75-90th	2.53	0.7334	1.19	0.2897
	90-95th	3.12	0.6927	2.59	0.0681
	95-99th	4.53	0.0006	4.27	0.0008

FEV_1 – Forced expiratory volume in one second; ** - Data is mean difference as compared to the 50-75th percentile.*



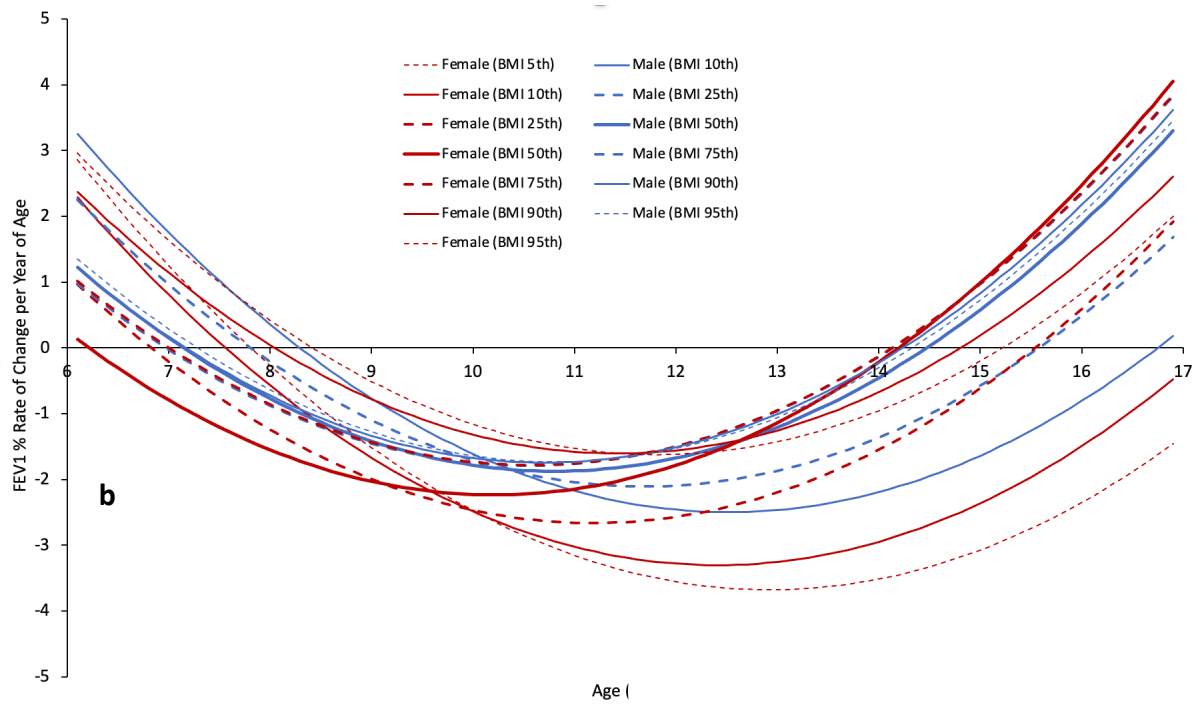


Figure 5.1. a) ppFEV$_1$ trajectory from 6-17 years when stratified by BMIp; **b)** Rate of change in ppFEV$_1$ through adolescence, stratified by BMIp.

5.4 Discussion

This is the first study to provide evidence that female ppFEV$_1$ is significantly influenced by BMIp, to a greater extent than their male counterparts, when accounting for age and sex. The compact linear mixed model provides a prediction of ppFEV$_1$ in relation to age, sex and BMIp, which can be utilised in clinical practice. Furthermore, the model highlights that there is a decrease in ppFEV$_1$ around the pubertal age range (Brix et al., 2019), with the rate of change influenced by BMIp. Specifically, there were earlier and larger overall declines in ppFEV$_1$ for individuals categorised below the 50th percentile, with those with a BMI above the healthy range (>85th percentile) associated with more favourable ppFEV$_1$ and a slower rate of decline up to the age of 17 years.

Nutritional status is significantly associated with morbidity and mortality within a CF population in both children and adults (Boëlle et al., 2012). Building on previous research which identified a positive association between better nutritional status and pulmonary function values (Konstan et al., 2017), the present study found the relationship between BMIp and sex to have the largest effect when assessing an individuals ppFEV$_1$ over time. BMIp

influenced female pulmonary function to a significantly greater extent than males as they aged. Specifically, for every percentage change in BMIp, females exhibit larger changes (-2.267%) in their $ppFEV_1$ as they get older versus males (-1.747%). These findings corroborate early research from Corey and Farewell (1996), which demonstrated a more complex relationship between sex, body mass and $ppFEV_1$ in relation to females specifically.

Given the sensitivity of female $ppFEV_1$ to changes in BMIp, it could be suggested that poorer weight management may play a significant role in influencing such health inequality. Whilst improved dietetic care and the emphasis on a high-calorie, high-fat diet has resulted in a significant reduction in the instance of malnutrition with a CF population (Yen et al., 2013), weight management and variations in BMI remain a consistent challenge within CF care. Indeed, instances of acute weight loss (~2% of total body mass) have been shown to result in changes of up to 12% in $ppFEV_1$ (Cano Megías et al., 2015). Many challenges around weight management are a result of an increased resting energy expenditure (REE), with people with CF exhibiting an increased REE of 100-150% above that of the general population (Moudiou et al., 2007), which is associated with pancreatic insufficiency and recurring pulmonary infections (Dodge and Turck, 2006; Litvin et al., 2019). Due to the pleotropic effect of oestrogen on immunity and vulnerability to infection, female's susceptibility to infection is higher with females evidenced to colonise CF pathogens earlier than males (Harness-Brumley et al., 2014). As such, there is an elevation in percentage precited REE is elevated in females when compared to males, which persists throughout puberty (Magoffin et al., 2008). Together, it could be postulated that females may experience more consistent challenges with regards REE due to more frequented pulmonary exacerbation. This is further confounded by the expectation that an individual's energy intake will also drop during a period of exacerbation (Naon et al., 1993). With female $ppFEV_1$ more sensitive to change in BMIp, decreased energy availability may contribute to a significantly lower BMI and consequently larger declines in $ppFEV_1$ when compared to males. Collectively, these findings suggest that, regardless of nutritional status, females may benefit from more aggressive intervention during times of exacerbation to maintain a favourable nutritional status through adolescence, as well as more vigorous monitoring of nutritional status to minimise BMI related declines in $ppFEV_1$ (VandenBranden et al., 2012).

In line with epidemiological studies, the data from the present study reinforces current recommendations that children and adolescents maintain a BMI above the 50th percentile, due to its positive association with pulmonary function across time (HuiChuan and Suzanne, 2008; Stallings et al., 2008). The present data refutes previous research which suggested that lower BMIp was only associated with decreased pulmonary function if individuals were classified as being in 'nutritional failure' (defined as BMI < 10th percentile; Hanna & Weiner, 2015). Indeed, adolescents with a BMIp below the 50th percentile within the current cohort had a substantially greater decline in ppFEV$_1$, with those below the 25th percentile demonstrating a faster rate of decline, poorer mean ppFEV$_1$ at aged 17 years and poorer recovery of ppFEV$_1$. These findings therefore highlight the problematic nature of the guidance of the Cystic Fibrosis Foundation (CFF) which only identifies those below the 25th percentile as 'at risk'. Whilst analysis of children has shown that even those between the 25-50th percentile are at considerable risk of nutritional complications, such as stunting, poor rate gain and poor long-term lung function (Konstan et al., 2017), we demonstrated that this may have more importance for females, with male ppFEV$_1$ in the 25-50th percentile range not considered to be significantly different from the 50th percentile standard. Whilst it is advised that such guidelines consider all those who fall below the 50th percentile 'at risk', this may be of particular significance when considering females.

Regardless of BMIp, individuals experienced significant declines in ppFEV$_1$ in their early teen years, which manifested at years associated with the manifestation of puberty (as defined in Brix et al., 2019). Interestingly, there were no sex differences in the rate of change in ppFEV$_1$ for participants classified as having adequate nutritional status (≥50th percentile), thereby suggesting that when nutritional status is controlled, a disparity in clinically-relevant outcomes may not be as prevalent. Whilst the aetiology of this decline in pulmonary function between the years of 7-14 years cannot be attributed to changes in BMI alone, it could be postulated that, given the 6% rise in post-pubertal REE, weight management around the manifestation of puberty may be an issue, irrespective of sex. With our understanding of increased variability in female ppFEV$_1$ in response to changes in BMI, nutritional interventions around the onset of puberty and throughout adolescence should be implemented to ensure that BMI-related declines in ppFEV$_1$ are minimised, with particular focus given to those below the 50th percentile. Such recommendations are congruent with findings from Yen, Quinton

and Borowitz (2013), in which early nutritional intervention has been linked to individuals achieving higher weight percentiles and subsequent increases in pulmonary function, fewer pulmonary exacerbations, and better pubertal growth. However, this is not without challenge, as females have been found be more resistant and less adherent to nutritional interventions due to a reported desirability of having a lower bodyweight (Patterson et al., 2009; Simon et al., 2011). As such, it is imperative that any nutritional evaluation and intervention considers attitudes and behaviours which may impact on intervention adherence.

In contrast to reported trends within the general population, our analysis also infers a protective effect of higher BMI on pulmonary function. Increasing BMI percentile above what is considered the 'healthy range' for the general population (>85th percentile), is associated with greater mean ppFEV$_1$ and an enhanced maintenance of ppFEV$_1$ as an individual ages. Whilst within the general population the incidence of overweight/obesity is associated with a significant impairment of pulmonary function (Leone et al., 2012), our data does not support this association. Indeed, individuals above the 90th percentile illustrate the greatest ppFEV$_1$ by age 17 years, with a slower rate of decline between 8-14 years. Such a relationship denotes the beneficial effect of overweight/obesity within a CF population, and has been well-documented as part of the 'obesity paradox' (Gruberg et al., 2002). Here, higher BMIp is linked to improved prognosis, reduced levels of pulmonary exacerbation and preservation of pulmonary function (Kastner-Cole et al., 2005; Stephenson et al., 2013; Sun et al., 2019). Whilst within an adult population it is suggested that taking BMI beyond a threshold of 28-29 kg•m^{-2} has no additional benefits to ppFEV$_1$ (Harindhanavudhi et al., 2020), the cubic BMI term leads to a positive trajectory of ppFEV$_1$, even for those above the 90th percentile.

The introduction of triple modulator therapy is expected to rapidly change the outlook for many individuals with CF, with significant improvements seen in sweat chloride, pulmonary function, body mass and quality of life (Heijerman et al., 2019). It is pertinent to note that this analysis was done *prior* to the implementation of modulator therapy and, as such, it is unclear as to whether the same trends in BMI and ppFEV$_1$ trajectory will still be evident in a post-modulator CF scenario. Further research is needed to ascertain whether modulator therapy alters the relationship between BMI and ppFEV$_1$, whilst identifying whether there is a sex

disparity in magnitude of improvement in clinically significant outcomes. Whilst the current study evidences the protective effect of overweight/obesity on pulmonary function it is believed that the prevalence of overweight/obesity within the CF population may soon mirror that of the general population (Hanna and Weiner, 2015). In the general population, obesity and its repercussions represent a significant risk factor of morbidity, mortality and impaired quality of life (Abdelaal et al., 2017). Given the risk of obesity within CF is a relatively modern problem, there is currently no longitudinal data to suggest that overweight/obesity would predispose this population to an increased risk of mortality (Harindhanavudhi et al., 2020). However, as there is considerable risk associated with overweight/obesity and subsequent comorbidities prevalent within the general population, there is consensus that modern nutritional advice for people with CF should consider an individual's respective BMI, with management strategies focusing on a more nutrient dense, moderate caloric intake in patients who are classified as overweight/obese (Haak et al., 2020).

Whilst this are numerous strengths to this study, several limitations are important to acknowledge. First, the study relies on retrospective data, prior to the introduction of triple modulator therapy. It is therefore imperative that future research seeks to ascertain whether such relationships are evident post therapy-implementation. Further, the full range of covariates potentially associated with pulmonary function incorporated within the registry were not included. Indeed, the main hypothesis focused on the effect of BMI on pulmonary function and, therefore, confounding factors, such as genotype, CF-related diabetes and rate of exacerbation, were not included within the longitudinal analysis. It is also pertinent to note that BMI was used as a proxy measure of nutritional status and may, particularly, misrepresent nutritional status in those with stunted growth (Konstan et al., 2017). More specifically, the lack of body composition data is also important to acknowledge, given the association between fat-free-mass and pulmonary function (Sharma et al., 2001). Future cohort studies should therefore account for additional variables associated with pulmonary function within the model. It is advised, due to the population age studied, that these findings should not be extrapolated beyond the age of 17 years. Future research should therefore seek to investigate this relationship across the lifespan. Finally, data was not available to accurately assess individuals' onset of puberty, as such the 'onset' of puberty was based on secondary

data. To conclusively answer the question of whether puberty has a significant effect on $ppFEV_1$ and BMI the use of a Tanner scale is recommended.

In conclusion, the rate of change in $ppFEV_1$ during adolescence is significantly influenced by an individual's sex and BMIp, with females $\%FEV_1$ influenced by BMIp more significantly in comparison to males. As declines in pulmonary function manifest from 7-14 years, given the protective effect of BMI on pulmonary function, there is a need to support individuals with an appropriate nutritional treatment plan, regardless of nutritional status. Nonetheless, whilst our data suggests more favourable pulmonary function values in response to overweight/obesity in CF patients, more research is needed to ascertain the negative implications associated with this nutritional status on cardiovascular risk factors and mortality.

CHAPTER 6
EVALUATING THE EFFECT OF KAFTRIO ON PERSPECTIVES OF HEALTH AND WELLBEING IN INDIVIDUALS WITH CYSTIC FIBROSIS

6 EVALUATING THE EFFECT OF KAFTRIO ON PERSPECTIVES OF HEALTH AND WELLBEING IN INDIVIDUALS WITH CYSTIC FIBROSIS

6.1 Introduction

Cystic Fibrosis is the most common and severe autosomal, recessive genetic disorder in the Caucasian population, currently affecting over 10,000 individuals in the UK (Cystic Fibrosis Trust, 2019). Complications caused by a compromised function of the Cystic Fibrosis Transmembrane Regulator (*CFTR*) gene (Riordan et al., 1989; Rommens et al., 1990) result in impaired chloride ion transport in the epithelial cells, affecting pancreatic, respiratory, gastrointestinal, reproductive and skeletal function (Ridley and Condren, 2020). Despite CF being a multi-organ disease, respiratory failure represents the main cause of morbidity and mortality. Specifically, the absence or dysfunction of the CFTR protein results in abnormal mucus secretion, recurring infections, inflammation, airway obstruction and, ultimately, progressive decline in pulmonary function (Penketh, Wise and Mearns, 1987; Cantin, 1995; Kadoglou et al., 2007; Heijerman et al., 2019; Lopes-Pacheco, 2020).

The majority of treatments available for CF focus on treating the complications and symptoms associated with disease process, independent of the genetic defect. However, over the last decade treatment has gradually been directed towards restoring CFTR protein function, thus targeting the underlying cause of the disease (Elborn, 2020; Paterson, Barry and Horsley, 2020). CFTR modulators are targeted therapies that increase the processing and delivery of CFTR to the cell surface (correctors) and increase the flow of ions through activated CFTR proteins at the cell surface (potentiators; van Goor, Hadida and Grootenhuis, 2008). The introduction of Ivacaftor for individuals with class III and residual function mutations (e.g. G551D), followed by Tezacaftor/Ivacaftor combinations in individuals homozygous for F508del, have evidenced significant improvements in sweat chloride, pulmonary function, body weight and overall quality of life (QoL; Ramsey et al., 2011; Connett, 2019; Paterson, Barry and Horsley, 2020). As of June 2020, NHS England and Europeans Medicines Agency (EMA) approved for the use of the highly effective triple modulator therapy Tezacaftor/Ivacaftor/Elaxacaftor in individuals over 12-years, who present with at least one F508del mutation (Elborn, 2020).

It is widely purported that initiating triple modulator therapy (Kaftrio) will change the course of CF lung disease for many individuals. Indeed, the triple modulator therapy has been shown to have beneficial effects not only in those with mild-to-moderate CF, but also those with more severe pulmonary status (Shteinberg and Taylor-Cousar, 2020). Whilst current research is unequivocal in its evidence for positive respiratory outcomes, findings are yet to truly understand the effects that chronic triple therapy treatment has on patient outcomes related to mental health and quality of life. Di Mango *et al.* (2020) reported that three months of treatment with elexacaftor/tezacaftor/ivacaftor resulted in significant improvements across the majority of domains of the CFQ-R questionnaire, with the exception of emotional functioning, health perceptions, body image, and digestive symptoms. However, such objective data fails to explore the intricacies of the true patient experience, of which remain unknown. Given the diverse nature of CF, it is imperative to understand patients' perspectives of the impact of Kaftrio in order to inform and shape future clinical practice.

