Exploring the lived experience of triple modulator therapy for those with Cystic Fibrosis

Bethany Jayne Cope

BSc (Hons)

Submitted to Swansea University in fulfilment of the requirements for the Degree of Master of Science (by Research)

Swansea University

2023

Swansea University
Prifysgol Abertawe

Abstract

Introduction: CF is an incurable, multi-system disease, severely impacting quality-of-life. Kaftrio is a recently approved triple-combination therapy reported to lead to significant improvements in lung function and health-related quality-of-life. The longevity of these benefits and patient's perceptions and experiences related to them remain to be elucidated, especially in those aged 6 to 11 years for whom the therapy was more recently licenced. The aim of this thesis was to investigate the effects of Kaftrio on the lived experience of those with CF.

Methods: The current thesis comprises of two studies: study one involved six children with CF (9.3±1.7 yrs, 3 girls) and eight carers; study two involved nine adults with CF (32.9±6.6 yrs, 7 females). Individual semi-structured interviews were conducted to explore their perceptions and experiences of Kaftrio alongside either the initial impacts of Kaftrio (children) or the impacts following one year (adults). An inductive thematic analysis was carried out.

Results: Four overarching themes were identified amongst the children and carers: i) perceptions of Kaftrio; ii) benefits, included improved quality-of-life, lung function, psychological impact and impact on future; iii) negatives, included adverse effects; iv) relationships with carers. Five dimensions were identified amongst the adults: i) perceptions of Kaftrio; ii) benefits, included increased quality-of-life, lung function and impact on the future; iii) negatives, included side effects, sustainability and appetite; iv) psychological impact, ranged from improved psychological well-being to a negative impact on emotions; v) relationships.

Discussion: Overall, Kaftrio was very beneficial to the lived experience of those with CF and their carers. These positives were perceived to greatly outweigh the negatives associated with Kaftrio and did not lead to discontinuation. The current findings highlight the need for further study, specifically regarding psychological well-being among children with CF and the impact of Kaftrio in the long-term for those aged <12 years.

Declaration 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.

Signed... [redacted]

Date.....28/04/2023.....

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.

Signed.. [redacted]

Date.....28/04/2023.....

I hereby give consent for my thesis, if accepted, to be available for photocopying and for inter-library loan, and for the title and summary to be made available to outside organisations.

Signed... [redacted]

Date.....28/04/2023.....

The University's ethical procedures have been followed and, where appropriate, that ethical approval has been granted.

Signed... [redacted]

Date.....28/04/2023.....

List of Contents

Acknowledgements

To begin I would like to express my deepest gratitude to my supervisors, Professor Melitta McNarry and Professor Kelly Mackintosh, for offering me this opportunity to develop my knowledge and research within my area of interest. Thank you both for providing continued support and guidance throughout.

I would also like to thank all of the participants, the children, their carers and the adults, who willingly sacrificed their time to share their experiences in aid of research. Thank you all for being so open and honest when it came to talking about your experiences.

Lastly, I want to thank my parents, family and close friends who have supported me throughout my life but especially during this journey, providing me with all of the love and encouragement I could need.

Bethany Jayne Cope

List of Tables

Abbreviations and Symbols

BMI	Body mass index
CBAVD	Congenital bilateral absence of vas deferens
CF	Cystic fibrosis
CFTR	Cystic fibrosis transmembrane conductance regulator
CL^-	Chloride
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
IV	Intravenous
IVs	Intravenous therapies
Kg	Kilograms
M	Metres
Na+	Sodium
NICE	National Institute for Health and Care Excellence
NHS	National Health Service
PA	Physical activity
SD	Standard deviation
$\dot{V}O_{2peak}$	Peak oxygen uptake

Chapter 1: Introduction

Cystic Fibrosis (CF) is a genetic disease whereby mutations in the cystic fibrosis transmembrane conductance (*CFTR*) gene affect the function of the *CFTR* protein, leading to a build-up of mucus within the body which can lead to systemic infections (Emmanuelle et al., 2021; Ferrera et al., 2021 ; National Health Service, 2018). This disease affects around 80,000 people and causes complications leading to premature mortality, with respiratory disease being the leading cause of death (Bessonova et al., 2018; Ferrera et al., 2021; Middleton et al., 2019). Although there is no cure for CF, treatments have significantly evolved over the past few decades, most recently with the evolution of *CFTR* modulator therapies that target the underlying causes of CF (Dagenais et al., 2021; NICE, 2017). There are currently four modulator therapies, developed by Vertex Pharmaceuticals, that include single and combination therapies. Kaftrio is the most recently developed and is a triple-combination therapy drug, combining elexacaftor, tezacaftor and ivacaftor (Dagenais et al., 2021; Hine et al., 2022). Ivacaftor acts as the “potentiator”, facilitating improvement of transport, whilst elexacaftor and tezacaftor act as the “correctors” (Dagenais et al., 2021; Davis et al., 2012). Overall, the treatment seeks to specifically target the effected *CFTR* protein. Consequently, Kaftrio has been widely touted as a drug that will revolutionise the lives of those with CF.

Kaftrio is currently available for those with CF aged six years and over with either two *F508del* mutations, or one *F508del* mutation in addition to one other ‘minimal function mutation’ (Dagenais et al., 2021). Kaftrio was approved following evidence of significant improvement in lung function in adults with CF (Heijerman et al., 2019; Middleton et al., 2019) in 2020, but has only recently been approved for use in children between the ages of 6-11 years (Cystic Fibrosis Trust, 2022). As such minimal research has been conducted into Kaftrio’s effects on children under 12 years old.

In adults, global studies have predominantly focused on the physiological effects of Kaftrio, such as an improvement in lung function (Heijerman et al., 2019; Middleton et al., 2019). Specifically, Middleton et al. (2019) found that

Kaftrio had a significant improvement in lung function and health-related quality-of-life. However, there remains a scarcity of global data surrounding real-world experiences, which are vital for long-term adherence, and subsequently Kaftrio's effects. Nonetheless, wider research has shown that Kaftrio has caused an increase in body mass index (BMI), and decreased antibiotic use and hospital stays for those with severe CF, as well as improving fitness in adolescents (Causer et al., 2022; Morrissy et al., 2021; Petersen et al., 2022). However, research into the effects on quality-of-life remains scarce. Nonetheless, Middleton et al. (2019) and Heijerman et al. (2019) found a positive impact on respiratory-related quality-of-life, although it is pertinent to note that this was derived from questionnaires, which largely fail to provide insight into the lived experience. Conversely, a case study found Kaftrio use to have a negative psychological impact, leading to worsening symptoms of anxiety and depression (Tindell, 2020). In addition, a systematic review highlighted that *CFTR* modulator therapies can lead to discontinuation and adverse effects highlighting that there may not be enough support for people with CF whilst taking Kaftrio (Dagenais et al., 2021). This important aspect of Kaftrio warrants further investigation, to be able to provide recommendations to support people with CF, as well as ways to monitor and manage the adverse effects (Dagenais et al., 2021). Given the recent approval of Kaftrio, there remains a dearth of research into the long-term effects and indeed perceptions.

Due to the recent approval, and subsequent prescription, of Kaftrio for children, the effects for younger children remain largely to be elucidated in those with CF aged 6-11 years. However, an open-label study on children aged 6-11 years concluded that Kaftrio is safe and effective in this age group, paving the way for the treatment to be approved for children under 12 years (Zemanick et al., 2021). Although minimal research into the effects of children has been conducted, recent studies in adolescents showed the benefits of Kaftrio, such as an improvement in aerobic fitness and pulmonary oxygen uptake, which could predict similar effects happening in younger children (Causer et al., 2022). It is anticipated that Kaftrio could lead to similar benefits shown in adults and adolescents and, with CF being a progressive disease,

using this treatment from an early age could help slow the progression of the disease and lead to a longer, better, quality-of-life for children. However, further research is warranted in order to discover the effects on children and to understand the impact of Kaftrio on younger age groups, especially in areas surrounding the effects on quality-of-life.

Therefore, the aim of the present thesis was to investigate the effects of Kaftrio on the lived experience of those with CF. Specifically, the thesis sought to ascertain the perceptions and experiences of Kaftrio and understand whether it impacts upon quality-of-life, for both children aged 6-11 years and adults. The specific research questions were:

- What are the effects of Kaftrio on the lived experience of adults with CF after one year?
- What are the initial effects of Kaftrio on the lived experience of children aged 6-11 years?
- Does Kaftrio impact upon the lives of carers of those with CF?

Chapter 2: Literature Review

2.1 Cystic Fibrosis

2.1.1 Characterising Cystic Fibrosis

Cystic Fibrosis (CF) is a complex autosomal-recessive disease which predominantly affects Caucasian individuals and leads to a build-up of mucus (Capurro et al., 2021; NHS, 2018; Veit et al., 2020). CF affects around 80,000 people worldwide and is characterised by mutations in the gene which encode the cystic fibrosis transmembrane conductance regulator (*CFTR*) protein (Capurro et al., 2021; Middleton et al., 2019; Southern et al., 2018). There are over 2000 *CFTR* mutations currently identified with mutations in both *CFTR* alleles being the cause of CF (Emmanuelle et al., 2021).

The *CFTR* protein primarily transports chloride and bicarbonate ions which maintains the balance of fluid and electrolytes within organs (Dagenais et al., 2021; Vallières & Elborn, 2014). A mutation within the *CFTR* protein causes defective *CFTR* channel functioning, whereby the *CFTR* protein is insufficient or dysfunctional, leading to an ion imbalance with chloride (Cl^-) secretion being disrupted and resulting in an increased absorption of sodium (Na+; Emmanuelle et al., 2021; Proesmans et al., 2008; Vallières & Elborn, 2014). This ion imbalance then causes a further uptake of water, decreasing airway surface liquid, dehydrating the epithelial surface fluids of several organs (Emmanuelle et al., 2021; Proesmans et al., 2008). Within the respiratory system, this mutation leads to an impaired airway defence as dehydration of the airway surfaces leads to an increase in fluid viscosity (Emmanuelle et al., 2021). This subsequently leads to failed mucociliary clearance, which is the respiratory systems defence against pathogens, causing a build-up of mucus which can then lead to infection (Emmanuelle et al., 2021; Proesmans et al., 2008; Vallières & Elborn, 2014). In addition to this, *CFTR* impacts the immune response, with CF causing an inefficient inflammatory response to infections, which leads to recurrent infections causing lung degradation (Castellani & Assael, 2017; Emmanuelle et al., 2021; Vallières & Elborn, 2014). The mutation of the *CFTR* protein also impacts upon other organs such as the

hypothalamus as well as those in the digestive and reproductive system in addition to other systems (Castellani & Assael, 2017; Emmanuelle et al., 2021).

CFTR mutations are classified into six different categories, with classes I, II and III reflecting little *CFTR* activity as a result of the mutation and causing more severe clinical outcomes, whilst classes IV, V and VI retain greater *CFTR* activity (Castellani & Assael, 2017; Emmanuelle et al., 2021). Class I mutations cause fewer messenger ribonucleic acid (mRNA) to be able to be translated and those that are successfully translated produce shortened and non-functional proteins causing an absence of functional protein in *CFTR* channels (Emmanuelle et al., 2021). The most common mutation is the *F508del* mutation which is a class II mutation and is found in 80-90% of the CF population (Emmanuelle et al., 2021; Southern et al., 2018). This mutation causes abnormal processing and trafficking with few proteins able to reach the cell surface (Emmanuelle et al., 2021; Vertex Pharmaceuticals, 2020). This is further exacerbated by those proteins that do reach the surface failing to open correctly due to defects in channel gating making them unstable (Emmanuelle et al., 2021; Southern et al., 2018). Consequently, the permeability of the epithelial cells is reduced preventing the movement of chloride ions and leading to excessive mucus and secretions (Capurro et al., 2021; Dagenais et al., 2021; Vertex Pharmaceuticals, 2020). Class III mutations largely effect gating, with a decrease in the ability of proteins to open due to ATP failing to activate (Emmanuelle et al., 2021). Although class IV, V and VI mutations have a greater *CFTR* activity, it is still affected, with class IV mutations impacting upon ion conductance and therefore the function of proteins, class V mutations impacting mRNA products and reducing the density of *CFTR* channels, and class VI mutations resulting in a low concentration of functional *CFTR* proteins at the cell surface (Emmanuelle et al., 2021).

Individuals with CF are usually diagnosed in infancy or early childhood due to the presence of clinical manifestations that can include but are not limited to stunted growth and/or meconium ileus which affects around one in seven new-borns. (Accurso et al., 2005; National Institute for Health and Care Excellence,

2017). CF can be diagnosed from a positive test result from sweat and/or gene tests which are carried out due to either having clinical manifestations or a positive blood spot immunoreactive trypsin test for those with no symptoms (NICE, 2017).

2.2 Effects and Treatments

CF affects all organs in the body, however, the impact on the respiratory system is a leading cause of morbidity and mortality (Emmanuelle et al., 2021). CF can manifest through pulmonary symptoms, such as cough, sputum, wheeze, chest tightness, breathing difficulties, and fever (Goss et al., 2009). In addition to this, CF leads to an emotional impact causing frustration, depression, irritability, worry, and difficulty sleeping, and also impacts upon the ability to do things, such as school or work (Goss et al., 2009). Individuals with CF are at a higher risk of developing certain complications relating to the condition which are associated with a reduced life expectancy and high premature mortality, with the median survival rate of 50 years in 2020 (Bessonova et al., 2018; Hurley et al., 2014; NICE, 2017; UK Cystic Fibrosis Registry, 2020). Table 1 shows the common complications associated with CF.

NICE (2017) developed recommendations for specialist CF multi-disciplinary teams to use in the diagnosis and management of CF in order to prevent, or limit, the effects of CF. Available evidence was used in the development of these recommendations with an emphasis on tailoring treatment to each individual in order to meet their needs. Early diagnosis and improved treatment have led to increased survival with the median life expectancy of a child born in 2000 in the UK being over 50 years in comparison to a survival rate of only 21 years in 1994 (Davis et al., 2012; Fogarty et al., 2000; Keogh et al., 2018). Although there is no known cure for CF initial treatments for CF target the symptoms of the disease, however recently, treatments have been developed which treat the underlying cause of CF (Dagenais et al., 2021; NICE, 2017).

Table 1 Common complications associated with CF (NICE, 2017; UK Cystic Fibrosis Registry, 2020)

Common complications	**Prevalence statistics**
Being underweight/malnutrition at diagnosis	31.1%
Meconium ileus (affects 1 in 7 new-born babies) at diagnosis	21.3%
Malabsorption at diagnosis	21.9%
Liver disease (the prevalence increases with age until early adulthood)	15.7%
Upper airway complications, including nasal polyps and sinusitis (prevalence increases with age)	31.2%
Distal intestinal obstruction syndrome	
Male infertility caused by obstructive azoospermia (almost all males with cystic fibrosis are infertile)	4.9%
Reduced female fertility	0.4% became fathers
	0.5% had babies

2.2.1 Respiratory System

The lungs are one of the primary organs affected by the *CFTR* mutation (Ramsey et al., 2011). Reported respiratory symptoms of CF include coughing, production of sputum production, wheezing and shortness of breath (Goss et al., 2009). The excessive mucous secretions associated with CF restrict airway clearance and provide an ideal medium for bacterial infections, resulting in colonisation (Abbott et al., 2008). Indeed, a retention of sputum

leads to recurring chest infections, inflammation and progressive airway damage (Abbott et al., 2008; Bradley et al., 2006; Elborn, 2016). These airway complications can lead to lung damage, with lung disease and respiratory failure amongst the leading causes of mortality and morbidity in those with CF (Abbott et al., 2008; Elborn, 2016; NHS, 2018; NICE, 2017).

Treatments for the respiratory system-related complications include antibiotic therapy which is recommended on a daily basis for all people with CF and is used to combat respiratory infections through oral or intravenous broad-spectrum agents (Cohen-Cymberknoh et al., 2011; NHS, 2018). Airway clearance is also recommended on a daily basis, although treatment is individualised, with the aim of limiting disease progression by increasing mucociliary clearance of the lungs through expectoration (Bradley et al., 2006; Cohen-Cymberknoh et al., 2011; NICE, 2017). However, treatments for CF are time consuming, taking up to four hours per day, burdensome, require adherence and many cause the individual pain (Blackwell & Quittner, 2015; Gifford et al., 2020). Nonetheless, there are no alternative treatments, with the only final treatment option being lung transplantation for end-stage respiratory insufficiency with people with CF being one of the largest groups of recipients (Andersen et al., 2006).

2.2.2 Digestive System

The digestive system is also affected by the disease, with organs such as the pancreas and gastrointestinal tract being affected (Ramsey et al., 2011). This can cause digestive issues such as exocrine pancreatic insufficiency which can lead to malnutrition as well as severe nutritional deficiencies, including fat-soluble vitamin deficiencies, hence being underweight is a common complication of CF (Accurso et al., 2005; NICE, 2017). The digestive complications are also associated with CF-related diabetes, the risk of developing which increases with age, with a 50% prevalence by the age of 30 years (Andersen et al., 2006). Other complications include chronic liver disease, which is the third most common cause of mortality in people with CF, affecting between 10-30% of the population (NICE, 2017). CF-related liver

disease causes inflammation due to blockages in the liver, resulting in insufficient draining of bile, which can lead to the development of gallstones and scarring (fibrosis; Cystic Fibrosis Trust, 2020).

In order to overcome nutritional issues, including vitamin deficiencies, NICE guidelines recommend a high-calorie intake focused on consuming high-energy and high-fat foods in order to maintain body mass, with an addition of supplements to the diet when needed to combat malnutrition (Abbott et al., 2008; NICE, 2017; Smyth & Rayner, 2017). Pancreatic enzyme replacement therapy is also used in order to help the absorption of nutrients (Abbott et al., 2008). Ensuring good nutrition has been shown to be key in maintaining health, especially in infants, as growth in height and body mass has been linked to an improved pulmonary outcome (Abbott et al., 2008; Accurso et al., 2005; Konstan et al., 2003). Body mass has also been shown to be associated with lung function with normal body mass resulting in less of a decline (Steinkamp & Wiedemann, 2002).

2.2.3 Fertility

CF can also cause fertility issues for both males and females (Hughan et al., 2019; Popli & Stewart, 2007). The subfertility and infertility rate of women with CF is 35% in comparison to only 5-15% in the general population (Hughan et al., 2019). Although this can be caused by a variety of reasons, nutritional deficiencies, as well as other complications from the disease, can cause menstrual irregularities, including anovulation, reducing fertility (Hughan et al., 2019). The mutation which impacts upon the *CFTR* can also affect fertility by preventing sperm fertilization due to greater cervical mucus (Hughan et al., 2019). Infertility in men with CF is also high with CF causing a range of issues from decreased sperm count to absent sperm count (Bieniek et al., 2021). One of the most common issues is congenital bilateral absence of vas deferens (CBAVD), which causes infertility and affects over 95% of the male CF population (Bieniek et al., 2021; Popli & Stewart, 2007). NICE (2017) recommended teams to refer people with CF to expert professionals in order to discuss fertility and contraception. However, it has been expressed that

there is a lack of standardization in the care and counselling for sexual and reproductive health and so it is underused (West et al., 2022).

2.2.4 Quality-of-life

Health-related quality-of-life can describe a persons' ability to function in life and encompasses their perceived well-being in physical, psychological, and social areas of health (Karimi & Brazier, 2016). Perhaps unsurprisingly, CF has been shown to negatively impact health-related quality-of-life (Bell et al., 2020). This can be associated, at least in part, to CF causing pain which is associated with health-related quality-of-life (Blackwell & Quittner, 2015). The condition affects individuals' overall functioning with complex treatments impacting upon their day-to-day life (Abbott et al., 2008; Blackwell & Quittner, 2015). Females with CF typically report a lower quality-of-life than males, with complications, such as lung disease and respiratory exacerbations, being more common amongst females (Abbott et al., 2008; Hillian et al., 2008; Sutton et al., 2014). These complications demonstrate a negative correlation with health-related quality-of-life (Abbott et al., 2008). Encouragingly, treatments are generally associated with an increase of quality-of-life (Horsley, 2015), although this is tempered by their burdensome nature for many. CF also impacts the people close to the individual as the families are given a great responsibility of care for those affected with CF (Bell et al., 2020). It is therefore suggested that both the individual with CF and their family receive emotional and psychological support, especially during initial diagnosis and transitioning from child to adult care (NICE, 2017).

2.2.5 Physical Activity

CF can impact upon individuals' ability to do physical activity (PA) due, in part, to a reduction in exercise capacity, fatigue, impaired oxygen delivery and to breathlessness on exertion, resulting in those with CF avoiding or limiting PA (Bradley et al., 2006; Curran et al., 2022; Wilkes et al., 2009). In addition to this, people with CF face barriers to engaging in PA, being limited by factors

such as lung function, muscle function, nutritional status, and inability to meet the metabolic demands of exercise (Wilkes et al., 2009). Wilkes et al. (2009) found children with CF were less active than their peers, whilst Schneiderman-Walker et al. (2005) found only girls to have reduce PA following a decline in lung function. An issue arises as the decline in PA leads to further decline in lung function, skeletal muscle weakness and exercise intolerance amongst those with CF, although physical inactivity contributes to this it is reported these effects are in excess of what would be expected (Curran et al., 2022; Troosters et al., 2009). Despite this, Schneiderman et al. (2014) found that an increase in habitual PA is still feasible regardless of progression of lung disease and that reduced PA is related to a decline in lung function.

Although CF can impact an individual's exercise capacity, PA has been shown to be a beneficial form of treatment recommended by NICE (2017) as it can lead to numerous health benefits for people with CF (Bradley et al., 2006). Specifically, previous research has shown that aerobic exercise can increase peak oxygen uptake ($\dot{V}O_{2peak}$) in children as long as it is maintained, whilst anaerobic exercise impacts upon aerobic performance and can improve health-related quality-of-life (Klijn et al., 2004; Santana-Sosa et al., 2014). PA improves lung function as well as reducing loss of bone mineral density and maintains chest wall mobility whilst also increasing self-esteem (Horsley, 2015; NICE, 2017). Engaging in vigorous-intensity activity also helps to improve physical function, cardiovascular performance and muscle strength, whilst having the potential to reduce lung function decline (Rand et al., 2013). This leads on to improve quality-of-life and reduce hospital admissions with those that are aerobically fit living longer lives (Curran et al., 2022). The limitations to using PA as a form of treatment is that there are no current universally accepted guidelines to be utilised by clinical teams, with issues surrounding PA due to the burden of disease and lack of adherence (Schneiderman et al., 2014; Wilkes et al., 2009). However, there are benefits to different forms of PA and exercise therefore it should be encouraged (Bradley et al., 2006; NICE, 2017).