Whilst the introduction of modulator therapy brings hope for many, there remains many unanswered questions. Given the magnitude such therapy is expected to have on an individual's day-to-day life, understanding the real-world experience is key. Prior to therapy, previous lived experience has described CF as unpredictable and challenging, with individuals striving for equality and to experience opportunities their healthy peers take for granted (Knudsen et al., 2018). As individuals begin to experience the physiological effects of the treatment, this study aims to explore the effect these changes have on an individual's perception of reality, and to what extent modulator has changed their life, beyond just the physical.

6.2 Methods

Twelve individuals (10 Females) with CF provided informed consent and participated in the study. Eight individuals had received treatment for 6-months prior to the interview, two individuals for 10-months prior on compassionate grounds and two individuals had been prescribed Kaftrio for over one-year as part of phase 3 clinical trials. The study was approved by the Research Ethics Committee at Swansea University (Application reference number: MN_22-10-22).

To explore individuals' experiences and perceptions of Kaftrio (ELX/TEZ/IVA, Vertex Pharmaceutical), participants were asked to take part in a semi-structured interview via video conferencing software (Zoom, Zoom Video Communications Inc, San Jose, California) lasting up to 60 minutes. The flexible interview guide was devised in line with Evans et al. (2021) to facilitate in depth discussion of personal experiences of Kaftrio and was pilot tested to ensure questions were sensitive and appropriate. The interview involved the exploration of commonly reported benefits and side-effects of Kaftrio, with social challenges, disease management, anxiety, and identity explored in line with the extant literature (Quittner, Saez-Flores and Barton, 2016). To maintain anonymity, individuals were given a pseudonym so as not to be identifiable within the manuscript. As shown in Table 6.1, whilst the interviews probed both positive and negative effects of Kaftrio, participants were prompted to expand on how these personal experiences shaped their perceptions of Kaftrio.

Table 6.1: Example interview questions. Full set of questions available in appendix.

Example Questions	Prompts
What (if any) are the most positive (valuable) impacts?	Why/how/in what way? Did anything exceed expectations?
Did any members of the clinical team influence perceptions of how you felt since the new therapy / and how you feel now?	If so, in what way?

The interviews were recorded and subsequently transcribed verbatim. All data were analysed through qualitative content analysis (Hsieh and Shannon, 2016) by the first author. The data was subject to line-by-line coding to identify appropriate and accurate themes. These codes identified features of the data that the first author considered pertinent to the research question. A member of the research team verified independently that these themes were reflective of the narrative, thus representing the data appropriately. The first author then identified quotes that were congruent with the overarching themes. These quotes were then

grouped into subthemes which were aligned with the overarching themes and related to the overall story and research question. These extracts aimed to identify issues within the theme to provide a clear example of the individual's point.

6.3 Results

The main themes identified were: (i) The Fairy-tale Story; (ii) A New Concern; and (iii) The Patient Voice, as shown in Table 6.2.

Table 6.2. Identified themes around individual perceptions of Kaftrio.

Perception of Kaftrio	
DIMENSION	**THEME**
The Fairy-tale Story	Improved Quality of Life
	Pulmonary Function and the Purge
	Reduced Rate of Exacerbation
	A Sense of Normality
A New Concern	Side Effects
	Removal
	Loss of Identity
The Patient Voice	Clinical Team
	Psychological Support

6.3.1 The Fairy-tale Story

Of the study population, 10 individuals demonstrated positive perceptions towards Kaftrio, with many rereferring to an increase in quality of life as the main positive outcome. Health prior to Kaftrio therapy appeared to be a strong indicator of perception, with those of poorer health perceiving more substantial increases in quality of life.

Improved Quality of Life: All individuals who identified an increased quality of life stated that they noticed the positive effect of Kaftrio on multiple aspects of day-to-day living within a few days of treatment commencement. Specifically, participants cited: (i) reduced coughing; (ii)

reduced breathlessness; (iii) more energy; (iv) increased appetite; (v) improved sleep duration and quality; and (vi) the ability to complete daily tasks easier. Angie described:

…a week in I would say I didn't cough… I'd get up in the morning and cough for hours… now I test my cough and be like, god can I actually still cough?"… Also, there's a block that we walk now and I never in a million years thought I would ever be able to walk around that… now I walk around it and I'm like what? I've just walked that I can't believe it.

Craig also noted the profound effect Kaftrio had on sleep quality:

… one of the major things is sleeping at night and not coughing. So, I would be tossing and turning and coughing… even when I went on antibiotics. My second night on Kaftrio… I just hadn't coughed yet. Even to this day [over six months] it's the same and it's something I can't get my head around.

One outcome that resonated with all participants, regardless of pulmonary function, was the obvious change in energy levels on a day-to-day basis. As an example, Ben, suggested:

I am fitter and healthier now than I've ever felt in my entire life. Like on Saturday I rode 50 miles on a bike. Could never comprehend that in my entire life. Like ever doing that.

Pulmonary Function and the "Purge". Prior to taking Kaftrio, many individuals expressed concern at watching their pulmonary function regularly decline. For those who had not yet experienced significant decline in forced expiratory volume (FEV_1), they believed it was 'only a matter of time' until their condition deteriorated significantly. Self-reported increases in pulmonary function varied substantially between individuals, ranging from 1% - 20%. For many, an increase in pulmonary function brought comfort that Kaftrio was making a substantial difference at a cellular level. Marin spoke of her recent changes in pulmonary function:

Pre-Symkevi I was 55%, Symkevi gave me 10%. Kaftrio pushed me to numbers I had had when I was 13 [years old] – the best was 83% and now it's more around 78-80%... all those percentages mean a lot don't they?

Prior to this increase, many individuals highlighted experiencing the infamous 'purge', whereby individuals expectorate large quantities of mucus from their lungs in the 24-72 hrs after they commenced Kaftrio treatment. Many individuals placed value on this as a sign that the medication was starting to work:

Had the purge, enjoyed it! It only lasted around 12-24 hours, my lungs felt so much clearer than ever before, I thought wow this is fast acting but you don't believe it somehow. My lung function increased straight away. I stopped coughing within a week.

However, the percentage increase in FEV_1 was not the main positive health outcome expressed by participants. Many found value in the perception that Kaftrio would help preserve their lung function, thereby reducing anxiety associated with pulmonary function tests, for they now placed less significance on test outcomes given their increased quality of life. Individuals often professed that clinical perceptions of health and decisions on their care were made based on pulmonary function alone, without taking into considerations patient perceptions of health and quality of life. Indeed, an absence of acknowledgement around the effects that pulmonary function readings had on anxiety and an individual's mood had led some individuals in the past to actively avoid clinic visits. Participants noted that a low FEV_1 value during routine clinic visits when they felt otherwise well had been mentally challenging. Hence, critically, Kaftrio was suggested to provide some confidence that these decreases in FEV_1 may be less frequent, with Cynthia discussing how recent infections and declines were hopefully not going to have too much of an impact now:

Over the last year I was suffering more with haemoptysis and I got MRSA (methicillin-resistant Staphylococcus aureus) and NTM (Nontuberculous mycobacteria) all in one year. I could see edging toward 30 [years old] that this is going to be the decline basically and I was hoping that it [Kaftrio] would sort of, not let it [lung function] go down too much.

Reduced Rate of Exacerbations: A characteristic of CF is that many individuals experience frequent exacerbations that may require hospitalisation for intravenous (IV) antibiotic therapy. Depending on disease severity, individuals spoke of how they can experience IV therapy every four to 12 weeks. For Ben and Charlie, who had previously been under frequent antibiotic regimes, Kaftrio significantly reduced the need for hospital visits. Ben described:

They [the clinical care team] have tried to put me on IV's at least four times this year because they said to me, you 'normally' have them every three months. I have now accepted to go on it, but [since Kaftrio] that will be almost a full year without them, which is unheard of for me.

Similarly, Charlie spoke of the decreased frequency of her hospital visits:

I was in hospital like four or five times per year… [on Kaftrio] about 14 months is the longest I have been without and that's the longest it's been for seven years.

Whilst individuals accept that their CF is not cured and that they may be prone to IV treatment in the future, the significant reduction in treatment burden brings participants a sense of relief. Whilst the requirement for IV treatment echo's life pre-Kaftrio, it is something Rosie is willing to live with if it remains as infrequent:

…the other part of me was like, if I only have IV's once a year for the rest of my life, then that's cool, I can totally accept that.

A sense of normality: independence, opportunity and hope: The accumulative perceived effects of improved quality of life and management of pulmonary function had substantial effects on the mental state of many individuals. Angie spoke of how she feels ever closer to living a 'normal' lifestyle – or a lifestyle closer to that of her peers:

It does gives us that chance, like I can be like everyone else….as a woman, I can start to think about having kids, the door is still open for me now… I have more chances to take

risks. Whereas before, I would just not even consider attempting things… there is nothing there now to stop me, these things are in my hands.

Individuals commonly mentioned the increased *choice* they had. Cynthia believed that whilst choices were not specifically taken away from her, her CF played a substantial, subconscious role in the choices and decisions that she made:

With time extending [due to Kaftrio] it just means you are like, 'oh well maybe I could get that retirement plan, maybe I should think about that'. I never got a lifetime ISA (Individual Savings Account) because I was never going to get to 50 [years] to use it. I thought I had another 15 years tops… So I am sort of allowing myself to think about these things, whereas otherwise I would put them in a box.

Individuals felt the opportunities they had in life had increased considerably. Videl, for example, explained that she is starting to make plans to participate in activities that her CF had previously placed restrictions on:

… so I have ridden dressage for years… and that has slowly decreased because of my health… I had lost sight of everything that was important to me because I was so poorly… I dreamt about it (competing) but now I am like, come on, you can do it… I feel like I am making up for lost time.

For most within the study, Kaftrio represented the catalyst for a new illness narrative that was characterised by a sense of hope. Hence, Kaftrio signified a 'new start', where CF did not play such a critical role in their life. Kaftrio also represented substantial advances in treatment in a short space of time, with the hope that this may just be the beginning of further successful treatment options until the point that diagnosis with CF is no longer a *"life sentence."*

6.3.2 A New Concern

The experiences associated with negative perceptions of Kaftrio centred around: (i) side effects; (ii) removal of therapy; and (iii) loss of identity. Whilst most individuals spoke of side-effects, a truly negative experience was found in six individuals. It was noted that two

individuals had had to cease Kaftrio therapy due to both physiological and psychological side-effects.

Side effects. A decrease in quality of life: Those who displayed predominately negative perceptions of Kaftrio had experienced serious side effects, where quality of life had deteriorated below that of pre-Kaftrio. Katie noted that she had tried to persist with the treatment for 10-months despite side effects, that included debilitating migraines, '*brain fog'* and sound sensitivity, but eventually chose to stop treatment as her quality of life had become so poor that getting out of bed was difficult:

I was elated. It felt like I didn't have CF but the headaches started on day one - we know migraines now. I would have to go be in a dark quiet room. That helped me a little... I did not feel like I was on this planet. I forgot my date of birth and sound sensitivity was crazy, even talking became a struggle… I went on for 10 months, I felt ungrateful. I thought this was how my new life was supposed to be (before I decided to come off it). I have no regrets – it is easier to live with CF than on Kaftrio.

Rachel documented the significant effect Kaftrio had on her body image, perception of self and confidence, to the point where, despite her improved pulmonary function, she chose to cease treatment in the hope that she could better manage her weight and mental health:

I felt every time I was going to clinic, it was a few more kilograms… then it reached the point where I was the heaviest I have ever been and was really not comfortable. My lungs got better but I couldn't enjoy and reap the benefits because I was putting on all this weight. I was looking at myself and wanting to cry because I was so unhappy in how I looked.

Removal: Returning to a life pre-Kaftrio: Unpleasant side-effects were something that many individuals within the study were willing to live with, given the trade-off for long-term health benefits. However, others worried that the potential side effects would mean that they had to discontinue Kaftrio. Similarly, all participants were wary of the effect that Kaftrio had on their liver, with the worry that potential increases in liver enzymes would result in their team removing access to modulator therapy. Laura who had CF-related liver disease noted that

Kaftrio had elicited major positive changes to her pulmonary health, but she was concerned that this may only be short-lived should her liver status change:

Back in 2020, around June, my liver disease became fatal and failed… after being on it [Kaftrio] for a couple of weeks… my liver function rose… for me it was very stressful… The liver thing is never going to get better, that's always going to be there. I have got the fear that… because your liver function can just go up, I get scared in case they stop you… would I revert back to how I was and everything that has improved be ripped away from me?

Accordingly, as many participants had seen the positive changes that Kaftrio had on their day-to-day life, a number of participants lived in fear of Kaftrio subsequently being removed due to other health complications. For many, returning to a life pre-Kaftrio was now unimageable, with Ben describing:

I think my main anxiety comes from the fact that I've now been given this opportunity or like dangled carrot of, look what your life could be like, and in the back of my mind is when is it going to go away. All the time.

These feelings where echoed by Marin:

…It's all riding on it [Kaftrio] now… there's no other alternatives… and if it stops working, where do you go, even in your head with that?

As a result, a sense of uncertainty around the future was something the majority of individuals reported, regardless of overall experience. These participants stated that lack of knowledge available regarding the long-term efficacy of Kaftrio raised concerns that their health may start to deteriorate without warning. For older individuals such as Katie and Marin, they referred to Kaftrio as their 'last chance', and Marin expressed a desire for additional understanding as to how their health may hypothetically look in the short-term future:

What happens if I go back to where I was [pre-Kaftrio]? This was the be all and end all, this was supposed to solve all my problems and if this doesn't work then what? I have had to

speak with a psychologist... It is [the worry] more the idea of what happens when this goes away – how long is that going to be there? Nobody knows.

Many described CF as a proverbial rollercoaster, with emotional highs and lows. The participants were accustomed to "looking over their shoulder" for negative health outcomes to present themselves, and Kaftrio was suggested to represent for some a scenario that was almost too good to be true and *"something that never happens to us [CF individuals]"*. As such, individuals consistently professed they were "*not allowing themselves to get carried away"*.

Loss of identity: For some, modulator therapy resulted in an "identity crisis" and a feeling of being overwhelmed. Four individuals noted their understanding as to the path in which their life was following pre-therapy, however, as a result, the prospect of an extended life left a lot of unanswered questions and thoughts regarding both short- and long-term goals. Individuals spoke about how their CF has always been 'road mapped' out, whereas since Kaftrio, the road was unclear. Ben spoke about his struggles of having to alter his perception of self:

"…this is how I summed it up. I completely lost my identity. Like, I didn't know who I was or what I am doing or what is going on… I felt like my identity was my health and my job and now they are not the same."

Indeed, the concept of a loss of identity highlights that, for some, Kaftrio may represent a period of trauma in which individuals find it hard to manage or conceptualise their new health status. For two participants, the issues lay in having to disassociate with the person they were, and the life they were used to, when the future remained so uncertain.

Overall, the perceived negative impact of Kaftrio found within this sample were mainly focused on: the side effects; having the taste of a 'normal' life cruelly removed; fear and uncertainty regarding a drug in its infancy – leaving the participants unable to let themselves get *"too carried away".*

6.3.3 The Patient Voice

As life with CF begins to change following Kaftrio, some participants called for a change in their clinical care. Individuals professed that they "*know my body better than anyone".* It was explained that the clinical focus pre-Kaftrio was centred too closely on clinical outcomes, namely FEV_1, over everything else. For Claire, she did not have the confidence to challenge their clinical care team and felt at the mercy of their decisions. The ever-rotating team in adult clinics only enhanced the feeling that she was simply a number on a spreadsheet, with solid relationships coming few and far between:

They change so often, I don't even know their names… to be honest I don't know my doctors, they don't know me as a person, they are nice, but half of the time I am not involved in any of their discussion.

Now, with the changing landscape of CF, there was an even stronger call among the participants for the clinical care teams to listen more to their views. For those participants who were more confident, Kaftrio initiated a desire to take charge of their health and make decisions they felt were in their best interest, with Rachel expressing her hope that her input could be taken seriously:

I want my input to mean something to my clinic team – at the moment they roll their eyes as if to say, oh here she goes again. I feel judged, I might not know the science, but they forget I am the one living with the condition daily. I am hoping that with Kaftrio I can have a firmer stance on things I do not agree with – I hope it gives me the chance to show them I actually am right.

However, Rachel spoke of how her previous experience with the clinical care team had prevented her from reaching out for the support she needed while taking Kaftrio:

[In the past] I called my psychology team nearly in tears, I was really struggling. All they told me was that the waiting list was long and that I would likely not be seen for at least eight weeks… if that was someone's cry for help, there is no-one listening. With Kaftrio, I lost

my identity straight away, I was overwhelmed and didn't know where to turn – I didn't even try to phone clinic as I knew no-one would answer.

Charlie also called for psychological support to be routinely available at clinic visits, alongside the dieticians, physiotherapists and consultants:

The teams need to do more. This is a life changing event that we have just been told to be grateful for and get on with it – I don't know how to get on with it.

For those struggling with weight and perception of self, CF dietary care had been quoted as '*not the best',* with individuals feeling like the concept of nutrition / dieting and CF having a stigma attached to it, even in the face of Kaftrio. With the introduction of Kaftrio, some individuals within the current study were seeking methods to control weight, though were met with a lack of importance placed on weight and physique from their clinical team. Rachel spoke of her experience when she met her team to raise weight-related concerns:

I told them I was struggling with perception of self. I did not like how I looked, it was damaging my confidence. I have always struggled with weight and managed to lose some of it myself pre-Kaftrio. But when I gained weight on Kaftrio, the only thing they had to say to me was, 'no don't worry, … your lung function looks great'. That's not what I needed to hear – I felt lost.

Other individuals acknowledged the great work their clinical care teams did for them, but there was a consensus that there needed to be a deeper empathetic understanding around the new psychological and physical challenges that come with Kaftrio. Hence, there was a call from the participants for care teams to gain a further understanding of the existential concerns regarding the dramatic change of health status for many (but not all) in an extremely short time-period.

A message to the 10%: Finally, all participants explained their hope that, just like themselves, one day there would be a treatment available for the 10% who's genetic mutation does not support therapy with Kaftrio. Many referenced a phenomenon they described as similar to

'survivor's guilt'. They alluded to how difficult they would find it, looking in from the outside, whilst somebody with the 'same' condition was starting to make plans about their new life. Individuals currently taking Kaftrio alluded to the fact that they wanted to make the most out of Kaftrio and adopt further health-seeking behaviours in honour and respect of those that were not able to take Kaftrio. For those who had ceased treatment with Kaftrio, they felt guilty that they were choosing to discontinue something that another individual would wish to have. Importantly, Kaftrio was not simply seen as just 'another treatment' but as a gift that they had to cherish.

I've got so much guilt that I can't think about it too much. I have this like, it's not survivors' guilt but something along those lines… They [the ineligible] are just watching it all unravel. They [Vertex] have to do something for them.

Accordingly, the participants receiving Kaftrio felt a sense of responsibility to those who were unable to receive the therapy. Given the positive changes that it had made to many participants' quality of life, they felt they owed it to those not taking Kaftrio to try and live life to the fullest. At the same time, all individuals expressed sorrow that not everyone would tolerate or could take Kaftrio. The individual messages aimed at the 10% were that of belief, hope and to keep fighting, as all individuals believed it was only a matter of time before they had alternative treatment. For most, their personal adherence to Kaftrio was in honour to them as a way to ensure they never take this 'gift' for granted.

6.4 Discussion

By employing a qualitative approach, this study has offered a unique, in-depth insight into the lived experience of modulator therapy for CF individuals, highlighting the multi-faceted implications associated with the changing landscape of the disease and its treatment. The participant narratives revealed the positive impact that Kaftrio had on the individual's disease state, with an improved overall quality of life and a significant reduction in 'classical' CF challenges (i.e., breathlessness, sleep disruption, treatment burden and hospitalisation). Moreover, the accumulative effect of these positive changes were reported as facilitating a sense of hope, normality, and independence, thereby allowing individuals to live a lifestyle

which they considered to resemble that of their healthy peers. However, individuals also narrated negative experiences associated with the therapy, revealing significant inter-patient variability outside the physiological context (Eckford et al., 2014; Chevalier and Hinzpeter, 2020). The current narrative was ultimately dictated by an individual's ability to tolerate the therapy, with individuals expressing feelings of fear and resignation. Some individuals expressed increased anxiety and distress with relation to uncertainty around the removal of therapy and, for some, dealing with a redefining of one's identity. Regardless of perception, individuals mentioned their relationships with their clinical teams and called for additional counselling and psychological support to be offered to meet the new psychological needs of the individual, given the significant change in landscape of the disease.

The implementation of Kaftrio represented a positive shift in the illness narrative of those who were able to tolerate the therapy. For example, for the first time, many individuals noted a sense of control and optimism for the future due to Kaftrio's substantial effect on quality of life. Indeed, many participants viewed Kaftrio as a second chance at life in which individuals had the opportunity to use previously negative experiences to reconstruct a positive self-transformation for the future they didn't previously have (Pals, 2006). Although data on modulator therapy and life expectancy is not yet available, Kaftrio gave individuals hope and a representation of trust in an imagined future. The components of hope involve the anticipation of a good future, feelings of personal competence and meaning in life with a sense of possibility (Miller and Powers, 1988). Given the life limiting nature of CF, individuals spoke of how they did not trust in their future enough (pre-Kaftrio) to believe they would reach milestones such as retirement and parenthood. The implementation of Kaftrio elicited a reality-based belief that a positive future did exist in which an individual could now plan for life events they previously perceived as impossible.

Drawing on experience, individuals recounted the limiting effect CF had on their life prior to modulator therapy, with many professing that they had lost sight of things that were important to them due to poor health status. Prior to the initiation of therapy, individuals alluded to how activities as simple as walking were restricted due to the careful planning needed to manage factors such as breathlessness and coughing. As such, individuals experienced a vicious cycle of self-limitation, further limiting opportunities and resulting in a

sense of helplessness, anxiety, and depression (Williams and Carel., 2018). The implementation of Kaftrio was the catalyst for the subsequent reduction in these CF challenges, which decreased the burden that CF had on individuals' day-to-day lives. This sudden respite was expressed in the narrative as gratitude, with individuals speaking of how thankful they were to have their *lives back*. Longitudinal analysis has shown that gratitude is associated with a number of positive traits such as increases in self-esteem, satisfaction with life and fewer symptoms of depression (McCullough, Emmons and Tsang, 2002; Lambert, Fincham and Stillman, 2012), suggesting that as well as positive physical change, modulator therapy may also enhance an individual's mental well-being. As in Davidai and Gilovich (2016), CF forced individuals to focus on the obstacles and difficulties in life, given they demanded immediate action. Kaftrio represented a metaphorical tailwind, in which individuals were given a reprieve (Bhalla and Proffitt, 1999) and a chance to focus on the things in life that bring them positive emotions. For those who felt they had been simply existing, Kaftrio represented an opportunity in which they could now truly live.

Although for many the experience of modulator therapy was a predominately positive one, for some, the sudden change in perspective had negative psychological effects. Whilst individuals expressed hope and gratitude, the narrative highlighted the difficulty of dealing with this rapid change in health, with individuals experiencing anxiety and fear, as seen in cancer survivors, in response to uncertainty, unanswered questions and fear of relapse (Hewitt *et al.*, 2007). The prevalence of anxiety and depression is higher within CF individuals when compared to the general population (Garcia et al., 2018)**.** Although classically linked to an impaired quality of life, the current study identifies that modulator therapy may elicit feelings of anxiety associated with the overwhelming and uncertain future individuals now faced with regards to themselves, their identity and their future. As reported in those who receive a non-diagnosis of Huntington's Disease, the prospect of a prolonged life can be one that is intimidating and stressful, as individuals perceive demands that they now must do something they were unprepared for, extraordinary and / or meaningful with their new, longer lives (Winnberg et al., 2018).

In the context of planning their new lives, some individuals spoke of a loss of identity and a need to redefine their sense of self. As with other chronic conditions, one's illness identity is

dictated by the degree in which the disease has affected the way in which them see themselves, and the degree of which the illness is integrated into one's sense of self (Charmaz., 2016). Whilst many professed a state of acceptance around their CF, for those who felt their illness dominated their identity, the shift in health, and thus identity, was described as *"almost post-traumatic".* For those who experienced a change in identity, albeit one of positive health, there was a need for meaning reconstruction, which elicited emotions commonly associated with the grieving process and the loss of self (Gillies and Neimeyer, 2006). It is worth noting however, that whilst the initial loss of identity can be a negative experience, as individuals construct new meaning to their new lives, Tedeschi and Calhoun (1996) argue that this process can breed positivity through the phenomenon of post-traumatic growth (PTG). For individuals who do experience PTG, through continuous reappraisal of themselves, individuals report feelings of becoming more resilient, confident, and independent, whilst also developing a greater awareness of life's fragilities (Gillies and Neimeyer, 2006). Whilst many individuals had developed coping strategies for their CF, many felt surprised and unprepared to deal with this emotion in response to a wholly positive event. Given that it is known that PTG can initiate feelings of stress and anxiety, the development of psychological programs promoting coping strategies should be considered in the management of life post-initiation of therapy, as it is likely that this initial transition is met with fear and uncertainty (Rajandram et al., 2011; Ness et al., 2012).

It is clear from this present study that the effect of modulator therapy had a strong impact on the relationship an individual had with their clinical team. Prior to the initiation of modulator therapy many spoke of limited or poor relationships with clinical teams. The concept of a 'bad relationship' has been defined as clinical teams distancing towards a patient, continuous conflict, scarce communication, a decreased time spent dedicated to patient concerns and a relationship based purely on technical aspects (Molina-Mula and Gallo-Estrada, 2020). The narrative highlighted these concepts both prior and post the implementation of modulator therapy, with individuals stressing their clinical teams failed to understand them as an individual or the effect their authoritarian decisions had on their physical and mental well-being. As such, many individuals felt they had no input in their own treatment decisions, or didn't feel confident in disagreeing for fear of judgement or guilt. This experience has been identified within the broader literature, with CF individuals often finding difficulty in

communicating with their clinical teams given issues in how clinical teams often discuss sensitive topics (Eaton et al., 2020). Whilst it is understood that clinical teams understand CF as an *illness*, there is often a failure to understand how each individual conceptualises the disease (Varilek., 2020). Given that many individuals receiving Kaftrio will now have to contest with the phenomena of survivorship, it is key for clinical teams to ascertain the psychological effects this can have on an individual. Common concerns within this narrative mirror that of cancer survivors, with issues around managing stress, fear of recurrence [or in this instance treatment removal] and living with uncertainty (Ness *et al.*, 2012). As individuals begin to redefine their constructs of reality, without the burden of CF, the need for clinical teams to understand the new existential concerns of living with CF is imperative, to ensure the post-Kaftrio era is not defined by poor clinical relations. As such this study has implications for service delivery, with a heavier focus needed on teams understanding the complexities and new challenges facing those with CF (Varilek., 2020). There is a call from participants to establish more meaningful relationships with clinical teams. Ultimately, a consistent, empathetic and respectful communication will formulate better perceived patient-provider communication, which has been shown to lead to higher trust in clinical care and consistent adherence with treatment (Young *et al.*, 2017). Whilst clinical care teams perceive the life-changing nature of Kaftrio to be one of positivity for the CF individual, it must be understood that simply increasing one's quantity of life does not necessarily increase one's psychological wellbeing and quality of life in the long term (Varilek and Isaacson, 2020).

The present study also identified feelings of survivor's guilt in both those who could and couldn't tolerate the therapy - a concept also seen in the context of other life limiting diseases (Huggins et al., 1992; Valverde, 2006). The concept of survivor's guilt has been defined into four specific areas: *altered identity, altered relationships, mental health and physical symptoms and resolution* (Hutson, Hall and Pack, 2015; Winnberg et al., 2018). The narrative identified all these depictions besides resolution (e.g., the feelings of guilt disappearing). Whether survivors guilt underpins the psychological experience of modulator is yet to be established and cannot be concluded from this narrative. However, the study identified that individual's conceptualised survivors' guilt according to their treatment experience. For those able to tolerate therapy, feelings centred around a sense of substitute guilt or unfairness in relation to those who are ineligible or could not tolerate the therapy. Indeed, individuals'

manifested feelings of guilt in the fact that they could now begin a life less compromised by CF, whereas others are not able to have that luxury. Similarly, as described in Hutson *et al.* (2015), this shift in identity may have further repercussions when considering identification with others and feelings of belonging with a CF community. Alternatively, where treatment failed, feelings of guilt centred around the idea that they were *ungrateful* or had *wasted* treatment in which others could have benefited. Given individuals were aware of the substantial cost associated with the therapy, the guilt was further exacerbated with perceptions of their personal burden on the healthcare system being heightened. As the occurrence of survival guilt in the context of modulator therapy is yet to be understood, there is a need for further research to ascertain when it occurs and develop potential preventative methods to aid patients.

6.5 Limitations

The perceptions of modulator therapy from this qualitative study were based on the lived experience of 12 individuals. Whilst individuals were interviewed from across the United Kingdom, the study did not explore patient perspective from other countries in which modulator therapy is available. Furthermore, the study population included significantly more females than males, as such we are unable to ascertain whether these perspectives are also affected by sex or gender. Given both factors, the generalisability of this information is somewhat limited.

Although genetic mutation was discussed, this was not a variable in which was explored in detail. As suggested in Varilek and Isaacson (2020) further research is needed to ascertain as to whether there are differences in the experience of modulator therapy between genotypes.

Although primarily considered a strength, the researcher having an experience of CF can also be considered a weakness. The autoethnographic nature of communicating the research would suggest that the researcher must connect their own personal experiences to the data (Bochner and Ellis, 2016). As such, although measures were put in place to control for bias (a member of the research team verified independently that the themes were reflective of the narrative, thus representing the data appropriately; peer review of the paper), it cannot be

ruled out that personal experience may have impacted the analysis and communication of the results within the study.

6.6 Conclusion

For many individuals, Kaftrio represents 'as close to a cure' as CF individuals will get in their lifetime, with substantial changes in quality of life, opportunity and optimism for the future. However, this does not come without negatives, with individuals experiencing anxiety with regards to side-effects, efficacy of long-term treatment, and fear of a return to life pre-Kaftrio. For the few who feel left behind, those who it did not work for, or the 10% who are not eligible, the message remains one of hope. An important overarching theme is that more needs to be done by clinical teams to help manage the magnitude of effect that Kaftrio has both physically and mentally. Whilst individual's express gratitude toward Kaftrio, for many that does not come in the absence of negative emotions.

CHAPTER 7
THE IMPACT OF CFTR MODULATORS ON NUTRITIONAL STATUS IN INDIVIDUALS WITH CYSTIC FIBROSIS: AN ARGUMENT FOR REBOUND HYPERPHAGIA

7 THE IMPACT OF CFTR MODULATORS ON NUTRITIONAL STATUS IN INDIVIDUALS WITH CYSTIC FIBROISIS: AN ARGUMENT FOR REBOUND HYPERPHAGIA

7.1 Introduction

Cystic Fibrosis (CF) is the most common life-shortening genetic disorder within the Caucasian population, caused by a defect in the CF transmembrane regulator protein (CFTR) gene (Riordan et al., 1989). Dysfunction in, or the absence of, the CFTR protein results in defective ion transport across the epithelial cell, leading to the accumulation of thick mucus secretions in the pulmonary and gastrointestinal systems (Brown, White and Tobin, 2017; Heijerman et al., 2019). Whilst the main burden of the disease is related to the pulmonary system, 85-90% of individuals are pancreatic insufficient (PI). Thick mucus secretions in the pancreas result in obstruction of the ducts, leading to deficient pancreatic enzyme production and subsequent fat malabsorption (Lavelle et al., 2015; Li and Somerset, 2014). As such, poor nutrient absorption coupled with a considerable energy requirement due to an increased energetic cost associated with breathing and recurrent pulmonary infections, represent a significant challenge to achieving adequate nutritional intake in those with CF (Ratchford, Teckman and Patel, 2018).

The role of nutritional status and body mass index (BMI) in determining clinical outcomes are well established. Specifically, malnutrition is strongly associated with a decline in pulmonary function and increased rates of morbidity and mortality in individuals with CF (Harindhanavudhi et al., 2020; Hauschild et al., 2018), with low energy availability (EA) purported to have further deleterious implications on immunity, protein synthesis, cardiovascular function, and bone health (Troosters et al., 2009; Mountjoy et al., 2018; Langan-Evans et al., 2021). Recognising the significance of adequate EA, clinical management focuses primarily on achieving BMI-based nutritional goals for all patients (BMI ≥ 50th percentile in children; ≥ 22 kg/m^2 in adult women; and ≥ 23 kg/m^2 in adult men; Castellani et al., 2018) through the implementation of a high calorie diet, pancreatic enzyme replacement therapy and, more recently, CFTR modulator therapy (Harindhanavudhi et al., 2020; Stallings et al., 2008).