2.2.6 Cystic Fibrosis Transmembrane Conductance Regulator Modulators

One of the greatest limitations to the conventional treatments is that they do not treat the underlying cause of CF. However, progress has recently been made with the development of more advanced treatments, namely *CFTR* modulator therapies. These therapies were developed with the aim of directly targeting the underlying cause of CF by potentiating the function of *CFTR* proteins, allowing for greater activity and trafficking and thereby altering disease progression (Dagenais et al., 2021; Davies et al., 2013; Sawicki et al., 2022; Schneider et al., 2016). *CFTR* modulators are small molecule therapies that have been developed as either single or combination therapies (Dagenais et al., 2021). Currently, there are four different therapies available which include Kalydeco (Ivacaftor), Orkambi (Lumacaftor/Ivacaftor), Symkevi (Tezacaftor/Ivacaftor) and Kaftrio (Elexacaftor/Tezacaftor/Ivacaftor; Dagenais et al., 2021).

2.3 Kalydeco (Ivacaftor)

Ivacaftor was the very first modulator to be developed by Vertex Pharmaceuticals being approved by the Food and Drug Administration in 2012 (Davis et al., 2012; Schneider et al., 2016). Ivacaftor acts as a *CFTR* “potentiator” to enable the *CFTR* protein channels to remain open for a prolonged period of time, facilitating improved chloride transport (Dagenais et al., 2021; Davis et al., 2012). Ivacaftor has been approved for those with CF who are four months old and over (Meoli et al., 2021). It specifically aids those with mutations which impact upon channel gating and conductance (Dagenais et al., 2021). This includes at least one copy of certain class III mutations, such as *G551-D* which accounts for 4-5% of the CF population, *R117H,* a non-*G551-D* gating mutation or a residual function mutation (Dagenais et al., 2021; Meoli et al., 2021; Schneider et al., 2016; Wainwright et al., 2015). In addition to the class III mutations, it has also been approved from class IV mutations, such as R117H, making Ivacaftor available to ~8% of the CF population (Meoli et al., 2021).

2.3.1 Kalydeco's Effect

A phase-three international study was conducted in 2011 to evaluate the potential of Ivacaftor as a form of treatment in people over 12 years of age with at least one *G551-D* mutation (Ramsey et al., 2011). The clinical trial highlighted the efficiency of Ivacaftor which resulted in a significant improvement in lung function by 10.6 percentage points in comparison to the placebo, in addition to increasing body mass and reducing respiratory-symptoms, pulmonary exacerbations and sweat chloride concentrations (Keogh et al., 2018). Similarly, studies in those aged 6-11 years of age highlighted similar impacts on pulmonary function, body mass, *CFTR* activity and sweat chloride concentrations (Davies et al., 2013; Meoli et al., 2021). McKone et al. (2014) investigated the long-term effect over 144 weeks in those aged six years and over, reporting that Ivacaftor maintained improvements in lung function, body mass and the rate of pulmonary exacerbations. Therefore, Ivacaftor was determined to be well tolerated and effective. However, it was recommended that liver function was monitored in those aged under six years (Meoli et al., 2021).

Whilst phase-three trials are able to indicate some of the effects of new treatments, they are unable to determine the effect of the drug in the real-world. Kirwan et al. (2019) investigated the long-term effects over 36 months, reporting similar improvements in clinical outcomes to those reported in the clinical trials. However, for those aged 6-11 years there was no initial increase in lung function, but this did improve over time. In addition, it was observed that Ivacaftor led to a reduction in healthcare resource utilisation, with less antibiotic treatments for pulmonary exacerbations, although this may be due to physicians tolerating more present symptoms prior to prescribing antibiotics due to Ivacaftor (Kirwan et al., 2019). A more recent study explored the effects over a five-year period in those aged over 18 with the Gly551Asp mutation, suggesting that whilst Ivacaftor led to an initial increase in lung function over the first six months, lung function subsequently declined to back to baseline by five years (Mitchell et al., 2021). In contrast, body mass index (BMI) continued to increase over four years and the reduction in hospitalisations and

intravenous antibiotic days were sustained over the entire five-year period (Mitchell et al., 2021). Bessonova et al. (2018) reported that Ivacaftor led to a significantly lower risk of death, transplantation, hospitalisation or pulmonary exacerbations in both children and adults. These studies highlight that although lung function may return to baseline, there are still benefits to the treatment.

Studies focused on the impact of Ivacaftor on quality-of-life reported similarly beneficial effects, with significant increases in quality-of-life, wellness, energy and exercise (Button et al., 2015). McCormick et al. (2019) highlighted that Ivacaftor had a positive effect on rhinologic, psychologic and sleep-related quality-of-life in those over six years of age. However, both studies relied on questionnaires which do not allow for a deeper insight into the individual's perceptions of the effect of Ivacaftor on their life (Martin et al., 2016). Nonetheless, Martin et al. (2016) used semi-structured interviews to investigate perceptions with participants and their caregivers who cited that, Ivacaftor led to an improvement in day-to-day life. Specifically, fewer negative impacts were perceived whilst also having a greater control over their CF (Martin et al., 2016). Moreover, people with CF expressed feeling less worried and having more energy, with a positive outlook for the future (Martin et al., 2021).

In contrast to the largely positive findings surrounding Ivacaftor, a systematic review highlighted that *CFTR* modulator therapies may be discontinued due to adverse effects (Dagenais et al., 2021). The most common adverse effects were respiratory-related which included pulmonary exacerbations and respiratory infections, although these were typically attributed to the disease and resolved over time (Dagenais et al., 2021). The phase-three study by Ramsey et al. (2011) highlighted that common adverse effects included headaches, upper respiratory tract infections, nasal congestion and dizziness although this did not lead to discontinuation. Contrastingly, Dagenais et al. (2021) suggested that adverse hepatic effects warranted an interruption in therapy or a decreased dose of Ivacaftor in some cases. In addition to hepatic effects, gastrointestinal-related adverse effects also led to interruption or

discontinuation of treatment in severe cases of abdominal pain or vomiting (Dagenais et al., 2021). However, headache and rash only led to interruption in one study (Dagenais et al., 2021). It is also important to highlight serious adverse events were less common for those on Ivacaftor than in the placebo group due to better overall health (Ramsey et al., 2011).

2.4 Orkambi (Lumacaftor/Ivacaftor)

Orkambi was approved in 2015 and is one of the first combination therapies, composed of two modulators, Ivacaftor and Lumacaftor (Meoli et al., 2021). Whilst Ivacaftor functions as the “potentiator”, Lumacaftor acts as a “corrector” with the purpose of the correctors being to improve conformation, correct misprocessing and trafficking of proteins to the cell surface which targets class II mutations such as the *F508del* mutation (Dagenais et al., 2021; Emmanuelle et al., 2021; Schneider et al., 2016; Wainwright et al., 2015). Orkambi can be prescribed for those with CF two years and over who have two copies of the *F508del* mutation (homozygous), representing around 45% of the CF population (Dagenais et al., 2021; Meoli et al., 2021; Wainwright et al., 2015).

2.4.1 Orkambi’s Effect

Orkambi has been shown to lead to a greater increase in chloride transport as a combination therapy than single modulator therapies alone (Wainwright et al., 2015). However, it is thought that the impact of the combination therapy could be limited due to the interactions of the two modulators which both have hydrophobic properties, limiting the free drug concentration (Schneider et al., 2016).

Two phase-three studies (Wainwright et al., 2015) were conducted to explore the efficacy of Orkambi in those aged 12 years and over, following a phase two study (Boyle et al., 2014), which suggested an improvement in clinical outcomes. Similar to Ivacaftor, these studies both reported that Orkambi led to an improvement in lung function along with a decrease in pulmonary exacerbations, and events leading to hospitalization or intravenous antibiotics

(Wainwright et al., 2015). Overall, these studies concluded that Orkambi benefitted individuals with CF. A continuation from Wainwright et al. (2015) demonstrated that Orkambi maintained the initial benefits and was linked with a slower decline in lung function (Konstan et al., 2017). Further, Milla et al. (2017) investigated the effects of Orkambi on those aged 6-11 years, indicating that the treatment was well tolerated and led to several improvements, such as lung clearance index, sweat chloride, nutritional status and quality-of-life. Additional research involving those aged 2-5 years also highlighted similar changes, with a decrease in sweat chloride concentration and an increase in growth (Meoli et al., 2021).

A real-world study was conducted in France to explore the relative impact of continuous, intermittent or discontinued treatment in those over 12 years of age, finding that participants with continuous treatment had an increase in lung function and BMI in addition to a decrease in intravenous antibiotic use (Burgel et al., 2020; Goetz & Savant, 2021). Continuous treatment in adolescents was associated with a greater increase in lung function than observed in adults, whilst rates of discontinuation of treatment was substantially higher in adults than adolescents, which was often due to adverse effects and, following treatment cessation, had a significant decrease in lung function and BMI (Burgel et al., 2020). Additionally, a study in the Netherlands involving those aged six years and over with a lung function of over 90% predicted forced expiratory volume in 1 s (FEV_1) investigated the effect of Orkambi after a year (Aalbers et al., 2020). FEV_1 is an important lung function marker, assessing the amount of air a person can exhale in the first second of a forced exhalation. It concluded that lung function was unchanged whilst BMI and quality-of-life increased and sweat chloride and exacerbation rate decreased (Aalbers et al., 2020). It was also noted that treatment was well tolerated by the participants and suggested the treatment be adopted for this group (Aalbers et al., 2020).

In contrast to these beneficial effects, Orkambi has been associated with significant psychological impacts due to an onset or worsening of depression and anxiety in several studies, leading to discontinuation and, in some cases, this was followed by a decline in lung function (Dagenais et al., 2021).

Although this couldn't be directly attributed to Orkambi *per se*, it is important to consider the impact upon mental well-being as there has been minimal research and so it is not thoroughly understood (Dagenais et al., 2021).

Orkambi has also been shown to be related to higher rates of respiratory-related adverse effects compared to other modulators (Dagenais et al., 2021). Specifically, symptom onset occurred within the first few days of treatment and included chest tightness, dyspnea, increased sputum and a decline in percent predicted expiratory volume (Dagenais et al., 2021). In most cases, these symptoms resolved or improved, with a lower dose aiding in overcoming intolerable respiratory adverse effects (Dagenais et al., 2021). However, it did lead to discontinuation in some cases, with the most common causes being chest tightness and dyspnea that resolved after discontinuation (Dagenais et al., 2021). Orkambi's effect on those with severe lung disease also led to 30% discontinuing treatment due to adverse respiratory effects (Hubert et al., 2017). Similar to Ivacaftor, there were hepatic and gastrointestinal adverse effects which only warranted discontinuation in some studies (Dagenais et al., 2021). In addition to this, elevations in blood pressure and creatine kinase were also experienced, with 4.2% discontinuation in the phase-three studies showing an elevation of creatine kinase being a factor (Dagenais et al., 2021; Wainwright et al., 2015). It has also been shown that those discontinuing treatment due to adverse events were at a higher risk of clinical deterioration (Burgel et al., 2020).

2.5 Symkevi (Tezacaftor/Ivacaftor)

Symkevi was developed as a combination therapy with Tezacaftor and Ivacaftor; being approved in 2018 (Meoli et al., 2021). Whilst Ivacaftor acts as the "potentiator", Tezacaftor is considered to be the "corrector" (Dagenais et al., 2021). Tezacaftor directly impacts the processing and trafficking of proteins to the cell surface (Dagenais et al., 2021). This treatment can be used for those with CF who are six years and older with the specific mutation requirements being either *F508del* homozygous or heterozygous with a residual function

mutation which accounts for 90% of the CF population (Dagenais et al., 2021; Middleton et al., 2019; Sawicki et al., 2022).

2.5.1 Symkevi's Effect

In a phase-three clinical trial, Taylor-Cousar et al. (2017) reported that Symkevi led to an increase in lung function and a decrease in pulmonary exacerbations, whilst Rowe et al. (2017) highlighted similar effects with an increase in lung function in addition to respiratory-related quality-of-life. A long-term study highlighted that the efficacy of Symkevi was maintained over 96 months (Flume et al., 2021). This led to the conclusion that Symkevi was safe to be used in the long-term (up to 120 weeks), being efficient and well-tolerated (Flume et al., 2021). In addition to this, three global studies have been conducted investigating the effect of Symkevi on those aged 6-11 years (Davies et al., 2021; Sawicki et al., 2022; Walker et al., 2019). Results from these studies suggest that Symkevi was safe and tolerable to be used in this age group and supports long-term use (Sawicki et al., 2022).

A routine-care study was conducted to evaluate Symkevi's effectiveness over a year in those with CF aged 17 years and older (Paterson et al., 2021). This study demonstrated that the use of Symkevi resulted in no change in lung function but was associated with increases in body mass and a reduction in hospital stays and antibiotics (Paterson et al., 2021). Although these results vary from initial trials, it still demonstrates an overall benefit. In addition to this study, a small study by Ahmed et al. (2021) found that Symkevi led to an increase in $\dot{V}O_{2peak}$ as well as lung function, body mass index (BMI) and quality-of-life.

It has been reported that Symkevi led to at least one treatment emergent adverse effect in 95% of the participants, with 2% of participants discontinuing treatment according to six prior studies (Flume et al., 2021). This is corroborated by Taylor-Cousar et al. (2017) who had 2.9% of their participants discontinue, with over 80% experiencing mild to moderate adverse effects. Those heterozygous for *F508del* who have one *F508del* mutation in addition to a residual function mutation, experienced mild to moderate adverse effects,

however there was no discontinuation (Rowe et al., 2017). Neuropsychiatric adverse effects of Symkevi are notable, with 11% of 44 adults experiencing them (Perez et al., 2019). These effects included an out-of-body experience and visual hallucination, depersonalization and “brain fog”, and sleep pattern disturbance causing majority experiencing those symptoms to discontinue treatment (Dagenais et al., 2021).

2.6 Kaftrio (Tezacaftor/Ivacaftor/Elexacaftor)

Kaftrio is a triple-therapy drug consisting of three modulators, Tezacaftor, Ivacaftor and Elexacaftor and was developed by Vertex Pharmaceuticals (Hine et al., 2022). Kaftrio combines Ivacaftor as the “potentiator” with two “correctors” - Tezacaftor and Elexacaftor (Dagenais et al., 2021). Elexacaftor increases mature *CFTR* protein and activity (Heijerman et al., 2019). This enables a greater efficiency of the *CFTR* proteins and a greater movement of chloride ions thus reducing the build-up of mucus (Vertex Pharmaceuticals, 2020). Kaftrio was made available to people over 12 years of age in 2020 and has more recently been approved for 6–11-year-olds (Cystic Fibrosis Trust, 2022). It is available to just under 90% of the CF population as the therapy primarily targets the *F508del* mutation which is the most common mutation and can treat those with at least one *F508del* mutation (heterozygous) alongside another ‘minimal function mutation’ or two copies of the *F508del* (homozygous; Dagenais et al., 2021).

2.6.1 Kaftrio’s Effect

Initial studies into Kaftrio focused on the short-term effects of the drug with the first studies being clinical trials carried out as part of two global phase-three studies funded by the producers of Kaftrio (Vertex Pharmaceuticals; Heijerman et al., 2019; Middleton et al., 2019). These studies showed that Kaftrio led to a significant improvement in lung function with a 10% increase in force expiratory volume in comparison to Symkevi, as well as an increased respiratory-related quality-of-life (Heijerman et al., 2019; Middleton et al.,

2019). A long-term phase-three trial by Griese et al. (2021) concluded that Kaftrio was well tolerated over 24 weeks and that improvements highlighted in initial studies, such as increase in lung function and sweat chloride concentration, continued, or even improved. Furthermore, an open-label study on children between the ages of 6-11 showed Kaftrio is safe and effective for this age group with consistent findings to older individuals (Zemanick et al., 2021). The study highlighted that Kaftrio led to an improvement in lung function, quality-of-life, body mass and sweat chloride levels (Zemanick et al., 2021). Although these studies offer an insight into the immediate physical effects of Kaftrio, they fail to provide an insight into the real-world effects of the treatment due to being clinical trials and in addition quality-of-life is measured using a questionnaire which does not provide a good understanding of the perspectives of the individual.

Due to Kaftrio only being approved in 2020, real-world studies are limited and Kaftrio's estimated benefits are drawn from studies of Ivacaftor (Barry & Taylor-Cousar, 2021; Cystic Fibrosis Trust, 2020). However, these studies are important as they focus on the impact of Kaftrio outside of clinical trials. One study has shown Kaftrio to increase BMI and blood pressure in adults, whilst also showing increased cholesterol on those with CF-related diabetes whilst those without CF-related diabetes had a decrease in blood glucose and haemoglobin (Petersen et al., 2022).This highlights the impact Kaftrio has on nutrition and recommends support for those on Kaftrio to prevent overnutrition in addition to monitoring blood pressure and lipids (Petersen et al., 2022). Whilst the clinical trials did not show real-world effects, they also excluded those with severe CF (Morrissy et al., 2021). Morrissy et al. (2021) investigated the compassionate use of Kaftrio, highlighting the efficacy and safety of Kaftrio for those individuals, with effects being a decrease in antibiotics and stays in hospital (Morrissy et al., 2021). In addition, Burgel et al. (2021) found that in those with CF and advanced pulmonary disease, Kaftrio led to rapid improvement and reduced the need for lung transplantation. Whilst, Causer et al. (2022) investigated Kaftrio's effect on exercise and physical activity in adolescents and found the treatment led to improved aerobic fitness as well as increased pulmonary oxygen uptake, although this was a small study which

emphasised more research is needed (Causer et al., 2022). Real-world studies have yet to be researched into those under 12 years of age due to the recent approval of the treatment at the start of 2022, however from the clinical trials and extensive research into the other modulator therapies it is hoped Kaftrio is as effective (Cystic Fibrosis Trust, 2022; Zemanick et al., 2021).

More recent research has investigated Kaftrio's effect on fertility. Indeed Kaftrio has been shown to be associated with an increase in pregnancies of females with CF (Lillis et al., 2021). Lillis et al. (2021) highlighted that it could have been impacted by coronavirus, however mentioned that the improved health status and the potential of Kaftrio to directly impact fertility highlighted that further research needs to be carried out (Lillis et al., 2021). Another focus has been respiratory microbiology which has delved into the effects of Kaftrio on airway infection and the development of respiratory bacterial milieu (Jenkins et al., 2021).This study observed the initial effects of Kaftrio and discovered Kaftrio results in either none or significantly less development of bacterial growth in chronically infected participants, also warranting a need for further study (Jenkins et al., 2021).

Studies to date have failed to focus on the perspectives of the participants and the psychological effects Kaftrio had, with limited research conducted in this area. However, with Kaftrio being released earlier into the United States of America (USA), further research has been carried out with one study focusing on the psychiatric adverse effects of Kaftrio which highlighted that Kaftrio worsened symptoms of anxiety and depression in a case study (Tindell, 2020). This highlighted the need for further research to come to a conclusion as a single case study could have been impacted upon by external factors and with minimal studies being carried out it highlights a gap in the research. Since the initial rollout of Kaftrio more studies have been carried out with one study by Martin et al. (2021) highlighting the positive effects of Kaftrio on symptoms, well-being and self-esteem. However, this study did highlight some participants were concerned with changes to their body. Although this study was large and collected a lot of data, the method of questionnaire means that many of the questions were closed and so would not allow for greater

expression from the participants. Aspinall et al. (2022) focused on the perceptions of adults with CF discovering the positive benefits of Kaftrio on quality-of-life whilst also expressing the challenges faced. Although this study gave an in-depth look into the individual experiences, there was uncertainty in the efficacy of long-term treatment which still needs research into. Almulhem et al. (2022) also discovered the impact on adolescents, labelling Kaftrio as “life changing” and the hope to lessen the treatment burden. This study was able to give several perspectives of the individuals with CF, carers and healthcare professionals. However, there has yet to be a study on those under twelve years of age due to Kaftrio only recently being approved.

Alongside psychological impacts, Kaftrio also leads to adverse effects which were as high of a rate as in the other modulators, with 93% experiencing at least one adverse effect in Middleton et al. (2019) global study. Common side effects include stomach aches and the ‘purge’ which is an increased expectoration of sputum and although these were a negative effect of Kaftrio, the majority of adverse effects were resolved over time (Dagenais et al., 2021; Hine et al., 2022; Middleton et al., 2019). Discontinuation in clinical trials, such as Middleton et al.’s (2019) study, were low at only 1% however more recent observational studies have highlighted a greater rate of discontinuation as well as additional adverse effects not previously found (Dagenais et al., 2021). Body mass is an important focus, as although an increase in body mass is deemed a positive for some, too much weight gain can lead to discontinuation with Emmanuelle et al. (2021) expecting Kaftrio to lead to an increased incidence of overnutrition. In addition to the physical side effects, Kaftrio was also found to have a negative psychological impact with it being shown to be related to an increase in anxiety and depression which was suggested by Tindell (2020) and further highlighted by Dagenais et al. (2021). In addition to this it has been shown to cause testicular pain and biliary colic (Dagenais et al., 2021). Whereas, Zemanick et al. (2021) investigated the adverse effects in children, with the majority of adverse effects mild or moderate in severity, consisting of headache, cough and pyrexia (Zemanick et al., 2021).

Chapter 3: Study 1 - Assessing the initial perceptions and lifestyle effects of Kaftrio on children aged 6-11 years old and their carers

3.1 Methods – Study 1

3.1.1 Participants

Overall, eight families, including six children aged between 6-11 years old and eight carers participated in semi-structured interviews exploring their experiences of taking, or their child/dependent taking, Kaftrio. Child participant descriptives are shown in Table 2. Participants had been prescribed Kaftrio between four to 16 weeks prior to the interview. Eligibility was based on being aged between 6-11 years old, being diagnosed with Cystic Fibrosis (CF), having two copies of the *F508de*l mutation, or one copy alongside a minimal function mutation and prescribed Kaftrio. For carers to be included, they were required to be a carer for a child with CF taking Kaftrio.

Table 2 Children descriptives

	Overall n=6	**Female n=3**	**Male n=3**
Variable	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**
Age (years)	9.3 ± 1.7	9.0 ± 2.2	9.6 ± 0.9
Height (m)	1.32 ± 0.15	1.27 ± 0.19	1.36 ± 0.03
Body mass (kg)	31.3 ± 4.4	31.53 ± 6.12	31.03 ± 0.82
Time on Kaftrio (weeks)	9.5 ± 4.1	10.0 ± 4.3	9.0 ± 3.7
Change in FEV_1/FVC (%)	14.3 ± 4.6 (n=4)	10.5 ± 0.5 (n=2)	18.8 ± 4.2 (n=2)

Participants were recruited through social media and word of mouth, with a questionnaire given to interested carers to determine eligibility for the study and gain basic anthropometric variables, including age of their child. Both carers and children were able to participate independently, irrespective of whether their child/carer participated. Informed oral and written assent and consent from the children and their carers, respectively, was required prior to participating. Ethics approval was granted by the College of Engineering Research Ethics and Governance Committee (MM_22-10-20b).

3.1.2 Protocol

The participants were invited to take part in semi-structured interviews via Zoom (Zoom Video Communications, Inc., San Jose, CA, USA). Interviews were conducted online in 2022 to aid in the prevention of transmission of COVID-19, which was essential for the target population given the high risk to people with CF (McClenaghan et al., 2020). Indeed, the severity of respiratory infections and risk of complications experienced by people with CF, as well as the negative impact on lung function, was highlighted by Colombo et al. (2020). More specifically, Zoom was utilised given the ease of use, having demonstrated to be a positive experience for participants, and being a valid alternative to face-to-face interviews (Gray et al., 2020).