Whilst intensive efforts to promote adequate nutrition have significantly reduced the prevalence of malnutrition within the CF population since the 1980's, the methods used may have also facilitated an increased incidence in the prevalence of overweight/obese (Litvin et al., 2019). Indeed, it is suggested that 10 – 30% of the CF population may be overweight or obese (Hanna and Weiner, 2015; Kastner-Cole et al., 2005), with a recent study involving 484 adults with CF reporting that 25.6% of the cohort were classified as overweight and 6.6% as obese (Harindhanavudhi et al., 2020). Although the implications of high weight status are yet to be extensively explored within a CF population, it is reasonable to suspect that obesity would be associated with higher mortality rates due to the risk of hyperlipidemia, hypertension, impaired glucose tolerance, diabetes and atherosclerotic heart disease (Berrington de Gonzalez *et al.*, 2010; di Angelantonio *et al.*, 2016). Whilst nutritional counselling and a shift to a more nutrient dense, moderate energy diet has been suggested as a means of managing obesity risk in those with CF (van der Haak *et al.*, 2020), there is early evidence of significant weight gain following the implementation of new CFTR modulators, which may exacerbate the prevalence over overweight/obesity in this population (Bailey *et al.*, 2021).

Over the last decade, the development of targeted therapies known as CFTR modulators have fundamentally changed the treatment of CF by restoring function to the CFTR protein, thus addressing the underlying cause of the disease (Barry and Taylor-Cousar, 2021). Ivacaftor (IVA) demonstrated successful potentiation of the CFTR protein, increasing the time that the protein was open at the cell surface and subsequently eliciting unparalleled increases in pulmonary function and quality of life (Ramsey et al., 2011). The combination of IVA with the correctors Elaxacaftor (ELX) and Tezacaftor (TEZ) have demonstrated significant increases in mature CFTR protein, with phase 3 clinical trials reported unprecedented improvements in lung function (+10 percentage points), sweat chloride, and respiratory-related quality of life (Heijerman et al., 2019). However, in addition to improving lung function, CFTR modulators have the potential to enhance nutritional status and anthropometric parameters (height, weight, BMI), although this remains to be comprehensively explored (Bailey et al., 2021). In phase III clinical trials, treatment with ELX/TEZ/IVA evidenced an absolute change in bodyweight of +3.4 kg versus 0.5 kg in the placebo group *(Heijerman et al., 2019; Middleton*

et al., 2019). However, how these increases translate to incidence of overweight/obesity is still to be elucidated.

The primary aim of the present observational study was therefore to identify the magnitude of change in body mass and BMI following the implementation of triple modulator therapy according to age, starting nutritional status and duration of treatment and to quantify whether such changes resulted in an increased incidence in overweight/obesity in adults at a UK CF Centre.

7.2 Methods

7.2.1 Patient Population and Study Design

Annual review data between 2019-2021 for 186 adult patients (105 males) with CF, under the care of University Hospital Llandough in South Wales, UK, was retrospectively reviewed and analysed. We extracted data from the electronic records including age, sex, height, weight, genotype, body mass index (BMI) and pulmonary function ($ppFEV_1$). Participants were excluded from the study if they had received lung transplantation prior to or during the analysis period as this may have a significant effect on the parameters tested within the study. Individuals who presented with no copies of the *F508del* gene were removed from the sample. As this single centre analysis (a) used anonymised data and (b) results cannot be generalised beyond this CF centre, an NHS ethical application was not required as per NHS Health Research Authority Guidelines.

Table 7.1. Baseline characteristics of participants (2019).

	All	Treatment	No Treatment
N (%)	186	155 (83%)	31 (17%)
Male/Female (%)	105/81 (56/44%)	87/68 (56/44%)	18/13 (58/42%)
Age (years)	30 ± 11	28 ± 11	39 ± 10
BMI (kg/m^2)	22.81 ± 3.84	22.34 ± 1.03	24.46 ± 1.19
Weight (kg)	64.73 ± 13.10	63.50 ± 11.99	71.26 ± 16.41
$ppFEV_1$ (%)	73.00 ± 2.30	67.43 ± 7.88	79.75 ± 8.73
Nutritional Status (*N*)			
Underweight	15	13	2

Normal	118	101	17
Overweight	32	28	4
Obese	7	3	4

Age within the study was represented as 'Age at 31/12 of the respective year'. Individuals were assigned to 'male' and 'female' groups based on biological characteristics at birth. Forced expiratory volume in one second (FEV_1) was expressed in Litres (L) and as a percentage of predicted (%FEV_1) for height and sex using the Hankinson reference norms (Hankinson, Odencrantz and Fedan, 2012). Body mass index (BMI) was split into categories of underweight (< 18.5 kg/m^2), normal (18.5-24.9 kg/m^2), overweight (25.0-29.9 kg/m^2) and obese ($\geq$ 30 kg/m^2) (Weir & Jan, 2021b). Pulmonary function was split into categories of 'mild' ($\geq$ 70%), 'moderate' (40-70%) and 'severe' lung disease (< 40%) (Tomlinson *et al.*, 2020). Participants were grouped in accordance with normative values from the Centre for Disease Control (CDC) for BMI.

7.2.2 Statistical Analysis

Baseline characteristics were reported and presented as mean $\pm$ standard deviation (SD). To account for the unbalanced sample size and to control for missing data, a linear mixed-model was used. The model evaluated the effect of modulator treatment on BMI using a repeated measure design that accounts for the nested nature of the data. The initial model investigated the main effects of modulator therapy and time on BMI. To this model, additional fixed effects were added (sex, duration on therapy, age commencing therapy) to determine the effect and interaction of these variables on BMI. A second model was created to determine the effects of and BMI on ppFEV_1. The relationship between change in weight and change in FEV_1 was determined using a bivariate linear regression. Statistical significance was set at an alpha of 0.05. All statistical analysis were performed using IBM SPSS version 28.0 (Armonk, NY: IBM Corp).

7.3 Results

A total of 186 adults CF patients (105 males) were included in the analysis between the years of 2019 and 2021. Mean age of the cohort was 32 $\pm$ 11 years as of 31/12/2021. Of the 176

patients with complete BMI data, prior to the implementation of modulator therapy (2019),15 (8.7%) were considered underweight, 118 (68.6%) normal weight, 32 (18.6%) overweight and 7 (4.0%) obese. With reference to genotype, 91 (49%) of individuals were homozygous for *F508del*, with the remaining 95 (51%) heterozygous with at least one copy of the *F508del* mutation.

7.3.1 BMI

The mean predicted BMI of the cohort for the respective year was 22.81 $\pm$ 3.84 (2019), 23.15 $\pm$ 4.04 (2020) and 23.91 $\pm$ 3.71 (2021) kg/m^2. Mean BMI was significantly higher in patients who did not receive treatment with modulator therapy over the study period. There was no significant differences in BMI when accounting for sex. Individuals initiating treatment with ELX/TEZ/IVA in 2020 demonstrated a significant increase in BMI between 2020 and 2021 (+1.05 $\pm$ 0.43 kg/m^2; P < 0.05). In contrast, those who did not receive treatment evidenced no change in BMI over the same time period (0.30 $\pm$ 1.03 kg/m^2) (Figure 7.1).

Following treatment with ELX/TEZ/IVA, there was a decrease in the observed rate of individuals considered underweight (8.61% to 5.63%) and of normal weight (66.26% to 59.21%). Conversely, there was an increase in the incidence of overweight (21.85% to 30.99%) and obese (3.31% to 4.26%) individuals. Within the cohort of individuals receiving treatment the incidence of overweight/obesity increase from 25% to 35% between 2020 and 2021. When stratified by BMI category, significant increases in BMI were evident for those considered *underweight* (+1.98 $\pm$ 0.84 kg/m^2, P < 0.05), *normal* weight (+0.96 $\pm$ 2.8 kg/m^2, P < 0.001) and *overweight* (0.61 $\pm$ 0.48 kg/m^2), whilst those considered *obese* demonstrated a decreased BMI (-0.78 $\pm$ 1.2 kg/m^2) over the same time period. Of those classified as overweight or obese following treatment, 53% were heterozygous for *F508del*. Patients in the overweight and obese categories were also most likely to be older, male and pancreatic sufficient. Following the implementation of treatment, only one individual from the cohort saw a reduction in weight category (from *normal weight* to *underweight*), however this individual had only recently began treatment with ELX/TEZ/IVA.

There was a significant effect of age on BMI (P < 0.001), with BMI highest in those aged 30-35 years. Similarly, those aged 30-35 years were the only subgroup to evidence a significant

increase in BMI (+2.34 ± 1.12 kg/m^2) following the initiation of treatment with ELX/TEZ/IVA. There was also a significant effect of duration of treatment ($P < 0.05$), with 5-8 months post initiation of CFTR therapy evidencing a higher BMI than those at 1-4 months (22.67 vs 24.14 kg/m^2; $P < 0.05$). However, there were no further increases in BMI following 9+ months of treatment.

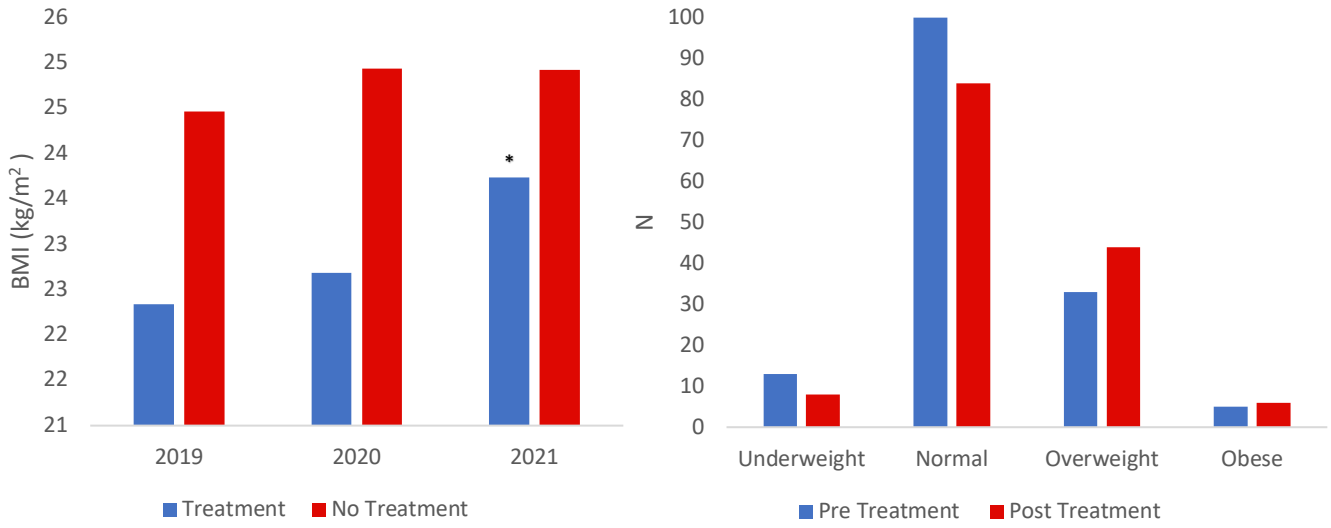


Figure 7.1. (A) Change in BMI in response to treatment with ELX/TEZ/IVA between those receiving treatment and those not, (B) Effect of treatment with ELX/TEZ/IVA on distribution of individuals based on nutritional status. * significant increase, $P < 0.05$.

7.3.2 Pulmonary Function

The mean predicted ppFEV$_1$ of the cohort for the respective year was 73.00 ± 2.30 (2019), 72.52 ± 2.45 (2020) and 76.46 ± 2.55% (2021). There was a significant effect of modulator therapy on mean ppFEV$_1$, with individuals *not* receiving treatment evidencing a significantly higher mean ppFEV$_1$ (77.14 ± 2.59 vs 70.84 ± 1.05%) in 2019. When standardised by year, only individuals receiving treatment demonstrated a significant increase (+7.71 ± 2.60%, $P < 0.05$) in ppFEV$_1$ when compared to the non-treatment group (+0.70 ± 6.58%) between 2020 and 2021. Despite mean ppFEV$_1$ being higher across three years in those who did *not* receive treatment, following the initiation of ELX/TEZ/IVA therapy there was no significant difference in ppFEV$_1$ between the treatment (76.16 ± 1.83%) and non-treatment group (76.75 ± 4.77%). Whilst individuals classed as *underweight* demonstrated the lowest mean ppFEV$_1$, these individuals experienced the largest, albeit not significant, gain (+14.00 ± 8.87%) following the

initiation of treatment with ELX/TEZ/IVA. The only group to demonstrate a significant increase in ppFEV$_1$ were those of *normal* weight prior to treatment (+8.88 ± 3.33%, P < 0.05). As with BMI, those who were *obese* saw a decrease in ppFEV$_1$ of -1.20 ± 13.04% between 2020 and 2021. When stratified by disease severity, all disease severities evidenced significant increases in %FEV$_1$ between 2020 and 2021. Patients categorised as having '*Severe*' and '*Moderate*' disease severity saw the largest increases with a shift in %FEV$_1$ of 11.3 and 10.3% respectively. Those considered to have 'Mild' lung disease increased by 5%.

Simple linear regression was used to determine whether rate of change in BMI significantly predicted rate of change in FEV$_1$ following treatment with ELX/TEZ/IVA. The results of the regression indicate that rate of change in BMI explained 3.4% of the variance (R^2 = .034, F(1,134) = 4.75, P < 0.05). It was found that rate of change in BMI significantly predicted rate of change in FEV$_1$ (β= 1.19, P < 0.05).

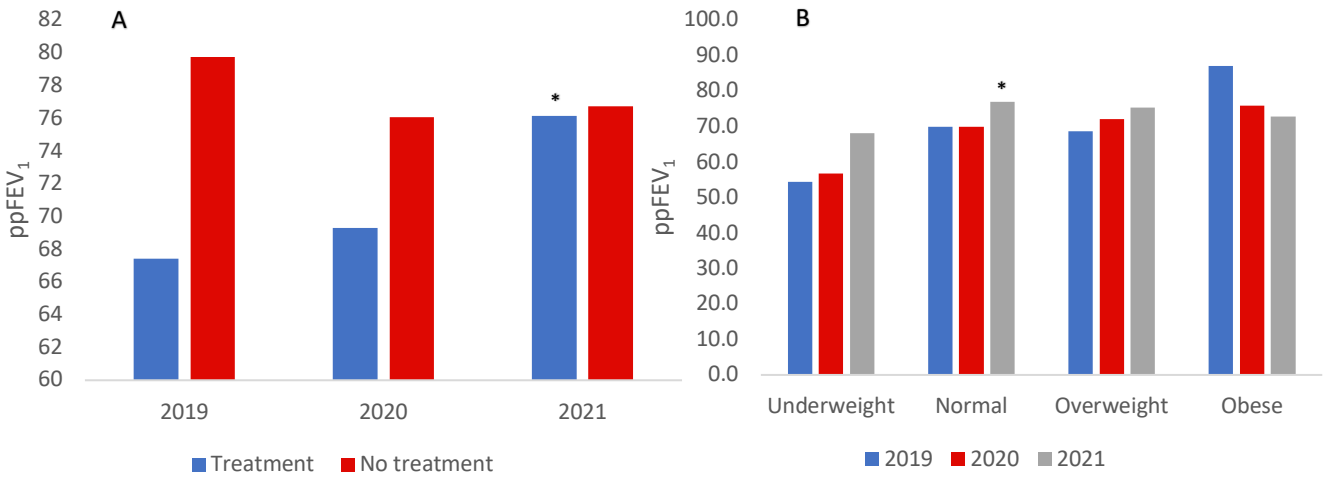


Figure 7.2. (A) Change in ppFEV$_1$ in response to treatment with ELX/TEZ/IVA between those receiving treatment and those not, (B) Impact of nutritional status on ppFEV$_1$. * significant increase post-treatment, P < 0.05

7.4 Discussion

Whilst malnutrition has been one of the primary issues of CF care, the prevalence of overweight and obesity is a growing concern (Hanna & Weiner, 2015b). Following the initiation of treatment, the incidence of overweight and obesity increased by 33% and 20%,

respectively, with 35% of the CF patients attending the University of Llandough adult CF centre subsequently falling into these weight categories. Findings validate previous research, with those considered to be overweight/obese were likely to be male, older and pancreatic sufficient (Gramegna et al., 2022). Over this same time period, average BMI of those *not* receiving treatment declined by -0.30 $\pm$ 1.03 kg/m^2. When categorised by nutritional status, individuals considered *underweight* or *normal* weight pre-treatment evidenced the largest increases in BMI and ppFEV$_1$. Rate of change in BMI was also considered a significant predictor of rate of change in FEV$_1$ following treatment.