Initially, anthropometric information, shown in Table 2, were sought via self-report. A semi-structured approach enabled questions to be determined prior to the interviews using previous knowledge of Kaftrio, whilst also allowing the interviewer to improvise follow-up questions dependent on the response of the participants (Kallio et al., 2016). Open-ended questions were utilised to explore individuals' thoughts and experiences, including any effects of Kaftrio, to fully understand their lived experience (Dworkin, 2012; Tong et al., 2007). This approach enabled the researcher to seek an understanding of the perceived immediate short-term effects of Kaftrio. The interviews were audio and video recorded via Zoom, lasting between 17- 63 minutes.

3.1.3 Data Analysis

All interviews were transcribed verbatim, allowing the researcher to familiarising themselves with the data. Data analysis was performed using NVivo (Version 12; *QSR International Pty Ltd.*, 2018) whilst maintaining an audit trail to convey clear decision breakdowns and prevent researcher bias, with the researcher also considering their own personal biases (Alhojailan, 2012; Noble & Smith, 2015; Zamawe, 2015). The transcriptions were analysed thematically using an inductive method, which was utilised in order to code the data and group into subthemes and themes (Vaismoradi et al., 2016). Once themes were developed, data triangulation was used to establish validity within the themes using multiple methods in order to have a true understanding of the data (Carter et al., 2014). Specifically peer-debriefing was utilised wherein initial findings were re-evaluated by an external researcher to prevent researcher bias, improving credibility, and reach a conclusion (Barber & Walczak, 2009; Connelly, 2016). Multiple data sources were also utilised through the use of two respondent groups, having both the child and their carers perspectives shared (Farmer et al., 2006). Results were also confirmed through member checking, which aimed to address bias whilst also allowing the participants to reflect, by evaluating the results and providing feedback to ensure that the themes accurately represented their thoughts and experiences (Noble & Smith, 2015; Candela, 2019; Buchbinder, 2010).

3.2 Results – Study 1

Thematic analysis of the interviews revealed 4 overarching dimensions, encompassing 10 key themes (Table 3). Whilst participants referred to the impacts of COVID-19 over recent years, most now felt their lives were “back to normal”. One child (C5; 9 years) briefly stopped taking Kaftrio due to adverse effects, which were reported to Vertex Pharmaceuticals, but had resumed taking it prior to taking part in this study.

Table 3 Dimensions and key themes regarding participant perceptions of Kaftrio

Dimensions	Key themes
Perceptions of Kaftrio	Pre-conceptions
	Meeting expectations
Benefits	Improved quality-of-life
	Improved lung function
	Psychological impact
	Impact on the future
Negatives	Adverse effects
Relationships	Carer
	Clinical team
	Friends and family

Perceptions of Kaftrio

3.2.1 Pre-conceptions of Kaftrio

Pre-conceptions of Kaftrio were generally positive, with Kaftrio described as a *"life-changing drug"*, and hope surrounding the potential benefits it may elicit. Specifically, the potential benefits mentioned by the children often included increased lung function due to creating *"a big difference"* in adults. The potential to also prevent a decline in overall health was also highlighted, with hope that Kaftrio may reduce symptoms and lessen treatments. P2 explained their child had said "*Oh, when I get the magic tablets [I] won't have to do*

physio". However, there were also concerns shared by the children and their carers, regarding the possible side effects; indeed, P3 perceived Kaftrio could "bring on an awful lot of side effects very, very quickly". Feelings of uncertainty were also evident as P1 revealed, *"we didn't really know what it did"*. In addition to this, the risk of discontinuation due to side effect severity was raised.

> *"I've seen people saying about their side effects, and some people took themselves off it"* (P4)

3.2.2 Meeting expectations

Both children and their carers reported that Kaftrio was *"even better"* than expected. This tended to be in relation to the number of improvements Kaftrio caused, with C3 (9 years) expressing, *"My mum was saying she would be happy, even if it [lung function] was just in the seventies, and then we got 86".* So, although an increase in lung function was hoped for, the huge jump was not expected.

> *"I was thinking, 'Yes, an increase of 10% would be amazing', not expecting it to be over"* (P4)

However, for some, Kaftrio was *"in accordance"* with their expectations or they were still hopeful it would meet their expectations, with P1 expecting a change in absorption, *"I probably expected that [bowel problems] to stop a little bit"* but speculating that *"maybe it will"* as it was still *"early days".*

Benefits

3.2.3 Improved quality-of-life

The importance of quality-of-life was expressed by the children, with Kaftrio making a *"big difference"* to day-to-day living. This included a perceived increase in energy, ability to do more, physical activity levels, and appetite, and a reduction in symptoms, by both the children and their carers. Specifically, the children felt they had an increase in ability as they felt they were *"able to do more"* than before, whilst the carers saw the opportunity Kaftrio gave children to *"achieve more",* with P6 explaining that, they could

now go to places as a family that *"there's no way we could have contemplated going to".*

Prior to commencing Kaftrio, the lack of energy was described as "lows" and impacted children's ability to be physically active as *"before he'd run off, and then he'd stop and he would just need to take a bit more time"*. Whereas, since starting Kaftrio, a surge in energy levels was reported to have been observed. C4 (10 years) described the energy increase as, *"it's kind of just boosting me up and whenever I kind of just run out, it [energy] always comes back".* Importantly, P2 described their child as being almost *"too energetic"* and that *"he's like a different child"*.

A reduction in symptoms was also experienced, with the main changes reported to be associated with breathing, tiredness and achiness. Participants felt they were able to breathe easier, were *"less wheezy"* and less likely to get out of breath, with P5 noticing, *"she was completely dry [her chest], I've never heard her chest so clear and breathe the way she's breathed".* Aches, a common symptom experienced pre-Kaftrio, specifically headaches and stomach aches, were also relieved following initiation of Kaftrio:

> *"I haven't had any tummy aches for the last ten weeks. And I normally would have had about six or five."* (C2; 11 years)

Changes in physical activity levels were also reported. Specifically, prior to Kaftrio, as described by P4, those with Cystic Fibrosis (CF), *"used to play out with his friends…come in and have to have a bit of a rest because he was tired"*, since starting Kaftrio the increased energy was associated with physical activity being less tiring and reduced breathlessness. This was reported to have resulted in an increased ability to be active for longer and at higher intensities. This was exemplified by C4:

> *"I'd have to do less because I'd always be super out of breath, and then going on to my next thing after, say, three minutes, I'd still be trying to catch my breath… And then I'd go on and like, you know, lose more energy. But now, if I've done my first one, I'm not really out of breath, and then until the end, I only get a bit out breath and then I'm able to carry on…"* (C4; 10 years)

P2 described the difference in their child:

> *"…he was always moaning so we'd have to stop, and I'd always have to take a drink, and maybe even sweets or something because he'd struggle. He likes going for a walk but it would spoil it because he'd have to, you know, halfway need to stop and just lacking in energy. But now we've gone up the same hill in the same walk and he's got no problem at all."* (P2)

Another important factor was the increase in appetite experienced by the participants with them being described as *"really hungry all of the time".* This increase in hunger resulted in increased food consumption as they *"just can't stop eating"*, with an increase in portion sizes and an increase in snacking noticed by carers. This led to an increase in body mass, which was a struggle to achieve prior to Kaftrio.

> *"…he would grow but no weight would go on or he'd put weight on but no growth. It never happened at the same time and then when we had our six-week check after the first six weeks of Kaftrio, we were just completely blown away that he'd grown a centimetre and put on over a kilogram in weight. He never does that ever, which is…- that's amazing…"* (P3)

Although an increase in body mass was perceived as a positive, P3 mentioned, "there's going to be a point where that's going to have to change" in which portion sizes will be reduced.

Additional physical changes were observed by both the participants and their carers. Some participants stated that they felt fitter, whilst the carers noted that they looked healthier; before they had been described as *"pale", "puffy"* and *"grey"*, whereas now they are described as having *"rosiest cheeks"*, *"brighter in himself"* and *"it's like he's got a spark back".*

3.2.4 Improved lung function

Lung function was highly important to children and their carers, with increases in lung function considered by all to be an indicator of the effectiveness of Kaftrio.

> *"When I found out it [lung function] had gone up, I was just thinking 'my first shot of Kaftrio'…it was really working and was doing really good and my lung function's going up lots."* (C4; 10 years)

A notable increase in lung function was experienced by participants, with many describing the increase as *"unbelievable"*. On average, Kaftrio was associated with a ~14 percentage point improvement in lung function over ~9 weeks, ranging from ~10% to ~23%.

> *"…when he first did it, I didn't believe it and then made him do it again. And just one more time, and let's do it again. He was like 'I'm literally feeling faint now from blowing'. But it was! It was the same every time, which is amazing!"* (P3)

3.2.5 Psychological impact

Kaftrio was reported to have significantly impacted psychological well-being, with increased confidence being experienced in comparison to pre-Kaftrio. Indeed, it was mentioned that, prior to Kaftrio, CF negatively impacted confidence as P4 expressed, *"it was more about the breathlessness because it was knocking his confidence"* which resulted in them stopping football. P2 highlighted the impact of Kaftrio: *"he didn't have as much confidence before but now seems to be like bursting with energy and speaking to everybody".*

Happiness was also highlighted as having improved following Kaftrio, with C3 (9 years) described as, *"he just seems a happier, happier, brighter child"*. C6 (6 years) also expressed that *"every time I do it [take Kaftrio], it makes me feel happy all the time"*. This could also indicate a change in attitude towards treatment, with P7 sharing, *"the fact that he feels more positive towards his medicine is a huge weight off of me, because I'm not the oppressor now, do you know?"*

3.2.6 Impact on the future

A key focal point expressed by the participants was the impact Kaftrio would have on their future. The perceptions were that Kaftrio would lead to a *"better future"* and longer life, with P6 expressing, *"the years that lie ahead is beyond what we could hope for".* Indeed, participants felt that Kaftrio could prevent a decline in health, meaning the disease would be less burdensome due to less infections and need for treatments. The carers cited hopes that, with time, the

children's "*condition will be under control"* and *"stable"*. Similarly, the children described how Kaftrio could make CF less burdensome when they grow up.

> *"I think I'll be able to have more physical activity when I grow up and I think it'll help clear away bugs quicker, and maybe not have to do as many treatments like with pseudomonas."* (C1; 11 years)

Treatment for most of the children *"all stayed the same".* However, it was noted this was for *"routine sake"*. In the future, there was hope for this to change, with a reduction in treatments eagerly anticipated, as a result of better health.

> *"…in the long run, this is going to stop all of the extra, the IVs (intravenous therapies), the nebulizers, and all the little things that you've got to take, you know, all those nasty tasting medicines for the pseudomonas… because hopefully with this stuff you won't be getting them."* (P7)

However, it should also be mentioned that although there is hope for the future, there is still uncertainty, as P5 explains:

> *"…it has very good results in a large percentage of this, you know CF population with common mutations in the early days, but we don't know whether three, four, five years down the line, those are sustainable, or whether the improvement in lung function is exponential, and then tails off completely, or has a limited lifespan. We simply don't know."* (P5)

Although there was uncertainty felt, markers such as the sweat test were viewed as an indicator into the effectiveness of Kaftrio and therefore it was hoped to reduce uncertainty and worry for the carers.

> *"…it'd be really interesting to see what her sweat test results are, cause that's the next thing… if her sodium chloride levels or anything approaching normal, then that just provides another layer of security, knowing that the Kaftrio is doing what it needs to do, and you can live a normal life without any of the little layers of worry."* (P6)

Furthermore, the development of Kaftrio was considered a step forward, with P6 expressing hope for even better treatments to be approved.

> *"We know that gene therapy is catching up as well. Those are the real holy grails."* (P6)

Negatives

3.2.7 Adverse effects

All participants experienced at least one adverse effect. However, they were predominantly short-term effects, with the most common being the ‘purge’, coughing and tiredness. The ‘purge’ is a known effect of Kaftrio, which causes the removal of mucus from the lungs. The ‘purge’ was linked with coughing, as P4 described it as *“he was coughing, bringing it [mucus] up and spitting it out”*. Whereas P5 explained how their child experienced a more severe ‘purge’ which made her *“very poorly”* and *“lifeless”*, and resulted in a pseudomonas infection. This caused a brief interruption in Kaftrio and upon reintroduction, which involved gradually increasing from a smaller dose, *“her body did adjust to it".* For this particular participant, lung function was low prior to Kaftrio and they *“didn’t want to give up”*.

Whilst the predominant negative of Kaftrio was perceived to be adverse effects, the timings of Kaftrio were also mentioned. Although considered *“a small price to pay”*, the timings of Kaftrio were brought up as a concern by two of the carers as the treatment *“has to be 12 hours apart”.*

> *“So, if we're up in the morning for school and he has it at eight, we’ve got to wait till eight and we're worried about not getting it right and so he’s getting tired because he’s got to take food and a drink at eight.”* (P2)

Although it was mentioned that this was something they could discuss with their clinic.

> *“I guess we could ask the clinic ‘if you go over by half an hour, an hour, does it matter?’ We don't really, really, know that because he's young, it's hard to keep him up.”* (P2)

Relationships

3.2.8 Carers

Initial feelings of the carers were mainly positive surrounding the excitement for the children to finally be able to receive Kaftrio after the long wait.

> *"…I heard about it a couple of years ago and then obviously we were just waiting until she hit six [years] so she could start taking it."* (P8)

Initial perceptions encompassed hope for Kaftrio to be *"the best thing ever",* with clinical teams describing it as *"a big turning point"*. Since starting Kaftrio, feelings of hope for the future were prominent amongst the carers, with Kaftrio being referred to as a *"safety net"*.

> *"Kaftrio provides the most hope that we could possibly have, and the overwhelming feeling is a huge gratefulness. Just huge gratefulness."* (P6)

The impact of Kaftrio was reported to extend beyond the immediate effects on the child with CF:

> *I guess it's not just about them [participant], it's about the whole family as well. So, it's hugely impacted all of us, which is brilliant."* (P2)

Many carers highlighted the positive impact their child receiving Kaftrio had had on their mental health, with P4 voicing, *"I feel in a better place. I really do."*. Carers expressed relief from the anxiety surrounding their child's CF, which had previously caused feelings of pressure and stress. Nonetheless, it was also noted that Kaftrio did not eliminate all of the anxiety, as it is not a cure.

> *"…it's [Kaftrio] taken away a worry. It's taken away the anxiety surrounding her health, you know? It definitely had a positive impact on my mental health 100%."* (P8)

3.2.9 Clinical team

The majority of participants and their carers felt they were supported by their clinical team. However, it was noted that this was not the case for all people.

> *"You know, they've been amazing. I mean they always have been amazing. I think we're very lucky with the team that we have. I'm aware that that's not the case for everybody. But we're very fortunate. And they've always been there to support and help."* (P3)

This was experienced by P5 following their child not tolerating Kaftrio and suffering with severe side effects. They resorted to reaching out on CF social media sites for support, reporting, *"I've got more help from people that take*

Kaftrio in the community than what I did [from] our local hospital." This was due to not being able to see their local team as they were *"so busy"* and resulted in them being sent to a normal hospital ward and not being seen by their team for two weeks. However, it was mentioned that even though they did not receive the much-needed support from their local team, they did have support from the children's hospital*, "when we spoke to the right doctor, we felt in safe hands and we felt like, you know, she understood, and, you know, we just felt cared for then."*

3.3 Family and friends

The reactions of close friends and family were overwhelmingly positive with excitement and happiness for the families and many noticing a difference in the child.

> *"Every time I come in; they're [grandparents] always saying 'He looks a lot better. He doesn't look that pale.'"* (P4)

The difference Kaftrio made was even picked up by a teacher without knowledge of the treatment.

> *"…. her swim teacher, we didn't tell her she'd started Kaftrio, but her swimming teacher was like 'What is the difference with her? She can swim so much further.'"* (P5)

3.4 Discussion – Study 1

The aim of this study was to assess the perceptions and initial impact of Kaftrio on the quality-of-life of children with Cystic Fibrosis (CF) and their carers. Overall, perceptions of Kaftrio were positive, with expectations being exceeded for lung function and several other benefits impacting quality-of-life. Furthermore, Kaftrio also impacted those close to the child with CF, specifically parents and families, who reported improvements in mental health. However, it is pertinent to note that there were negatives associated with Kaftrio, specifically in relation to the adverse effects caused. These findings are important as they explore the children and carer perspective of the impact of

Kaftrio, identifying areas of improvement leading to an increased quality-of-life.

3.4.1 Perceptions of Kaftrio

The majority of the participants had positive expectations prior to initiating Kaftrio treatment, primarily due to it being widely cited as a “miracle drug” for those with CF. Indeed, early studies reported significant impacts such as a 10% increase in lung function (Zemanick et al., 2021). However, these positive expectations were despite there being limited research or reports available in those <12 years at the time of this study. Although, many of the participants in the current study still had positive perceptions of gene therapies with hope for them leading to a cure for CF which is also shared by Donnelley et al. (2023). Social media may have also contributed to these expectations, with a previous study highlighting adolescents were comparing themselves to those who have shared personal experiences online, however this has resulted in disappointment (Almulhem et al., 2022). So, although pre-conceptions from the current participants were positive this posed the risk of the participants being disappointed if Kaftrio did not meet expectations.

The prior concerns held surrounding Kaftrio related to adverse effects and uncertainty. Uncertainty was evident amongst carers in the present study and was in relation to the limited knowledge of Kaftrio held at the time with Almulhem et al. (2022) finding carers were uncertain of sustained long-term benefits. Concern for adverse effects stemmed from the global study released at the time which highlighted the varying adverse effects caused by Kaftrio in children (Zemanick et al., 2021). Although the majority of adverse effects found in children were only considered mild or moderate in severity the small sample size entailed the possibility of uncommon and rarer adverse effects with a small number discontinuing treatment (Zemanick et al., 2021). Therefore, there were risks of adverse effects known to the carers in the present study, however previous literature showed discontinuation was less prevalent. Upon commencing the treatment, this was confirmed by the participants in the present study as all of the children experienced at least one adverse effect.

Upon initiation of Kaftrio, pre-conceptions were exceeded in relation to the expected increase in lung function, as the large impact was unexpected for many. Whilst some of the participants only found Kaftrio to meet expectations and another suggested that with time they may see further improvement. However, it is important to note that some with CF experience a greater benefit than others (Almulhem et al., 2022), therefore everyone has different experiences with CF and Kaftrio which may impact upon their perceptions. Perceptions of treatment are important to be taken into consideration when assessing the impact of treatment as it is vital in treatment adherence, with treatments perceived as important and having a large influence on quality-of-life being shown to improve therapeutic adherence (Arias Llorente et al., 2008). It is also important to consider the role of the parent in their child's adherence to treatment, with parents equating to a high level of adherence in childhood for those with CF, therefore making parents perceptions of Kaftrio equally important (Arias Llorente et al., 2008). For that reason, it can be concluded that the positive pre-conceptions and perceptions of Kaftrio held by the current participants will have impacted upon adherence to treatment, which will have ensured the best possible effect of Kaftrio.

3.4.2 Benefits

The perceived impact on quality-of-life observed in the present study supports findings from other recent questionnaire-based studies that found an increased health-related quality-of-life following Kaftrio in young children (Zemanick et al., 2021).These findings in young children are also in accord with those reported in adults. A reduction in symptoms was reported to have been experienced, with less breathlessness and coughing, as similarly reported by Aspinall et al. (2022) and Almulhem et al. (2022) in adults and adolescents, respectively. Prior to Kaftrio, these symptoms reduced the ability of those with CF to be physically active, thus the amelioration of these symptoms was also cited to be associated with improvements in physical activity in the current cohort. However, physical activity was not objectively assessed in the present study to confirm these perceptions, an area which

warrants further work in the future given the potential recall bias associated with self-reported physical activity levels (Prince et al., 2008). However, Kaftrio has been reported to be associated with improvements in aerobic fitness in adolescents (Causer et al., 2022), which may be hypothesised to have resulted from increased physical activity levels. In the present study, children reported experiencing increased endurance, requiring fewer breaks due to having more energy and feeling less tired, which was also observed by the carers. The implications of this were identified as improved physical activity impacted social engagement as the children were able to keep up with other children. In addition to this, an increase in PA could lead to further benefits such as health, fitness, lung function and health-related quality-of-life, which improve upon the impact already caused by Kaftrio (Bradley et al., 2006; Horsley, 2015; Klijn et al., 2004; Santana-Sosa et al., 2014). Therefore, these effects led to an increase in quality-of-life for the children, which is supported by current literature.

A change in physical appearance was noticed which was attributed to an increased appetite resulting in an increased body mass for the participants. An increase in body mass index (BMI) has previously been shown as a result of Kaftrio amongst adults following initiation of treatment (Petersen et al., 2022). The increase in body mass was predominantly perceived as a positive effect, with the carers mentioning prior issues with body mass, as CF can compromise nutritional status (Egan et al., 2022). Indeed, body mass is associated with lung function in those with CF, with a higher body mass associated with less decline in lung function according to earlier epidemiological studies (Egan et al., 2022; Steinkamp & Wiedemann, 2002) . Therefore, the increase in body mass in the present study may be related to the improvement in lung function reported by the participants. However, it is also important to note concerns raised by a carer regarding how this weight gain could impact in the future. This concern was also reported by Emmanuelle et al. (2021) who suggested that Kaftrio-related overnutrition could lead to treatment discontinuation in some with CF. This was subsequently shown to be a reality by Aspinall et al. (2022) who found that for some adults with CF, the increase in body mass impacted mental health and resulted in

discontinuation, despite the benefits they had observed and perceived. Whilst these findings are in adults, the growing body conscious at even younger ages raises worrying questions as to whether similar responses may be observed in children and adolescents. It has also become apparent that there is a growing issue of overweight and obesity within the CF population due to a change in eating habits as a result of cystic fibrosis conductance regulator (*CFTR*) -modulator therapies leading to an increase in appetite (Egan et al., 2022). This has led to overnutrition, however as previous nutritional advice focused on promoting a high-calorie, high-fat diet, adjusting diet will not be an easy transition (Almulhem et al., 2022; Egan et al., 2022; Petersen et al., 2022). Therefore, it is important for clinical teams to focus on providing support to help prevent overnutrition and ensure they are providing appropriate support to those with CF and their carers. Thus, albeit change in appearance, specifically body mass increase was perceived as a positive at the time, this perception could change in the future, becoming a negative effect.

Kaftrio has previously been shown to significantly improve lung function in adults and children (Heijerman et al., 2019; Middleton et al., 2019; Zemanick et al., 2021). Therefore, a similar increase was expected by the current study participants, although the reality even surpassed their hopes for many. An increase in physical activity of the participants could have also led to a further increase in lung function as physical activity has been shown to improve lung function (Horsley, 2015), In addition, as a decrease in lung function predicts a decrease in health-related quality-of-life in those with CF, the increase in lung function could therefore be related to the increase in quality-of-life shared by the participants in this study (Abbott et al., 2013). So, although lung function was primarily seen as a benefit in itself by the participants, it can also be suggested to have led to an impact upon other benefits identified by the participants, such as increased PA and quality-of-life.