Although classically at risk of malnutrition, the intensive effort to promote adequate nutritional status has lead to substantial increases in BMI in the CF population over the past 20 years (Harindhanavudhi et al., 2020). A 2005 registry analysis reported that 10% of children and adults with CF who were homozygous for *F508del* had a BMI exceeding 25 kg/m^2 (Kastner-Cole *et al.*, 2005). More recent reports suggest that the incidence of overnutrition among adults with CF to be between 7% and 30% (González-Jiménez et al., 2017; Gramegna et al., 2022; Hanna and Weiner, 2015; Harindhanavudhi et al., 2020; Panagopoulou et al., 2014). The observed incidence of overweight/obesity within this study validates findings above with 28.4% of individuals considered overweight/obese. However, following the implementation of treatment with ELX/TEZ/IVA the incidence increased up to 35% suggesting CFTR compounds may accelerate the rising trend in overweight/obesity within a CF population.

The introduction of CFTR therapies into clinical use represents a significant shift in the management of CF as a condition, transitioning from treating the downstream complications of the disease to addressing the underlying cause of the condition. CFTR modulators have been shown to improve pulmonary function and quality of life and to elicit an increase in weight and BMI (Griese et al., 2021; Heijerman et al., 2019; Middleton et al., 2019); a recent systematic review concluded that the magnitude of change is dependent on the therapy formulation (single vs combination) and the specific *CFTR* mutation (Bailey *et al.*, 2021). Long-term treatment with IVA was associated with the proportion of individuals categorised as overweight increasing from 16% to 25% over a 5.5-year period (Guimbellot *et al.*, 2021). Comparably, early data from phase III clinical trials of treatment with ELX/TEZ/IVA indicate

increases in BMI of 0.90-1.28 kg/m^2 over a 24-48 weeks follow up period (Griese et al., 2021; Heijerman et al., 2019; Middleton et al., 2019). When considered in a real-world setting, recent data from the Washington University Adult CF Centre demonstrated a 1.5kg/m^2 increase in BMI over a period of 12-months, which translated to an overall incidence of 41% (compared to 26.9% prior to treatment) overweight/obesity following the implementation of ELX/TEZ/IVA (Petersen *et al.*, 2022). Magnitude of increase observed within this study is in accord with such earlier reports. Given results demonstrated a significant effect of treatment duration on BMI, it must be noted that the average follow-up period of this study was 7-months, compared to 12-months in Petersen et al (2022). Therefore, considering findings from Petersen et al (2022) and Griese et al (2021), it would be reasonable to suggest that there may be further increases in BMI over time, which would be expected to lead to a further increased incidence of overweight/obesity.

The specific mechanism behind this increase in weight and BMI in response to treatment with ELX/TEZ/IVA is yet to be fully elucidated but is likely multi-factorial in nature. Data from Stallings et al. (2018) in response to 3-months of IVA treatment demonstrates a decrease in resting energy expenditure, a reduction in gut inflammation and a subsequent increase in fat absorption in children and adults with gating mutations. Similarly, Gelfond et al. (2017) suggest an increase in bicarbonate secretion in the small intestine that improves intestinal pH and subsequent absorptive capacity. However, findings from our own research (Chapter 6) and patient survey data report an increase in appetite and subsequent food intake in response to treatment (Martin *et al.*, 2021). Interestingly, qualitative reports of hunger mirror that seen following recovery from severe energetic deficits, in which participants exhibit exponential increases in energy intake (known as Hyperphagia), causing considerable increases in body fat over a short period of time (Keys et al., 1950). Following a period of semi-starvation, *ad libitum* food intake increases markedly above the pre-starvation level wherein this hyperphagic response persists for several weeks. As a result, the amount of fat gained is greater than that previously lost, known as 'fat overshooting' (Keys et al., 1950; Miles-Chan and Isacco, 2021). Whilst CF may not be considered a period of semi-starvation, there is debate with relation to energetic metabolism as to whether, despite presenting with an *appropriate* BMI, individuals with CF truly meet their natural 'set point' with relation to overall and skeletal muscle mass, due to the hypermetabolic nature of the condition (Soltman et al.,

2021; Speakman et al., 2011; Troosters et al., 2009). Given that treatment with ELX/TEZ/IVA is postulated to reduce resting energy expenditure thus regulating metabolism, it is possible individuals are now able to achieve this relative set point. As evidenced in patients treated for hyperthyroidism, individuals experience a considerable increase in BMI following treatment, of which is considered a replenishment of body mass to premorbid weight (Torlinska et al., 2019). Indeed, an increase in BMI and resultant 'fat overshooting' is thought to be driven by a hyperphagic response in an attempt to restore fat free mass following a period of decreased energy availability, in which hyperphagia may continue until fat free mass returns to levels close to an individuals set point (Dulloo, Jacquet and Girardier, 1997). However, as lean tissue can only be gained with a concomitant deposition of body fat, recovery of lean mass through over-eating is inherently accompanied by a simultaneous accumulation of body fat (Dulloo, 2017). Most studies report that individuals with CF have lower fat free mass and skeletal muscle mass when compared to the general population (Soltman et al., 2021), as such any potential recovery in fat free mass through a period of overeating would be expected to result in a significant accumulation of fat mass (relative to fat free mass) following the theory of collateral fattening (Dulloo, 2017). Interestingly, a long-term open label study of IVA found that both weight and fat mass significantly increased following 24-months of treatment, which 64% of weight gained attributable to fat mass (King et al., 2021). Whilst the current study was unable to quantify the relative percentage of fat mass vs fat free mass, only those considered *underweight* or *normal* weight demonstrated significant changes in BMI, possibly suggesting a larger hyperphagic response and subsequent return to proverbial set point in a population with a higher likelihood of reduced fat free mass.

Although BMI is used as an indicator of nutritional status in individuals with CF, it fails to differentiate between different body composition components (Bailey et al., 2021). Indeed, fat free mass is more strongly associated with pulmonary function in CF in comparison to BMI (Sheikh et al., 2014). Consequently, the pattern of weight gain and maximising lean mass accumulation following implementation of treatment with ELX/TEZ/IVA should be considered in more detail. Whilst nutritional counselling for individuals with CF has previously focused on achieving an energy intake of around 150% of the daily recommended guidelines for the general population (Castellani et al., 2018), given the prevalence of overweight/obesity and potential hyperphagic response to treatment, such advice could exacerbate these issues.

Although it is likely that changes in fat mass will be a direct consequence of total daily energy balance, macronutrient composition of this potential caloric surplus should be tailored to the individual in order to maximise the accumulation of lean tissue. Where possible, achieving a daily protein intake of ~1.6-2.2 g/kg has been shown to elicit substantial increases in fat free mass when coupled with a progressive resistance training plan (Engelen, Com and Deutz, 2014; Bandegan et al., 2017) which may support a more favourable body composition post treatment, however further work is needed to confirm this within a CF population. However, there is consensus that overall nutritional consideration should be shifted away from a high-fat, high-energy diet to a more nutrient dense, moderate energy diet for individuals receiving treatment with triple modulator therapy (Harindhanavudhi et al., 2020; van der Haak et al., 2020). As the response to CFTR treatment is expected to be highly individualised (Barry and Taylor-Cousar., 2021), it would be recommended that measures of resting metabolic rate are taken (through indirect calorimetry) during quarterly clinic visits to further inform nutritional practice and dietary prescription, as blanket energy intake recommendations are no longer appropriate in an era of corrective medicine.

This was a single centre analysis which is not without limitations. Given data was collected from an adult CF centre within an academic medical institution, such data may not be generalisable to a wider CF population. With the average duration of treatment with ELX/TEZ/IVA, further longitudinal studies are needed to confirm whether such changes in BMI are seen post a 12-month period. This study was unable to explore the cardiometabolic profile (blood glucose, cholesterol, Haemoglobin A1c, plasma lipids, blood pressure etc) of individuals pre/post modulator treatment which would have given a more detailed insight than BMI and weight alone. Similarly, BMI alone does not represent changes in body composition. Given the significant effect of fat free mass on pulmonary function, assessment of rate of change in fat free mass vs fat mass would have been insightful, especially when considering the hyperphagic response to treatment.

Overall, findings would suggest that treatment with ELX/TEZ/IVA is associated with an increased incidence of overnutrition within the CF population. As a means of managing post-therapy hyperphagia, individualised nutritional assessments should be scheduled in line with clinical visits in an attempt to manage fat overshoots and related downstream complications.

Finally, educational support is advised to transition individuals away from the classical ‘legacy CF diet’ to one of increased food quality and balance macronutrient content.

CHAPTER 8
SYNTHESIS

8 SYNTHESIS

The primary objective of this thesis was to further our understanding concerning the effects that therapeutic and non-pharmacological interventions have on the physiological and psychological health of children and adults with CF. Specifically, the studies addressed the following:

Chapter 4: Investigated the safety and efficacy of the REHIT protocol in an adult individual with CF.

Chapter 5: Investigated the influence of nutritional status on measures of pulmonary function over an individual's childhood and adolescence and establish whether this is further influenced by the sex of an individual.

Chapter 6: Explored the real-world 'lived' experience of treatment with ELX/TEZ/IVA and explore how this treatment has influenced an individual's perception of reality, and to what extent modulator has changed their life, beyond just the physical.

Chapter 7: Observed the change in BMI and subsequent incidence in overweight/obesity within an adult CF centre in the UK following implementation of treatment with ELX/TEZ/IVA

Data presented within the experimental chapters of this thesis have made important contributions to the current literature by identifying relevant lifestyle factors that should be addressed following the implementation of modulator therapy, whilst giving context to the immediate effects this therapy has on physical and mental well-being. Additionally, this thesis provides further insights to the effects of sex and highlights key considerations for future research given the significant disadvantage experienced by females in a pre- modulator era. The present chapter synthesises the key findings from each chapter and highlights their contribution to the field. Finally, experimental considerations and recommendations for future research are provided to conclude the thesis.

8.1 Health trajectory and the influence of exercise and aerobic capacity

Physical exercise training is considered a cornerstone of CF care given its positive association with an individual's quality of life and survival (Hebestreit et al., 2005; Nixon et al., 1992; Pianosi et al., 2005; Radtke et al., 2017). Whilst it is well known that improvements in an individual's $\dot{V}O_{2peak}$ result in favourable clinical outcomes, such improvements in aerobic capacity typically require specific, formal exercise programmes (Radtke et al., 2017). Although the benefits of such programmes are widely accepted and understood, the provision of and adherence to such programmes are often poor within a CF population. Qualitative findings from Chapters 4 and 6 provide evidence regarding the diversity of these barriers to not only formal exercise but also leisurely activities such as walking, with individuals referencing the debilitating effect CF has on their capacity and confidence to engage in activity. Whilst, in theory, implementation of an individualised training programme may aid in the implementation of successful, long-term interventions, current practice is some way off this standard (Gruet *et al.*, 2021). Due to the heterogeneity of disease profiles within a CF population, consideration needs to be given to the physiological and psychological responses to exercise and associated barriers to long-term engagement to truly facilitate exercise engagement. As it is expected that there will be a 75% increase in the adult CF population by 2025 (Burgel et al., 2015), there is urgent need for research regarding the long-term management of the disease as it is likely individuals will be at increased risk of developing other co-morbidities associated with ageing populations (e.g. cardiovascular disease, obesity, diabetes) (Schwarz and Hartl., 2015; Ronan, Elborn and Plant., 2017). As younger people with CF are expected to be healthier than ever, there is an ever-growing diversity in the needs of the individual, with further considerations needed about exercise suitability based not only on disease state, but also age, gender and psychological perceptions of exercise. As such, it is important to be cognisant of an individual's ability and exercise preference to ultimately achieve a sustainable exercise intervention.

Given that the rationale for many exercise interventions in CF individuals centres around the physiological efficacy, it is likely that these interventions are not adequately individualised. Whilst the use of CPET's allows for a somewhat individualised programme (such as setting training intensity based on GET), often such programmes fail to consider an individual's psychological barriers to activity. Indeed, many individuals with CF report disengagement

with exercise due to unpleasant symptoms, breathlessness, low energy, self-consciousness, capability, and a lack of good health (Dwyer, Elkins and Bye, 2011; Moola, Faulkner and Schneiderman, 2012; Burnett, Barry and Mermis, 2020; Hurley et al., 2021). To address some of these barriers, the testing methodology in Chapter 4 aimed to identify the lowest dose of exercise needed to elicit significant changes in an individual's aerobic capacity. Although limited by its case study deign, this study demonstrated the feasibility and safety of the REHIT protocol within a CF population, and evidenced increases in $\dot{V}O_{2peak}$ similar to those elicited within healthy populations (Metcalfe *et al.*, 2012). Although the use of MICT is well researched within a CF population, Chapter 4 adds to recent literature by demonstrating that HIIT/SIT could be as effective as MICT in improving aerobic capacity in individuals with CF (A. Sawyer et al., 2020). Furthermore, the use of semi-structured interviews identified REHIT as a tolerable and more favourable form of training when compared to MICT, with time-efficiency and lack of symptoms considered some of the main contributors to the individuals adherence. Whilst it is advised that findings should not be generalised to a wider population, it raises the question as to whether current HIIT/MICT protocols are unnecessarily arduous and whether successful adherence to exercise programmes in the long-term may benefit from a reduced training load (Metcalfe et al., 2012; Metcalfe, Atef, Mackintosh, et al., 2020).

Importantly, inter-individual variability should be accounted for when assessing suitability with a protocol of such intensity. Whilst we cannot conclude suitability of REHIT for subgroups based on age or disease severity, safety of HIIT/SIT within those who are of severe pulmonary limitation has been evidenced, suggesting that such protocols are feasible within such a population (Gruber et al., 2014). As it is likely that the REHIT protocol may be perceived as too intense for some individuals (Hardcastle *et al.*, 2014), given its promise, further research should centre around the identification of individuals with a particular affinity towards more intense exercise by utilising the Preference for and Tolerance of Intensity of Exercise Questionnaire (PRETIE-Q) (Ekkekakis, Hall and Petruzzello, 2005).

When considering long-term adherence, the relative influence of setting and supervision must not be overlooked, with supervised interventions evidencing better long-term adherence compared to those unsupervised (Kriemler *et al.*, 2013). Consequently, home-based training utilising web-based technologies may be a useful modality to facilitate long-

term adherence. Such exercise modalities have gained popularity following the COVID-19 pandemic given their advantages with regards to the management of cross-infections, remote supervision, use of minimal resources and allowing CF individuals to engage in group-based classes for the first time together (Gruet *et al.*, 2021). Recent studies have explored the efficacy of online software such as *BEAM*, reporting positive findings with regard to improvements in CF patient's perceived exercise tolerance and motivation towards exercise (Chen et al., 2018; McCrea, Morrison and Palmer, 2021). Prior to the COVID-19 pandemic, we were exploring the applicability of the REHIT model to a home environment as although such protocols have been shown to be highly effective within a laboratory setting, the efficacy of home-based, SIT protocols that overcome the need for specialist equipment is currently unclear, especially in clinical populations (Blackwell et al., 2018). In healthy populations, home-based bodyweight HIIT (Blackwell et al., 2018), whole body tabata resistance training (McRae et al., 2012) and low volume, intense stair climbing (Alisson et al., 2017) have elicited increases in $\dot{V}O_2$peak of up to 12%, consistent with those gained in a laboratory setting (Metcalfe *et al.,* 2012). Given that recent findings suggest that the greatest uptake of sessions online are HIIT (82% of sessions; McCrea, Morrison and Palmer, 2021), the relevance of exploring this research question is further emphasised to ascertain the optimal training intensity and frequency with relation to both physiological and psychological outcomes. Unfortunately, due to the impact of COVID-19, this comparative study was not able to be completed despite recruiting 15 participants as follow up lab-based measures were not possible.

In the era of personalised CFTR treatment, understanding the role of non-therapeutic interventions, such as exercise and nutrition, may seem less important but it is currently unknown whether modulator specific benefits to respiratory health translate to exercise ability (Gruet et al., 2021). Indeed, it is pertinent to note that research assessing the effect of IVA and IVA/LUM combinations suggest that CFTR modulation alone is not sufficient to produce meaningful changes in an individual's exercise capacity. Specifically, Saynor et al., (2014) and Savi et al., (2019) report significant improvements in an individual's $\dot{V}O_{2peak}$ following 12-weeks of treatment with IVA and 2-years treatment with IVA/LUM combinations, respectively, whereas Wilson et al., (2021) demonstrated no significant change

in $\dot{V}O_{2peak}$ after 24-week treatment with IVA/LUM. Long-term studies are still required to determine the effects of treatment with ELX/TEZ/IVA on physical fitness. As such, although it cannot be ruled out that modulator treatment has a beneficial impact on physical fitness, it is likely, as within the general population, that exercise interventions will remain a key cornerstone to management of CF in a post-modulator era.

Although modulator therapy may not directly influence aerobic capacity, initiation of treatment has been shown to induce positive changes in PA intention (Quon *et al.*, 2020). Specifically, for those who experience reductions in physical symptoms and large improvements in pulmonary function in response to modulator therapy, it is postulated they may be more *willing* to engage in more PA due to a decreased perception of barriers to such activity (Gruet et al., 2021). Narrative data from Chapter 6 supports this notion, in that many individuals reported the debilitating effect their CF had on their desire and ability to be active, with many noting that simple activities such as walking required careful consideration to manage fatigue and exacerbation of unpleasant symptoms. Independent of respiratory function, individuals cited that the significant reductions in day-to-day burden of CF challenges following Kaftrio had enabled them the opportunity to regain feelings of enjoyment they once experienced from exercise and PA. Although not explored within Chapter 6, it could be postulated that increases in PA in response to modulator therapy may be dependent on whether an individual was intrinsically motivated to exercise *prior* to their condition deteriorating. Specifically, where those with backgrounds in sport and exercise may relish the opportunity to re-live past exercise experiences with a newfound optimism, considerations must be taken to address the needs of those who previously perceived exercise and PA as burdensome (Moola, Faulkner and Schneiderman, 2012). It is suggested in Gruet et al., (2021) that priorities must focus on developing an individual's intrinsic motivation to exercise with considerations around an individual's preference, setting and modality. As it is expected that individuals with low intrinsic motivation may disengage from more vigorous exercise modalities, it is unlikely that findings and future direction with relation to Chapter 4 would suit such a population, further emphasising the need for a personalised approach to future exercise prescription.

What is pertinent to note is that whilst one may feel capable in relation to partaking in physical exercise and PA, for those who are older or severely deconditioned, such a return to activity is not without risk. Significant periods of detraining have been shown to cause alterations in body mass and composition, a loss of efficiency of neuromuscular and cardiovascular systems and, consequently, a loss in strength, speed, flexibility and endurance and an increase in the risk of injury (Bosquet et al., 2013; Bisciotti et al., 2020). As many individuals with CF present with skeletal muscle dysfunction or skeletal muscle weakness (Troosters *et al.*, 2009), sensible return to activity is advised to enable long-term PA adherence.

When considering suitable exercise prescription, it is also worthy of note that many inflammatory cytokines involved in the characterisation of the CF disease (TNF-α, IL-6 and CRP) remain elevated for a longer period after the cessation of exercise in CF patients when compared to a healthy population (Tirakitsoontorn et al., 2001, Ionescu et al., 2006). How this translates into long-term health outcomes is currently unknown and raises questions as to whether exercise above a certain threshold or duration has the potential to exacerbate disease symptoms in this population. With relation to exercise modality, there is an argument that HIIT may be preferable when considering inflammatory profile, with it well established that prolonged aerobic exercise induces a large systemic inflammatory response which may suppress the immune system and increase susceptibility to infection (Nieman, 1997, 2008; Nieman et al., 2007, 2012; Shanely et al., 2014). Whilst HIIT still engenders an increase in inflammatory cytokines, it appears to be of a much lower magnitude in comparison to aerobic training, likely due to the relative time spent exercising (Zwetsloot et al., 2014). Taking into consideration that most commonly studied HIIT protocols are “excessive” in terms of volume, there is scope to suggest that REHIT (Chapter 4) could potentially elicit not only more favourable adaptations in aerobic capacity and time effectiveness, but, due to the significantly reduced training load, could represent a more favourable option that minimises the stimulation of immunosuppressive inflammatory cytokines. Prior to the COVID-19 pandemic we initiated a study to assess whether low-dose REHIT provided a more favourable inflammatory response than traditional MICT, however, despite initial testing being underway, the study was not able to be completed due to pandemic-related restrictions. Nonetheless, as recent research following CFTR treatment has shown only modest

improvements in inflammatory markers (Hisert et al., 2017; Harris et al., 2020), management of inflammation with regards to exercise is still worth attention when considering personalised and safe exercise prescription.

8.2 Health trajectory and the influence of BMI

Management of nutritional status is considered an essential component of patient care given its clinical associations with pulmonary function, morbidity and mortality (Hauschild et al., 2018; Steinkamp and Wiedemann, 2002; Stephenson et al., 2013; Yen et al., 2013). Findings in the current thesis provide further support for the relationship between BMI and pulmonary function, especially in females. Indeed, despite the almost linear increase in predicted survival over the past decade, the gap in clinical outcomes between males and females with CF is well documented and undiminished (Lam et al., 2020). Whilst this gap is believed to be multi-factorial in nature, findings from Chapter 5 demonstrate BMI to have a more significant influence on pulmonary function in females when compared to their male counterparts, with every percentage change in BMI associated with a greater change in FEV_1. Given the sensitivity of female pulmonary function to changes in BMI, it is fair to postulate that poor management of nutritional status and subsequent larger declines in pulmonary function undoubtedly contribute somewhat to the disparity in survival between sexes (Lam et al., 2020). Whilst Chapter 5 validates the importance of attaining a BMI above the 50^{th} percentile for both males and females (HuiChuan and Suzanne, 2008; Stallings et al., 2008), reaching such a threshold may be easier in theory than in practice. Females with CF report greater treatment discouragement, lower self-esteem, and lower adherence to treatment, with specific reference to dietary intake (Patterson et al., 2008). It is of concern that 45% of females reported a dissatisfaction with their body and a desire to be smaller *despite* not achieving BMI percentile related goals (Abbott et al., 2000; Simon et al., 2011). Although the consensus among healthcare professionals is that a higher BMI is commensurate with more favourable clinical outcomes, females may be more unlikely to accept such a message in which poor engagement with nutritional treatment may further exacerbate clinical status.

Data from Chapter 5 highlights significant declines in FEV_1 as an individual enters early adolescence. Indeed, nutritional failure or achieving a BMI of less than the 50^{th} percentile was

associated with poorer long-term outcomes with relation to pulmonary function, with adolescent females at particular risk. Where clinical guidelines would advocate promotion of a diet equivalent to that 150% of the general population, such generic prescription does not address the psychological barriers associated with nutritional adherence at an age where social desirability is high (Simon et al., 2011). Further to this, understanding patient perspectives and health related goals during adolescence is of paramount importance when considering individuation, autonomy, and an increased responsibility for self-care during this developmental phase (Helms et al., 2017). Conversely, narrative data from Chapter 6 demonstrates patients felt a lack of empathy and understanding upon expressing desires surrounding body composition which led to individuals seeking alternative information with regards weight management. Whilst much more research is warranted for specific interventions that may improve an individual's body satisfaction, it is advised that clinicians are more sensitive and empathetic around the topic of body image, realising patients may wish to address the topic of body image separately from markers of other physical health markers (Helms et al., 2017).

The implementation of treatment with CFTR modulators accelerates the need for collaborative and strong relationships with clinical teams, especially when considering the realms of body image. Early data from clinical trials of treatment with ELX/TEZ/IVA confirm increases in BMI of 0.9-1.3 kg/m^2 in adolescents and adults with CF, in which real world evidence shows increases in BMI of up to 1.5 kg/m^2 following 12-months of treatment (Heijerman et al., 2019; Middleton et al., 2019; Petersen et al., 2022). Findings in Chapter 7 support this data with magnitude of increase in BMI comparable to previous research. Furthermore, response to treatment with ELX/TEZ/IVA increased the incidence of overweight/obesity by nearly 10 percentage points. Whilst previous challenges when managing body image have been surrounding sufficient intake (primarily in females), Chapter 6 highlights the need for a quick transition to the management of body dissatisfaction with relation to significant weight gain in both adolescents and adults. Whilst research into the psychological effects of weight gain and overweight/obesity in people with CF is limited, evidence from the general population would suggest individuals experience increased stress and subsequent avoidance of clinical care in response to true or perceived weight stigma (Phelan et al., 2015). Indeed, narrative data from Chapter 6 highlights that a change in body

composition represents a significant event, in which an individual may choose to cease treatment with ELX/TEZ/IVA *despite* the known benefits in pulmonary function and quality of life. Although management strategies specifically for a CF population have yet to be determined with relation to weight gain, body image and modulator therapy, it would be reasonable to utilise evidenced-based methods of management for the general population, where appropriate (Bailey, Krick and Fontaine, 2022).

Despite recorded weight gain and an increased incidence of overweight/obesity, there are no formally updated nutritional guidelines since the implementation of treatment with ELX/TEZ/IVA (Bailey et al., 2022). More recently, the Academy of Nutrition and Dietetics (AND) suggested that there is no evidence to support that people with CF gain any benefit from following dietary advice different to that provided for the general population (McDonald et al., 2021). For individuals who do experience overnutrition or unintended weight gain, it is advised that a record of caloric intake should be utilised in an attempt to manage energy balance (Litvin et al., 2019). Where targeted weight loss is concerned, within the general population an energy deficit of around 500 calories per day has been shown to produce an initial weight loss of around 0.45 kg per week (Finkler, Heymsfield and St-Onge., 2012). Given CF individuals have been conditioned to eat a high-calorie, high-fat diet, patience is advocated from clinical care teams as such a transition will likely take considerable time (Bailey, Krick and Fontaine, 2022). Indeed, whilst much conjecture exists with regards the *optimal* diet, it is advised that individuals are educated initially on the importance of calories and protein as, when these are controlled, there is no weight loss benefit from eating a high carb or low carb diet (Hall and Guo, 2017). Ultimately, given the wide variation in nutritional status and preference, CF dietetic teams should work closely with patients to produce individualised nutritional plans to meet both personal goals and optimal health considering clinical outcomes alongside psychological and psychosocial factors (Bailey et al., 2021).

Further to this, weight management must now be viewed as a key variable to be considered when devising individual diet and exercise prescription. A recent review of 12 systematic reviews concluded exercise to be an effective tool within the general population to improve body weight and body composition in adults who are overweight or obese, with an average weight loss of 2-3kg (Bellicha et al., 2021). With relation to modality, both HIIT and aerobic

exercise are considered effective methods through which to reduce total body adiposity, when matched on energy expenditure. However, given the scarcity of data with reference to safety in those considered overweight/obese, it is recommended that extensive health assessments are completed prior to exercise prescription. Even more recently, findings from Berge et al., (2021) imply that a combination of HIIT/MICT results in significantly larger weight loss versus MICT alone (5 vs 2 kg). Despite the success of the protocol, combinations of HIIT/MICT are associated with high attrition rates versus MICT alone. Given adherence rates to REHIT noted within the general population (Metcalfe et al., 2020), quantifying the effectiveness of the protocol used in Chapter 4 with relation to a weight management strategy deserves further attention. Beyond safety and efficacy, prescription must be guided be individual preference to maximise long-term sustainability and adherence (Bellicha et al., 2021).

Independent of weight loss, physical activity with particular emphasise on strength training is advised in order to promote the aggregation of skeletal muscle tissue given the association between higher fat free mass and more favourable values of pulmonary function (Prévotat et al., 2019). Findings suggest that a resistance training programme in individuals with CF significantly increased fat free mass without a concomitant increase in bodyweight or BMI (Prévotat et al., 2019). Given that resistance training alone has limited effect on aerobic fitness, it is intuitive to recommend that any diet and exercise plan provides a concurrent of both aerobic and resistance training as a means of maximising aerobic fitness, body composition and aggregation of lean mass (Gruet et al., 2021). In line with the initial thesis direction prior to COVID-19, the implementation of resistance training and weight management exercise still fits within the scope of home-based, online sessions as a means of maximising adaptation and adherence.

8.2.1 An argument for rebound hyperphagia

Whilst early research shows significant changes in both BMI and incidence of overweight/obesity following the implementation of ELX/TEZ/IVA, few studies have extensively explored the mechanisms of such weight gain. Whilst likely multi-factorial, decreased energy expenditure, improved fat absorption, increased intestinal pH and reduced

gut inflammation have all been postulated as potential mechanisms behind improved BMI (Stallings et al., 2018). Importantly, narrative data from Chapter 6 raised the possibility that individuals experience a hyperphagic response following the implementation of modulator therapy. Whilst reports of increased caloric intake and hunger have been identified in previous studies (Martin et al., 2021), the magnitude of hunger described in Chapter 6 warrants further investigation.

The first investigations into the hyperphagic response were presented in the landmark *Minnesota starvation Experiment* in 1950. Individuals engaged in a 24-week period of semi-starvation resulting in body mass loss of around 25%. Individuals were then refed under controlled conditions for 12-weeks before another 8-weeks of unrestricted feeding, in which all participants exhibited exponential increases in energy intake and concomitant increases in both fat mass and fat free mass beyond baseline (Keys et al., 1950). Interestingly, one individual consumed a total of 11,500 kcal and still expressed a sensation of being hungry. Such a phenomenon was described as 'post-starvation obesity', subsequently termed 'rebound hyperphagia' (Dulloo, Jacquet and Girardier, 1997). More recently, research has focused on the hyperphagic response following repeated cycles of making weight and weight cycling in combat sports athletes. Indeed, findings show a considerable energy deficit over a period as short as 8-weeks can elicit an ad libitum energy intake of >36,000 kcal per week, resulting in a body mass gain of 8.3 kg (Langan-Evans et al., 2021). It is noted that such periods of hyperphagia are of particular concern to individuals predisposed to continually fluctuating energy intakes given the subsequent gain in body mass later in life (Saarni et al., 2006; Pietiläinen et al., 2011; Langan-Evans et al., 2021; Morehen et al., 2021).

Whilst CF cannot be described as a period of starvation, it is believed that a hyperphagic response and dynamic change in body composition occurs as a compensatory mechanism to restore any deficit in fat free mass (Kennedy, 1953). The magnitude of such hyperphagic response is dictated by the degree of loss in fat free mass prior to ad libitum feeding (Dulloo, Jacquet and Girardier, 1997). As lean tissue can only be gained with a concomitant increase in body fat, the recovery process is therefore categorised as an excess accumulation of body fat, known as collateral fattening (Dulloo, 2017). As CF is characterised by significantly reduced fat free mass when compared to the general population (Sheikh et al., 2014), any

postulated recovery in lean tissue following the implementation of modulator therapy would inevitably come with significant increases in body fat. Indeed, findings from a long-term open label study of IVA found significant weight gain following treatment, in which 64% of weight gained was attributable to fat mass, suggesting the occurrence of collateral fattening occurring in response to CFTR therapy (King et al., 2021). Further to this, findings suggest that individuals categorised as *normal* or *underweight* would be at higher risk of fat overshooting when compared to overweight/obese individuals (Dulloo *et al.*, 2015). Whilst Chapter 7 did not quantify the percentage of fat mass accumulation, only those considered *underweight* or *normal* weight evidenced significant increases in BMI following implementation of treatment with ELX/TEZ/IVA. Although further conclusions are precluded on the basis of the data presented herein with regards to rebound hyperphagia, it is suggested that future studies quantify the absolute energy intake following the implementation of treatment with ELX/TEZ/IVA in relation to pre-treatment, with consistent monitoring of an individual's body composition over time to further answer this question.

What is apparent is that the implementation of ELX/TEZ/IVA will accelerate the incidence of overweight/obesity within a CF population (Petersen et al., 2022). Whilst the mechanisms are yet to be fully elucidated, many parallels can be drawn with the hyperphagic response seen as a result of continual periods of low energy availability. Guidelines on managing hyperphagia are limited, but recent research demonstrates the effectiveness of a high fat, low carbohydrate diet on circulating ghrelin which may contribute to a lower food intake within individuals with Prader-Willi syndrome (Tan et al., 2020). Advice for those with CF currently recommends dietary practices shift away from the classical high-fat diet; it could further be postulated that modification of the CF legacy diet to manage the initial hyperphagic response may have some merit. Furthermore, insight for clinical practice may be provided from the management of hyperthyroidism, the treatment for which commonly results in considerable weight gain with the incidence of obesity within this population increasing (Torlinska et al., 2019). Indeed, whilst the mechanisms of increase are unknown, it is believed that patients regain and overshoot their initial weight, thus drawing parallels with both a hyperphagic response and a CF response to CFTR treatment. As advised in hyperphagic practice and Chapter 6, there needs to be an increased awareness from clinical practitioners

in which a consistent, empathetic, and respectful communication will aid in the management of weight gain with relation to treatment (Young et al., 2017).