The psychological impact of Kaftrio was regarded as highly positive, resulting in growing confidence and happiness amongst the children. In adolescents, Kaftrio has been shown to result in a positive psychological impact, specifically surrounding improvements on their outlook on life and feeling healthy

(Almulhem et al., 2022). Due to the adolescents being older their understanding of the impact of Kaftrio is assumed to be greater than that of the present children as understanding of CF varies greatly among children and young people with children relying on carers for information (Fairweather et al., 2021). Therefore, although the psychological impact amongst different age groups may vary, the psychological impact was perceived as positive and thus warrants further research to explore in further detail the psychological effects of Kaftrio on children.

An improvement in attitude towards treatment was also discussed by the participants, resulting in improved adherence due to treatment being easier and generally feeling more positive. Adherence to treatment is associated with pulmonary status and longevity, therefore Kaftrio's impact on lung function and the impact on the future may have also been a factor in promoting adherence (Bucks et al., 2009). However, the current participants positive attitude towards treatment differs from Almulhem et al. (2022) as, although they found that attitudes towards airway clearance therapy changed following Kaftrio, these changes were reported to have resulted in a reduction in adherence to treatment. Such changes are not clinically indicated, as there is still insufficient evidence regarding which treatments can be safely terminated. However, there was hope that in the future following further research, there could be alterations to treatments, which would be a massive benefit to the participants as it would relieve the treatment burden felt. This has already been shown in some adolescents that have chosen to reduce treatment (Almulhem et al., 2022). Although for now individuals are maintaining the same treatment, it was discussed with one carer that airway clearance took up less time which is hugely impactful due to the treatment burden normally felt (Gifford et al., 2020). A previous study into the impact of Kaftrio, on treatment in adolescents shared these findings, as for those that did not alter treatments, treatments were easier to complete as a result of an increase of energy (Almulhem et al., 2022). This indicates, the increase in energy experienced by the participants in the current study could have led to the impact upon treatment. Almulhem et al. (2022) also discovered that reducing treatment resulted in diminished burden in adolescents, however it was expressed by the clinical team that altering

treatment is a difficult decision to make as there is still insufficient evidence for the long-term. Therefore, it is important that those with CF maintain current treatments until proven to no longer be needed, in order to ensure for the best possible outcome (Hine et al., 2022). This calls attention to the need for more research to be carried out in order to focus on Kaftrio's effect on the need for other treatment, which may be able to provide a more definitive standpoint on whether or not clinical teams are able to reduce treatments.

The hope for the future expressed by the current participants was predominantly related to Kaftrio preventing a decline in health. Whilst the long-term impact of Kaftrio is yet to be elucidated, Kaftrio has significantly benefitted those with severe CF by decreasing antibiotic use and hospital stays (Morrissy et al., 2021), suggesting that benefits are obtained across the spectrum of disease severity. However, although encouraging, this does not translate directly to long-term use and progressive declines in lung function previously associated with CF. Some tentative suggestions regarding the potential impact of Kaftrio on mortality can be drawn from comparisons with Ivacaftor, which has been reported to be associated with a lower risk of death (Balfour-Lynn & King, 2022). Given the preliminary findings that Kaftrio is more effective than Ivacaftor in terms of increasing lung function and normalising sweat chloride levels (Balfour-Lynn & King, 2022) , it is perhaps reasonable to hope for even better influences of Kaftrio on the long-term progression of CF. Sweat tests would be a key indicator into the effectiveness of Kaftrio for the participants and are hoped to have changed. This hope is suggested to be a possibility by Zemanick et al. (2021) due to an increase in sweat chloride levels as a result of Kaftrio. Although, there was still some uncertainty from the participants surrounding Kaftrio, this is down to the limited research that has been carried out into the impact of Kaftrio. Even though the long-term effects of Kaftrio are still unknown, the initial benefits imply the possibility Kaftrio could prevent a decline in health and thus warrants further research into the effects.

Overall, there were several positive effects of Kaftrio on the children's day-to-day life which tended to correspond with current literature. Quality-of-life was considered to have improved, an effect discovered in previous studies, leading

to the conclusion that Kaftrio leads to a positive impact on quality-of-life. Changes in appearance, specifically in relation with an increase in body mass, was perceived as positive which contrasted previous studies in adults as it led to issues with body image. However, it was suggested that if an increase in body mass continues this could become a negative, with carers already speculating this to be the case due to the evidence from adults. This highlighted the need for the clinical team to begin providing support, as a preventative measure, before body mass becomes an issue. Lung function was shown to improve which was inferred to have led to a further impact upon quality-of-life and PA levels. A positive psychological impact was also perceived amongst the children, also noted by carers, which reflects a study into adolescents, although suggests the needs for further study into the reasoning behind it and to explore the impacts further. Attitude towards treatment was also more positive which was shown to be important in the adherence to Kaftrio. Impact on future was also viewed as positive, however little research into the long-term impacts implores the need for further study in order to provide evidence to those beliefs. Therefore, Kaftrio led to many benefits which align with current research; however, it also establishes gaps in research areas which warrant further study.

3.4.3 Negatives

Adverse effects were experienced by all participants, something which was to be expected given that 98.5% of children have been found to experience at least one adverse effect (Zemanick et al., 2021). The effects reported by the present participants were in accord with those reported elsewhere, with the most common being the ‘purge’ and cough which were highlighted by Zemanick et al. (2021). Fortunately, the majority of the adverse effects experience were mild in severity which is suggested to be the case in Zemanick et al. (2021) study. However, one child experienced severe side effects resulting in interruption of Kaftrio, which although interruption occurred in the global study, the severity of the effects resulted in them being reported to Vertex Pharmaceuticals. Although it was clear the benefits of Kaftrio

outweighed the negatives of the adverse effects as discontinuation did not occur in this group.

The timings associated with taking Kaftrio was also discussed by some carers being perceived as a negative. Specifically, the medication must be taken twice a day, twelve hours apart and with food. Whilst this schedule does not pose issues for adults taking Kaftrio, for children it was explained by the carers that although they wanted to be strict with timings to ensure the best possible effect of Kaftrio it was interrupting normal routine. This was due to having to keep their child up later in the evenings and to delay eating, which impacted on their day. Treatment burden is traditionally very high for those with CF and barriers such as time management and forgetfulness can affect treatment (Almulhem et al., 2022; Modi & Quittner, 2006). Therefore, although it was not perceived as a major problem, this is a topic that requires more research into understanding the impact on routine and whether it could be feasible to alter timings in order to promote adherence.

Despite the discussed perceived negative impacts of Kaftrio, it was concluded from the participants that the severity of the negative effects did not equate permanent discontinuation of Kaftrio. From previous literature, discontinuation was low, highlighting that Kaftrio's benefits seem to outweigh any negatives occurred in the majority of cases (Zemanick et al., 2021). Although this was the case, it is still important for the negatives to be highlighted, as they should be a focal point in the development of new, adaptive treatments.

3.4.4 Relationships

Considering the impact of Kaftrio on the family and friends of children with CF is important as CF significantly impacts this wider network due to the responsibility of care for those with CF and the factors associated with CF (Bell et al., 2020). In addition, CF has shown to have a negative psychological impact on carers (Fitzgerald et al., 2018). The positive impact on mental health experienced by the carers was viewed as a huge positive. The impact was evident in the present study as carers experienced initial feelings of hope and

excitement regarding the potential of Kaftrio. Since initiating Kaftrio treatment, carers reported some relief from anxiety due to the knowledge that Kaftrio was helping their child and was shown to be effective, findings in accord with those of Almulhem et al. (2022). This implies Kaftrio aids in reducing the burden placed on carers and highlights the impact CF has on carers, which indicates the need for further study into the impacts of CF and it's changing landscape on carers.

Participants tended to have a positive view of their clinical team and perceived there was enough support provided for adjusting to Kaftrio. This differs from (Aspinall et al., 2022) study, in which adults felt their needs weren't met. This could indicate a difference between the paediatric and adult clinical teams as it has previously been highlighted that there is desperate need for more resources for adult CF care (Madge et al., 2017). However, this difference could also be due to there now being a greater understanding of Kaftrio, as when Kaftrio first became available to adults there was very little known about the treatment, which may have made the transition more difficult for both adults and their clinical team. Although, it was shared by the carers that they believed not everybody was provided with the right support, therefore care may have differed from clinical teams which was shown by Aspinall et al. (2022). Therefore, recommendations for clinical teams should involve keeping up to date with current research, clear communication with individuals with CF and their family, and a shift in focus to managing nutrition in order to ensure the best possible care is provided.

3.5 Implications – Study 1

The implications of this study are that it is the first to explore the effect of Kaftrio on the lived experience of those aged 6-11 and their carers. Kaftrio has shown to be greatly beneficial in the short-term to the quality-of-life of children with CF, in addition to having a positive impact on carers. In addition, this study utilised a qualitative approach to enable a good understanding of the participants perspectives and experiences. This study also highlights recommended areas of improvement for future treatments and provides

encouragement for clinical teams to continue support and be aware of changing areas within CF due to Kaftrio.

The limitation to the study is the small sample size due to low uptake, which may be as a result of low prevalence of CF and the severity of the disease (Bucks et al., 2009), however this allowed for an in-depth analysis. This leads onto the need for further study, in which research is required into the effects on a larger, wider sample.

3.6 Conclusion – Study 1

In conclusion, this study highlighted the benefits to the quality-of-life of those aged 6-11 with Kaftrio as well as the benefit to carers' mental health. Although it did highlight some negatives, such as adverse effects, the benefits were found to largely outweigh the negatives. The majority of findings corresponded current literature, however also highlighted the need for further research in areas, such as impact upon other treatments and physical activity in order to come to a definitive conclusion. It would also be beneficial for follow-up interviews to investigate the long-term effects of Kaftrio on children and their carers, with long-term study needed to ascertain whether the benefits are long-lasting and provide some certainty for those with CF and their carers.

Chapter 4: Study 2 - Assessing the perceptions and lifestyle effects of Kaftrio on adults with CF following one year of treatment

4.1 Methods – Study 2

4.1.1 Participants

Nine adults diagnosed with Cystic Fibrosis (CF) from positive sweat and/or gene tests (NICE, 2017), provided oral consent participate in the study. All participants had been prescribed Kaftrio and been on it for a duration between 16 to 25 months. The set inclusion criteria for the participants were a diagnosis of CF, had either two copies of the *F508del* mutation or one copy with another copy of a minimal function mutation, prescribed Kaftrio for over one year and aged 18 years and over. Participant descriptives are shown in Table 4.

Table 4 Participant descriptives

	Overall (n=9)	**Female (n=7)**	**Male (n=2)**
Variable	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**
Age (years)	32.8 ± 6.6	32.9 ± 6.5	33.0 ± 7.0
Height (m)	1.65 ± 0.08	1.64 ± 0.08	1.70 ± 0.06
Body Mass (kg)	68.8 ± 11.4	65.5 ± 10.9	80.3 ± 1.8
Time on Kaftrio (months)	19.6 ± 3.0	19.0 ± 2.6	14.3 ± 3.5
Change in FEV_1/FVC (%)	21 ± 11.3 (n=6)	20.8 ± 13.9 (n=4)	21.5 ± 0.5 (n=2)

Participants were recruited online from Aspinall et al. (2022) study as follow-up interviews, with additional participants recruited through social media. Ethics approval was granted by the College of Engineering Research Ethics Committee (MM_22-10-20b).