8.3 Health trajectory and the influence of CFTR modulators

The development of targeted CFTR therapies represents a significant change in CF care, with focus transitioning from treatment of disease complications to restoration of the defective protein itself. Prior to this thesis, whilst comprehensive clinical trials evidenced the efficacy of CFTR therapy, there was relatively limited data on the utilisation of these therapies within an everyday clinical setting (Barry and Taylor-Cousar, 2021; Gramegna et al., 2020a). The results from Chapter 6 and 7 provide evidence, corroborating findings from clinical RCTs (Griese et al., 2021; Heijerman et al., 2019; Middleton et al., 2019), that modulator therapy elicits significant positive changes in clinically relevant outcomes, such as pulmonary function and BMI. However, as a consequence of stringent inclusion criteria, many sub-groups of individuals with CF are underrepresented within clinical trials and associated literature, with limited understanding as to how efficacious these therapies are within a cohort of patients with advanced lung disease. Secondary outcomes from Chapter 7 build on recent case series data from O'Shea et al., (2021) and Djavid et al., (2021) which reported meaningful changes in pulmonary function for individuals with severe lung disease (ppFEV$_1$ <40%), with improvements similar to those reported in milder disease states. Furthermore, analysis of 245 individuals with advanced respiratory disease reported a reduction in the need for lung transplantation, with only two of an initial 37 individuals receiving transplantation between the years 2019 and 2020 following the implementation of ELX/TEZ/IVA (Burgel et al., 2021). Whilst it has previously been hypothesised that individuals with poorer pulmonary function may see smaller increases in ppFEV$_1$ as a result of morphological changes in the airway, collectively, literature appears to oppose this, at least in the short-term. Whilst such data is promising with relation to practice and clinical outcomes for the individual, whether these case series analyses can be generalised to a whole population is debatable. Indeed, it is advised that we await the publication of registry reports to provide true efficacy of real-world efficacy of modulator therapy on long-term disease modification (Barry and Taylor-Cousar, 2021). Although we are aware of the longitudinal effects of factors such as body mass and pulmonary function on an individual's health trajectory, the key question still remains as to

whether CFTR modulators will alter the trajectory of the disease in the long-term (Barry and Taylor-Cousar, 2021).

The scope for future research with regards modulator therapy is large, with several investigator-lead studies across the US, UK and Ireland currently aiming to address the effectiveness of modulator therapy on measures beyond those explored in clinical trials (Barry and Taylor-Cousar, 2021). Although treatment with ELX/TEZ/IVA brings great promise for the immediate future of people with CF, such change is not in the absence of other challenges for the CF community. To extend the findings from Chapter 7, Chapter 6 provides a novel insight into the subjective effects of modulator therapy from the patient perspective. Prior to this thesis, mental health concerns in relation to CFTR modulators had not been comprehensively appraised. To the author's knowledge, this is the first study to explore the real-world, patient perspective of triple combination therapy. Much as there is large inter-individual variability in physiological response to modulator therapy (Chevalier and Hinzpeter, 2020), Chapter 6 identifies the variability in lived experience of modulator therapy. The findings from this study are of clinical importance, providing key qualitative data which can inform future research and psychological care in a post-modulator era. Indeed, it is emphasised that psychological support needs to be realigned to provide contemporary CF information with relation to an individual's new perception of their illness (Havermans and Duff, 2020). Whilst relevant to an individual's mental well-being and quality of life, the findings in Chapter 6 must also be taken within the context of an individual's ability and/or desire to adhere to treatment. Adherence to treatment is a well-documented challenge within CF which is influenced by a range of factors including disease state and treatment burden (Nicolais et al., 2019). Although it is noted in Chapter 6 and 7 that disease burden was reduced in relation to physical CF challenges, early findings suggest that adherence to modulator therapy is not 100% (Siracusa et al., 2015; Mitchell et al., 2021), suggesting other psychological factors may be at play. Whilst the exploration of these factors is beyond the scope of this thesis, Chapter 6, and anecdotal evidence (Perez et al., 2019), demonstrate increases in anxiety upon initial transition to treatment. Given the incidence of anxiety and depression is high in a CF population, it is possible that initiation of modulator therapy may temporarily exacerbate symptoms (Garcia et al., 2018; Havermans and Duff, 2020; Snell et al., 2014), possibly leading to an initial negative perception of therapy. Whether this increases risk with regards to the discontinuation of treatment is unknown, but as it is expected that CF care is likely to remain

a significant burden, further understanding is needed around the facilitators of, and barriers to, treatment to ensure that individuals fully realise the anticipated clinical benefit of CFTR treatment (Havermans and Duff, 2020).

8.4 Limitations

There are a number of limitations associated with the studies presented within this thesis, some of which are inherent to the study designs and others which have arisen during interpretation. The main limitation is the introduction of treatment with ELX/TEZ/IVA. Given the rapid change in disease state in response to treatment (Heijerman et al., 2019; Middleton et al., 2019), the relevance of the findings within this thesis can be questioned for the majority of CF individuals. Indeed, both inception and completion of Chapter 4 and 5 was *prior* to the implementation of treatment, making comparison versus and future studies difficult. Although the concepts themselves, with relation to the importance of aerobic capacity and nutritional status still have considerable merit in a post-modulator era (Gruet et al., 2021; McDonald et al., 2021), it is likely that context will shift away from using these variables in the clinical management of CF and more to enhancement of quality of life. However, as stated, given not all individuals with CF are treated with CFTR compounds, such findings in Chapter 4 and 5 still hold clinical relevance within this population.

A further limitation relates to the design of Chapter 4 and 7, with relation to sample size and case-study nature of both chapters. Relative to Chapter 4, this study had a limited sample size in comparison to previous investigations (Metcalfe et al., 2012; A. Sawyer et al., 2020). Whilst data may prove useful in the context of safety and efficacy of the REHIT protocol, the findings are limited in their wider application. Similarly, although not limited by sample size, uneven comparison groups from Chapter 7 does not necessarily allow for a balanced comparison between those receiving treatment and those not. Given analysis was conducted using data from a single academic medical centre in the UK, in which individuals have access to multi-disciplinary CF team, whether these results can be generalisable to different practice settings is unknown (Petersen *et al.*, 2022).

Given the timing of the COVID-19 pandemic it is difficult to ascertain the true effect of CFTR treatment on both patient experience and physiology. As noted within Chapter 6, many felt as though they were yet to truly *experience* the true effects of CFTR treatment in the real world. There was also an unbalanced group with relation to sex, of which may suggest we have seen the *female* perception of CFTR treatment given the predominance of females within this study. Despite the researcher having familiarity with the scenario being seen as a positive, this could also be viewed as a negative given personal bias may construe lines of questioning or interpretation of the data. Further to this, with relation to the time on treatment, given follow up time was less than 7 months on average across all CFTR studies within this thesis, we are unable to quantify the long-term effects of CFTR treatment on clinically relevant outcomes. Given long-term follow up studies have shown larger changes in BMI and pulmonary function (Griese et al., 2021; King et al., 2021; Petersen et al., 2022), it could be postulated that a larger follow-up period may have altered the observed magnitude in both psychological and physiological response to treatment.

8.5 Future Directions

Based upon the findings of this thesis, future research is required to further our understanding of both therapeutic and non-therapeutic interventions on clinically relevant outcomes in individuals with CF. The following recommendations may be considered for research studies:

1. The repetition of Chapter 4 considering the effects of REHIT within a larger sample size
   As discussed in Chapter 4, to validate the efficacy of REHIT in a CF population, data is needed within a larger, diverse population. Further to this, as spoken in Chapter 8, understanding the acute and chronic inflammatory response to REHIT is likely a key consideration with regards long-term safety. Further to this, understanding the implementation of REHIT as a method of weight management has clinical relevance following the implementation of treatment with ELX/TEZ/IVA.

2. The design and validation of modified REHIT protocols for use within a home-environment

Given evidence of considerable preference for HIIT, utilisation of the REHIT in a home environment is an exciting opportunity, however, barrier with regards equipment need to be overcome. As such, formulation and testing of modified REHIT protocols will be needed to understand efficacy and feasibility prior to implementation. As stated in Gruet et al., (2021)*; "testing a given exercise modality which is intended to be used repeatedly in a training programme is an important (yet largely overlooked in people with CF) determinant of training efficacy." As such, given concerns from* Hardcastle et al., (2014) *with regards the tolerability of HIIT/SIT protocols, both physiological and psychological evaluation is needed prior to implementation within telemedicine.*

3. Measuring the effectiveness of HIIT/REHIT protocols in a real-world environment
Based on the success of the previous study, a real-world assessment is needed with particular reference to adherence and change in physiological variables to understand true efficacy of these protocols. This should also be considered with reference to adults and children/adolescents.

4. Understanding energy expenditure and the influence of these protocols on weight management
Given concerns around weight management within Chapters 5, 6 and 7, utilisation of accessible, feasible diet and exercise programmes could be an additional tool to manage the expected rise in obesity within individuals with CF. However, whilst CF is normally considered a hypermetabolic condition with relation to resting metabolic rate, this also gives opportunity to assess the effects of CFTR treatment on both RMR and activity energy expenditure.

5. Understanding the facilitators and barriers to exercise in a post-modulator era
Building on findings from Hurley et al., (2021) *and* (Denford, van Beurden, et al., 2020)*, facilitating activity and exercise will be of key importance to enable individuals to realise the true effects of modulator therapy on long-term health. Whilst much research has been done prior to the implementation of modulator therapy, whether these barriers are still evident in current clinical practice is unknown.*

6. Exploring the incidence of post-treatment hyperphagia and the concept of collateral fattening within CF individuals

   Building on findings in King et al. (2021), there is clinical relevance to documenting the immediate and long-term body compositional changes following the implementation of treatment with ELX/TEZ/IVA. Indeed, as CFTR treatment has just been approved for clinical use in Australia, this represents an ideal scenario in which to document energy intake prior to the implementation of treatment, as well as the long-term follow up effects of increased energy intake.

7. Exploring the psychological consequences of overweight/obesity in individuals receiving treatment with ELX/TEZ/IVA

   Given research into overweight/obesity with relation to CFTR treatment is in its infancy, there is need to explore the effects of this increase in BMI on weight stigma, body image, incidence of eating disorders and adherence to treatment, where cessation of treatment is related to change in body composition.

8. The effect of a chronic energy deficit on body composition, body mass, retention of lean mass and body image for individuals experiencing post-modulator over nutrition

   Whilst there is much data with relation to the effectiveness of a period of lower energy availability within the general population, such does not exist within the CF literature. Indeed, given the importance of fat free mass to clinical outcomes, it is imperative to identify the optimal threshold of protein intake needed to preserve lean tissue within this population. Furthermore, quantifying the effect of an energy deficit on an individual's cardiometabolic profile would provide solutions to an increased risk of cardiovascular issues as a result of obesity.

9. Revisiting the CF gender gap following the implementation of CFTR treatment

   Findings from Chapter 7 provide early evidence that there is no significant difference in clinically relevant outcomes following the implementation of modulator therapy when controlled for sex. Given female life expectancy within the general population exceeds that of males, understanding whether CFTR closes such a gap in life expectancy and clinical outcomes is of great interest.

10. A patient perspective of modulator therapy: Revisited

    Chapter 6 represents the immediate thoughts of individuals to modulator therapy. Many within the study professed that they were yet to experience the full effect of modulator therapy due to the COVID-19 pandemic restrictions. Whilst registry data will provide a comprehensive physiological picture to the real-world effects of CFTR treatment, truly understanding the effect of CFTR treatment on quality of life how it has shaped an individual's lives experience is of equal importance.

8.6 Conclusion

This thesis has provided a number of experimental chapters that explore the impact of pharmacological and non-pharmacological interventions in the clinical management of CF. Specifically, it has: a) provided novel insights into the lowest dose of exercise required to elicit changes in aerobic capacity in an individual with CF; b) provided context and considerations around future usage of REHIT in-line with original thesis aims; c) further evidenced the importance of nutritional status on trajectory of health, with novel findings in relation to the influence of BMI on female pulmonary function; d) highlighted the increased incidence of overweight/obesity following the implementation of CFTR treatment; and e) provided a patient perspective on treatment with ELX/TEZ/IVA.

The introduction of triple combination therapy in 2020 has rapidly changed the outlook and the needs of many individuals with CF in the UK. Whilst the impact of this therapy on an individual's quality and quantity of life is expected to be profound, this will not be without new challenges and considerations. As the landscape of the disease changes for the individual, it is likely that researchers and clinical care teams will be expected to adapt quickly to what is a familiar disease with a new face. Whilst many of the classical CF challenges are anticipated to remain, new issues require evidence generation in an attempt to manage these concerns appropriately. Whilst the COVID-19 pandemic drastically changed the course of this thesis, it has enabled the contribution of research in a new era for CF care. The research conducted with relation to modulator therapy represents the inception of a new age of research within a CF population, of which is expected to lead to the identification of many

more questions. As the burden of CF reduces for many, it must not be forgotten that there is still much work to do with relation to rare CFTR mutations in which modulator therapy is not currently a viable option.

Whilst at the moment we are unable to quantify the magnitude of impact CFTR modulator therapy will have on CF as a disease, for many the future has never looked brighter.

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APPENDICES

Appendix A: Ethical Approval for Chapter 4

Appendix B: Ethical Approval for Chapter 5

Appendix C: Ethical Approval for Chapter 6

Appendix D: Ethical Approval for Chapter 7

Appendix E: Participant Information Sheet (Patients 18+ Years) for Chapter 6

Appendix F: Rating of perceived Exertion

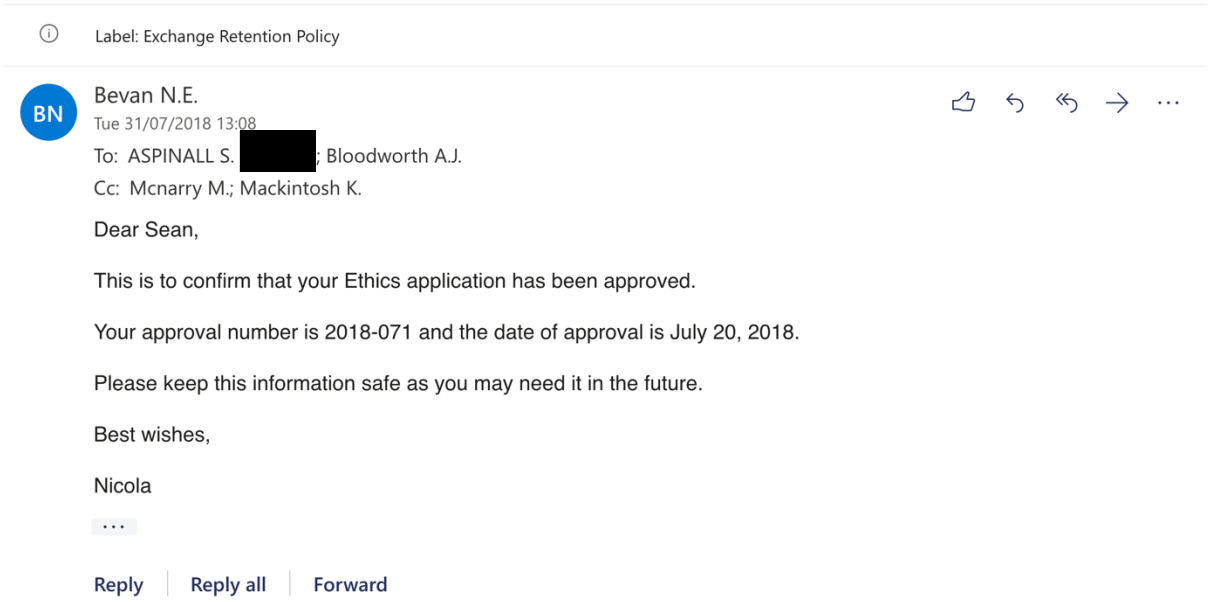
Appendix G: Rating of perceived Dyspnoea

Appendix H: CFQ-R Questionnaire

Appendix I: Semi-Structured Interview Schedule for Chapter 7

Appendix G: Consent form for Chapter 4

Appendix A



Label: Exchange Retention Policy

BN

Bevan N.E.
Tue 31/07/2018 13:08

To: ASPINALL S. [redacted]; Bloodworth A.J.
Cc: Mcnarry M.; Mackintosh K.

Dear Sean,

This is to confirm that your Ethics application has been approved.

Your approval number is 2018-071 and the date of approval is July 20, 2018.

Please keep this information safe as you may need it in the future.

Best wishes,

Nicola

...

Reply | Reply all | Forward

Appendix B

From: Registry <registry@cysticfibrosis.org.uk>
Sent: 30 November 2020 11:02
To: Mcnarry M. <[redacted]>
Cc: SARAH CLARKE <[redacted]>
Subject: RE: Data request 399 - Melitta McNarry

Dear Melitta
I am pleased to attach to this email the link to the data as requested in your attached data request.
https://cysticfibrosis.box.com/s/2s3d6hwcc8jk7x9ija8md40fszg1r6x7
NHS research ethics approval (07/Q0104/2 UK Cystic Fibrosis Registry, AB/AM04/1) has been granted for collection of data into the UK CF Registry. Each patient provided written informed consent for data collection and for use of anonymised data in research.
Under the terms of the NHS ethics approval the UK CF Trust steering committee approved the use of anonymised data in this study.
Acknowledge us in any publication using the following suggested citation:
"UK CF Registry. Cystic Fibrosis Trust, 2019"
We would also appreciate a copy of any publications.
Please do not hesitate to come back to me if I can help with anything.

Best wishes
Elaine

Elaine Gunn
UK CF Registry Clinical Data Manager
MOB: [redacted]
www.cysticfibrosis.org.uk
Cystic Fibrosis Trust, One Aldgate, London EC3N 1RE

N.B. Never send patient details by email to the UK CF Registry Team. If you need to reference specific data, please use the Registry CFTID.

Appendix C

LEAD APPLICANT NAME: Dr Melitta McNarry
DISCIPLINE/DEPARTMENT: SPEX
PROJECT TITLE: Evaluating the effects of Kaftrio on perspectives of health and wellbeing in individuals with Cystic Fibrosis
APPLICATION REFFERENCE NUMBER: Melitta_McNarry_22-10-2020

Swansea University
Prifysgol Abertawe

Date of review board: N/A
Committee members in attendance: Chairs approval

Date: 27th October 2020

Dear Melitta,

Thank you for your recent ethics application.

This decision letter is to inform you that the ethics application for the above titled project has been reviewed and approved. The ethical approval number for this application is MN_22-10-20 approved from 27/10/2020–01/10/2022.

This letter is for Swansea University, College of Engineering Research Ethics and Governance approval only. Local Health and Safety, in addition to appropriate risk assessment guidelines are required separate to this approval, unless otherwise stated herein, and must be adhered to.

Associated researchers must not deviate from the approved protocol or extend beyond the approval end date. Any desired deviations or approval date extensions are subject to the ethical approval amendment process. Upon completion of the approved project researchers responsible for this application must submit a final (short) statement to the ethical committee stating the completion of the project, unless a time extension is being requested through the amendment process.

Any significant un-anticipated adverse effects/events (i.e. not those predicted and stated in section 8 of the ethics application form) must be reported to the Ethics committee upon researcher realisation (email: coe-researchethics@swansea.ac.uk; with the subject title including the study approval number followed by "Adverse Effects/Events").

If you have any further questions relating to your application, please contact: coe-researchethics@swansea.ac.uk.

Please keep note of your approval number for future reference and correspondence relating to this application.

Best of luck with your research.

Warm regards,

Aynsley Fagan
(on behalf of the College of Engineering Research Ethics and Governance Chair)

College of Engineering Ethics and Governance Committee Administrator
College of Engineering | Y Coleg Peirianneg
Swansea University | Prifysgol Abertawe
Fabian Way | Ffordd Fabian Crymlyn Burrows
Swansea | Abertawe
Wales | Cymru
SA1 8EN

Email: coe-researchethics@swansea.ac.uk.

Appendix D

LEAD APPLICANT NAME: Sean Aspinall
DISCIPLINE/DEPARTMENT: SPEX
PROJECT TITLE: Gender differences in a UK CF population: A response to modulator therapy
APPLICATION REFFERENCE NUMBER: Sean_Aspinall_01-11-21

Date of review board: November
Committee members in attendance: Chairs

Date: Friday 26th November

Dear Sean,

Thank you for your recent ethics application.

This decision letter is to inform you that the ethics application for the above titled project has been reviewed and approved (subject to HRA approval). The ethical approval number for this application is SA_01-11-21 approved from 26/11/21 – end of approval 31/12/21.

This letter is for Swansea University, College of Engineering Research Ethics and Governance approval only. Local Health and Safety, in addition to appropriate risk assessment guidelines are required separate to this approval, unless otherwise stated herein, and must be adhered to.

Associated researchers must not deviate from the approved protocol or extend beyond the approval end date. Any desired deviations or approval date extensions are subject to the ethical approval amendment process. Upon completion of the approved project researchers responsible for this application must submit a final (short) statement to the ethical committee stating the completion of the project, unless a time extension is being requested through the amendment process.

Any significant un-anticipated adverse effects/events (i.e. not those predicted and stated in section 8 of the ethics application form) must be reported to the Ethics committee upon researcher realisation (email: coe-researchethics@swansea.ac.uk; with the subject title including the study approval number followed by "Adverse Effects/Events").

If you have any further questions relating to your application, please contact: coe-researchethics@swansea.ac.uk.

Please keep note of your approval number for future reference and correspondence relating to this application.

Best of luck with your research.

Warm regards,

Aynsley Fagan

(on behalf of the College of Engineering Research Ethics and Governance Chair)

College of Engineering Ethics and Governance Committee Administrator
College of Engineering | Y Coleg Peirianneg
Swansea University | Prifysgol Abertawe
Fabian Way | Ffordd Fabian Crymlyn Burrows
Swansea | Abertawe
Wales | Cymru
SA1 8EN

Email: coe-researchethics@swansea.ac.uk.

Appendix E

PARTICIPANT INFORMATION SHEET
(Version 1.0, Date: 16 /09/20)

Project Title: Evaluating the effects of Kaftrio on perspectives of health and wellbeing in individuals with Cystic Fibrosis

Contact Details:

Sean Aspinall (PhD Student)
Email: [redacted]
Dr Melitta McNarry (Supervisor)
Email: [redacted]
Telephone: [redacted]

We would like to invite you to take part in our research study. Before you decide if you would like to join in, it is important that you understand what the study is about, why the study is being done and what it will involve for you. So please read and think about this information sheet very carefully. Also, talk to your family, friends, doctor or nurse about it if you want to.

If something isn't clear or you have questions, you can give us a call or to email us and we can discuss it with you. If you don't want to take part, that is fine! Your care will not be changed by your decision of participating or not. **Thank you for reading this!**

What is the purpose of the study?

We know that getting Kaftrio is an exciting time! We have all heard of the positive effects the new drug might have on your lung function and your day-to-day life, but we want to understand what you think about Kaftrio, what hopes you have for how it might affect your life and how you do things. Once you have been taking Katrio for two weeks, we would love to hear about how you have found it and if it has done what you thought it would. We would then like to follow up with you again at three months and twelve months after you first took Kaftrio.

Why have I been chosen?

You have been invited to take part because you are aged 12+ years, have Cystic Fibrosis and are eligible to take the new Kaftrio therapy.

What will happen to me if I take part?

To start you will be asked to complete a short questionnaire online that you will find on social media or we can send you the link if you can't find it. This questionnaire will take about 10 minutes to complete and will ask you about how you feel and how CF is affecting you and your daily life. Once you have completed this, you will be asked if you would like to take part in a short one-to-one interview so we can get an idea of your feelings and emotions about your CF and about Kaftrio. You don't have to do this bit of the study if you don't want to, just filling in the questionnaire is fine! This interview will be via a video link, like Zoom. Your parents are welcome to be there if they would like to be. There are no right or wrong answers to the questionnaire or interview, we are just interested in you and what you think!

Then, once you have started on Kaftrio, we will ask that you repeat the questionnaire and, if you want to, the interview two weeks, three months and twelve months later so we can see how you feel and

what you think as time passes.

All of the questionnaires and interviews will be done online so you do not have to leave your house for any part of this research study!

What are the possible disadvantages of taking part?

You may find that talking about your CF is psychologically distressing, if you do find this we have measures in place and specialists on hand to help you through this. Remember, you are free to withdraw at any point.

What are the possible benefits of taking part?

The benefits are that you can help the whole CF community understand what to expect when they take Kaftrio. For those who have not started or are waiting to start it, they will have a better idea of the good things, the bad things and maybe some things that you did not expect. This research will also help your doctors understand how to manage things a little better too.

Will my taking part in the study be kept confidential?

All your information will be kept private. Only members of the research team will have access to it. You will be given a number so that no one knows who the results belong to. After the study is completed, all identifying information will be deleted.

Data Protection and Confidentiality

Your data will be processed in accordance with the Data Protection Act 2018 and the General Data Protection Regulation 2016 (GDPR). All information collected about you will be kept strictly confidential. Your data will only be viewed by the researcher/research team.

All electronic data will be stored on a password-protected computer file at Swansea University. Your consent information will be kept separately from your responses to minimise risk in the event of a data breach.

Please note that the data we will collect for our study will be made anonymous, Once you agree to take part in the study you will be assigned a unique person ID number. thus it will not be possible to identify and remove your data at a later date, should you decide to withdraw from the study. Therefore, if at the end of this research you decide to have your data withdrawn, please let us know before you leave.

Please note that if data is being collected online, once the data has been submitted online you will be unable to withdraw your information.

Data Protection Privacy Notice

The data controller for this project will be Swansea University. The University Data Protection Officer provides oversight of university activities involving the processing of personal data and can be contacted at the Vice Chancellors Office.

Your personal data will be processed for the purposes outlined in this information sheet.
Standard ethical procedures will involve you providing your consent to participate in this study by completing the consent form that has been provided to you.

The legal basis that we will rely on to process your personal data will be processing is necessary for the performance of a task carried out in the public interest. This public interest justification is approved by the College of Engineering Research Ethics Committee, Swansea University.

The legal basis that we will rely on to process special categories of data will be processing is necessary for archiving purposes in the public interest, scientific or historical research purposes or statistical purposes.

How long will your information be held?
We will hold any personal data and special categories of data for 5 years before it is destroyed.

What are your rights?
You have a right to access your personal information, to object to the processing of your personal information, to rectify, to erase, to restrict and to port your personal information. Please visit the University Data Protection webpages for further information in relation to your rights.

Any requests or objections should be made in writing to the University Data Protection Officer:-

University Compliance Officer (FOI/DP)
Vice-Chancellor's Office
Swansea University
Singleton Park
Swansea
SA2 8PP
Email: dataprotection@swansea.ac.uk

How to make a complaint
If you are unhappy with the way in which your child's personal data has been processed you may in the first instance contact the University Data Protection Officer using the contact details above.

If you remain dissatisfied then you have the right to apply directly to the Information Commissioner for a decision. The Information Commissioner can be contacted at: -

Information Commissioner's Office,
Wycliffe House,
Water Lane,
Wilmslow,
Cheshire,
SK9 5AF
www.ico.org.uk

8. **What if I have any questions?**

Re-iterate that further information can be obtained from the researcher contact stated above. Also state that "the project has been approved by the College of Engineering Research Ethics Committee at Swansea University. If you have any questions regarding this, any complaint, or concerns about the ethics and governance of this research please contact the Chair of the College of Engineering Research Ethics Committee, Swansea University: coe-researchethics@swansea.ac.uk. The institutional contact for reporting cases of research conduct is Registrar & Chief Operating Officer Mr Andrew Rhodes. Email: researchmisconduct@swansea.ac.uk. Further details are available at the Swansea University webpages for Research Integrity.
http://www.swansea.ac.uk/research/researchintegrity/."

Appendix F

20-Grade Scale	
6	
7	Very, very light
8	
9	Very light
10	
11	Fairly light
12	
13	Somewhat hard
14	
15	Hard
16	
17	Very hard
18	
19	Very, very hard
20	

Appendix G

0	No breathlessness* at all
0.5	Very, very slight (just noticeable)
1	Very slight
2	Slight breathlessness
3	Moderate
4	Somewhat severe
5	Severe breathlessness
6	
7	Very severe breathlessness
8	
9	Very, very severe (almost maximal)
10	Maximal

Appendix H

CFQ-UK **Adolescents and Adults (Patients 14 Years Old and Older)**

CYSTIC FIBROSIS QUESTIONNAIRE - REVISED

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.

Section I. Demographics

Please fill-in the information or tick the box indicating your answer.

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

CFQ-UK

Adolescents and Adults (Patients 14 Years Old and Older)

CYSTIC FIBROSIS QUESTIONNAIRE - REVISED

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 difficulty
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	Never
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	☐	☐	☐	☐

Please circle the number indicating your answer. Please choose only one answer for each question.

*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

CFQ-UK

Adolescents and Adults (Patients 14 Years Old and Older)

CYSTIC FIBROSIS QUESTIONNAIRE - REVISED

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?
1. Not at all
2. A little
3. Moderately
4. Very

18. How do you think your health is now?
1. Excellent
2. Good
3. Fair
4. 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	☐	☐	☐	☐

CFQ-UK

Adolescents and Adults (Patients 14 Years Old and Older)

CYSTIC FIBROSIS QUESTIONNAIRE - REVISED

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?	☐	☐	☐	☐

43. Has your mucus been mostly: ☐ Clear ☐ Clear to yellow ☐ Yellowish-green ☐ Green with traces of blood ☐ Don't know **Go to Question 44**

*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.

THANK YOU FOR YOUR COOPERATION!

Appendix I

Indicative Questions

Before:

- Current situation
  - Gain an overview of their current health, physical activity and wellbeing status

- What are your expectations / hopes?
  - Why hold these expectations / hopes?
  - What / who has driven them?
  - Have they changed as the change in standard care has approached? If so, why / how?

- Any concerns / fears?
  - Why hold?
  - What / who has driven them?
  - Have they changed as the change in standard care has approached? If so, why / how?

During / After:

- **How do you feel?**
  - Physically
    - In what way?
    - Impact on activity type and level?
  - Mentally
    - In what way?
    - Impact of day to day activities / life perceptions / appraisal / social activities?

- **Perceptions of the therapy?**
  - What (if any) are the most positive (valuable) impacts?
    - Why / how / in what way?
    - Anything exceeded expectations (what / how / in what way)?
  - Has there been any negative impact?
    - What / in what way / how / why?
    - Anything not matched expectations (what / in what way / how / why – and who established those initial expectations)?

- **Role of significant others?**
  - Relationship with the clinical team
    - What was the role of each of the main clinical team?
    - Did their role / your relationship change since starting the new therapy? (How / in what way / why?)
    - Did any members of the clinical team influence your perceptions of the new therapy (in what way)?
    - Did any members of the clinical team influence your perceptions of how you felt since the new therapy/ and how you feel now (physically and then, mentally). If so, in what way?

- Relationship with family / friends
  - What was the role of you family and (then) friends?
  - Did their role / your relationship change since the therapy? (How / in what way / why?)
  - Did any members of your family and (then) friends influence your perceptions of the therapy (in what way)?
  - Did any members of the clinical team influence your perceptions of how you felt since the new therapy / and how you feel now (physically and then, mentally). If so, in what way?

- Relationship with others
  - Did anyone (other than clinicians, family and friends – influence perception of the therapy (in what way), and how you feel now (physically and then, mentally). If so, in what way?

- **Moderators**
  - Any other factor before the new care- that affected your perception of:
    - The therapy?
    - How you feel (mentally and physically) now?
  - Any other factor since receiving the new therapy - that affected your perception of:
    - The therapy?
    - How you feel (mentally and physically) now?
  - Any other factor since the new therapy - that affected your perception of:
    - The therapy?
    - How you feel (mentally and physically) now?

- **Future aspirations**
  - Have your plans / aims / aspirations for the next few months / years changed as a result of this therapy?
    - In what way, why / why not?
    - How does this make you feel?
    - Impact of this on you, and significant others (family)
  - Have your perceptions of yourself changed as a result of this therapy?
    - If so, in what way / why / impact?
    - If not, how do you perceive yourself?
  - Have your perceptions of your future changed?
    - If so, in what way? Impact of this on yourself and others?
    - If not, why not? Impact of this on yourself and others?

Appendix G

Swansea University
Prifysgol Abertawe

Research Participant Consent Form

Title of Research Project: Reduced-exertion high-intensity interval training (REHIT) in an adult with Cystic Fibrosis: A case study

Name of Researcher: Sean Aspinall

Participant Identification Number for this project: N/A

1. Fitness to participate has been approved by the relevant medical professional ✓
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason and without there being any negative consequences. In addition, should I not wish to answer any particular question or questions, I am free to decline. ✓
3. I understand that my responses will be kept strictly confidential. I give permission for members of the research team to have access to my anonymised responses. I understand that my name will not be linked with the research materials, and I will not be identified or identifiable in the report or reports that result from the research. ✓
4. I agree for the data collected from me to be used in future research ✓
5. I agree to take part in the above research project. ✓

___Sean Aspinall_____	__13/07/2018____	____[redacted]____
Name of Participant (*or legal representative*)	Date	Signature
_____	__13/07/2018____	_____
Name of person taking consent (*if different from lead researcher*)	Date	Signature

To be signed and dated in presence of the participant

____Melitta McNarry_____	__13/07/2018____	___[redacted]_____
Lead Researcher	Date	Signature

To be signed and dated in presence of the participant

.