4.1.2 Protocol

All participants were invited via email to take part in individual semi-structured interviews to be conducted via Zoom (Zoom Video Communications, Inc., San Jose, CA, USA). This method was chosen as it has been shown to be a preferred method due to convenience and ease in comparison to face-to-face interviews, allowing for a greater number of participants to be recruited, notwithstanding potential technical difficulties (Archibald et al., 2019). Moreover, online interviews were necessary as it prevented the transmission of COVID-19 to those with CF who are at a higher risk of experiencing severe symptoms, as well as preventing any inter-participant cross-respiratory infections (McClenaghan et al., 2020; Moola, 2018).

To gain an insight into the participants' perceptions of Kaftrio use and to discuss their experiences, open-ended questions were utilised, defined from previous knowledge of Kaftrio, to facilitate in-depth interviews (Kallio et al., 2016; Tong et al., 2007). A semi-structured approach was adopted due to the sensitive subject, allowing for questions to be adjusted and expanded upon for each participant (Barriball & While, 1994). Additionally, anthropometric data, shown in Table 4, were collected through self-report. This approach enabled the long-term impact of Kaftrio on their quality-of-life to be understood, in addition to identifying factors that may improve their health care. The interviews lasted between 24-42 minutes and were audio and video recorded via Zoom.

4.1.3 Data Analysis

The interviews were transcribed verbatim and analysed thematically using NVivo (Version 12; *QSR International Pty Ltd.*, 2018), ensuring rigour (Alhojailan, 2012; Sotiriadou et al., 2014; Zamawe, 2015). An audit trail was

kept through NVivo to have a clear breakdown of decisions, preventing researcher bias, which was also addressed through the researcher being aware of personal biases which could have impacted the study (Noble & Smith, 2015; Sotiriadou et al., 2014). An inductive method was used, whereby key quotations were highlighted and subsequently coded to develop into key themes and overall general dimensions (Braun & Clarke, 2014). To ensure trustworthiness and credibility, data triangulation was utilised to confirm the themes found using several data sources (Candela, 2019). One of these methods was peer-debriefing, which was used with individual findings of the main researcher being re-assessed by an external researcher in order to come to an overall conclusion and prevent intrinsic bias (Connelly, 2016). In addition, findings were also shared with participants through member checking to ensure that the themes were an accurate representation of their perceptions and experiences (Noble & Smith, 2015).This involved giving participants the opportunity to evaluate the findings and provide feedback on how accurate the results were in respect to their own experiences (Buchbinder, 2011). Member checking has been shown to be important for research but also for the participants as it can be therapeutic, providing them the opportunity to use it as a reflective experience (Candela, 2019).

4.2 Results – Study 2

Five dimensions were identified through thematic analysis, alongside the relevant key themes (Table 5). Whilst, the primary focus of the interviews was the participants' experiences of Kaftrio, the impact of COVID was inevitably mentioned. Nonetheless, the general perception was that things were *"going back to normal now".*

Table 5 Dimensions and key themes identified regarding participant perceptions of Kaftrio

Dimensions	Key themes
Perceptions of Kaftrio	Living up to expectations
	Falling short of high expectations
Benefits	Increased quality-of-life
	Lung function
	Impact on the future
Negatives	Side effects
	Sustainability
	Appetite
Psychological Impact	Improved psychological well-being
	Negative impact on emotions
Relationships	Clinical team
	Friends and family

Perceptions of Kaftrio

4.3.1 Living up to expectations

The majority of participants found Kaftrio to be *"as good as I expected"* as it led to health stability and a reduction in symptoms.

> *"…it has met the expectations in terms of symptoms. So, I'm not getting as fatigued as I was."* (P8)

However, some participants did not expect *"such a massive impact"* in regard to quality-of-life and stability.

> *"I didn't realize that it would have such a massive impact, as in not feeling tired anymore, not having to do physio anymore, not having to have regular IVs anymore. So, I was excited for the prospect of an extension of quality of life, I should say, but not what it has been."* (P7)

4.3.2 Falling short of high expectations

The wide spread colloquial reference to Kaftrio as being a 'miracle drug' had led to high expectations for some participants that were, unfortunately, not met for all.

> *"It's not going to be for everybody sadly. Perhaps I think that term that miracle drug was thrown around quite a lot and that was the wrong title to give it"* (P5)

Furthermore, expectations regarding lung function weren't fully met for some.

> *"…you have all of these perceptions of like 'Oh well it's going to go up to like 80, 90% lung function and things' and mine didn't. And I wasn't happy about it at all… it's up 10, 15%, so it's better than what it was, yeah."* (P9)

After being on Kaftrio for an extended period of time, some participants faced a *"reality check"*. P6 explained how following commencement of Kaftrio they felt *"a bit untouchable again"*, but that an exacerbation made them realise that the *"bugs are still potentially down there"*. Therefore, whilst perceptions may have changed, Kaftrio was still considered "*life changing*".

Benefits

4.3.3 Increased quality-of-life

The impact on quality-of-life was *"very noticeable"* for the participants. In particular, the main benefits for quality-of-life were cited as their CF being more manageable, having the ability to do more, and an increase in PA and energy levels.

Cystic Fibrosis (CF) was suggested to be more manageable as participants experienced a reduction in their symptoms and an improvement in health which translated to impacts on treatment. Reduced symptoms included less coughing and mucus, with P9 explaining *"the coughing is the main thing for me, what I've noticed, just because yeah, it's just not there."* Health had also improved, as participants *"generally feel well"* which also led to a reduction in hospital stays and treatments such as intravenous therapies (IVs).

> *"I was having IVs every four to six weeks. And I've only needed them twice (since starting Kaftrio)"* (P5)

Although some participants had maintained the same intensive treatment regime on the advice from their clinical team, Kaftrio had still helped to relieve the treatment burden, with P3 explaining, *"even though I still do my treatments, they take a lot less time."*

The ability to do more was highlighted by the participants as they felt Kaftrio gave them the opportunity to live *"a normal life"* that was less *"limited"*. For example, Kaftrio enabled some to return to work or CF to no longer impact their work. Additionally, travelling was viewed as *"so much easier"*, as pre-Kaftrio, P2 explained, *"It just got worse and worse and worse and more of a faff".* Whereas now, P6 shared, *"we've had a couple of holidays and that freedom I would say is one of the biggest things I've felt and I actually can't put into words how it feels, how nice that feels."* Furthermore, participants felt able to relocate, with P3 stating *"I bought my first house after starting Kaftrio"* which is something they did not feel able to do pre-Kaftrio due to health concerns. It is also pertinent to note that two of the participants have had children since starting Kaftrio. P8 became pregnant a month after starting Kaftrio, although it was *"difficult for me to see the effects of Kaftrio",* she explains that Kaftrio was "*why I fell pregnant".* For P9, he felt able to adopt his children once he started Kaftrio as he explained, *"One of the reasons I was able to adopt my children was because we knew that I was having Kaftrio, and the doctors said 'Look, he's going to have a lot better life.'"*

An increase in PA since starting Kaftrio was discussed, with P2 stating they could now *"walk around town"* and P1 explaining they aren't *"feeling out of*

breath going upstairs". Participants also cited an increased ability to exercise, with fitness improving and having *"a better stamina doing activity".* P7 has been able to gradually improve upon fitness since starting Kaftrio.

> *"But since being on Kaftrio, I started the couch to 5K and was able to run well, about 7K. Whereas before I started Kaftrio, I couldn't have run at all so."* (P7)

Increased energy levels were also discussed as Kaftrio *"doesn't take up as much energy"* resulting in participants *"not feeling tired anymore".*

> *"Just being able to do things without being tired. It sounds silly, but I do the washing downstairs and then I think "Oh, I've got to take it upstairs." I'll psyche myself up to go up the stairs to do it. Now I don't have an issue with it. I can run up the stairs and I'm absolutely fine."* (P7)

4.3.4 Lung function

Lung function increased amongst all of the participants with a ~ 21% average change in FEV1/FVC ratio reported by six participants. P2 declared, *"ultimately my lungs were so much better I wasn't going to stop it [Kaftrio]".* P7 described the change in lung function as a *"massive, fantastic thing*", as before Kaftrio, *"you kind of accept in your life that your lung function is going to decline, because that's the nature of the disease".* Some reported that, since starting Kaftrio, their lung function has been *"pretty stable"*, whilst in some cases after the initial increase there was a further increase, with P6 saying, *"it [lung function] went up into the 70s for quite a long time and then at some point it's jumped into the 80s".* However, three participants experienced a decline in lung function since the initial increase. For P4, *"it went up quite high, to like over a 100, and then came back down again".* Whereas, for the two other participants, their lung function decreased but then increased again. P9 explains *"I think it went down to 44, but it's gone back up again now."*

4.3.5 Impact on the future

Hope for the future was evident amongst the participants, with the feeling of *"not just staying alive but living*" expressed in the hope of doing a lot more *"because my future looks a lot brighter and it's not as restrictive*". For those

who had not already gone back to work, focusing on their future career was discussed. It was explained by P6 that, pre-Kaftrio, their job was *"keeping alive"* and they were never able to *"focus on a career"* so it is something they hoped to do. Although, as P2 mentioned, *"you've obviously not done as much as other people in your peer group*" which might make it more difficult. P8 raised the possibility that *"my job will be a bit easier which would be nice and have a bit more energy to actually do that [job]".* Another aspect was feeling able to travel more as P6 said, *"on holiday and stuff… you just live a much more normal life".* In addition to that, family were also discussed, with many feeling that marriage and children were more of an option now. P1 described it as *"I can imagine me now getting married and stuff like that where I really couldn't before"* as well as *"having a child".*

In addition to the ability to do more, there was hope for a longer life, with P7 hoping to *"to grow old and to die of old age, rather than grow old and die of cystic fibrosis".* There was also hope for even better treatments. P2 said, *"it [Kaftrio] sort of preludes the fact that there will be better treatments in the future",* with P5 hoping for *"less side effects",* and P6 hoping for *"something less, you know, severe on the liver".* Although, it was mentioned that the future is still unknown and that things *"might change*".

Negatives

4.3.6 Side effects

Side effects were perceived as the primary negative aspect of Kaftrio although, the majority of effects had been resolved since starting Kaftrio and were therefore relatively short-term. For some adverse effects, such as the 'purge' which was described by P7 as, *"I had all the purges, you know a lot of coughing stuff up"*, they resolved with time whilst other side effects such as acne, required medication. For the majority of the participants, the side effects were not considered significant enough to warrant stopping Kaftrio as they would *"rather have this tablet that makes me feel better than just having a couple of spots"*. For some, however they still had side effects such as impairments in

memory recall, which was described *as "a bit off"* by P6. Kaftrio similarly caused brain fog and migraines for P5 initially, but after reducing to a lower dose, the more severe effects resolved aside from some aches and pain.

4.3.7 Sustainability

Participants cited concern regarding the potential issue that Kaftrio may cease working and they could become ill again. This stemmed from the changes caused by Kaftrio being *"unbelievable"*. P7 was concerned, *"is my bubble going to pop?"* and felt like they had been *"living a dream"*. With P1 admitting *"so far it's worked, but I don't think it will carry on working"*. However, P7 suggested *"as the years go on you will just get used to the fact that this is how life is now".*

4.3.8 Appetite

Appetite *"dramatically increased"* for many of the participants, with P5 explaining, *"I couldn't stop eating".*

> *"I was eating meals that I normally would and I was still hungry, even though I wasn't doing anything. So, I wasn't burning off any energy and I was still hungry."* (P9)

This was viewed as an initial effect and the participants *"adjusted to that [appetite]".* However, as a result of the appetite increase, an increase in body mass was also experienced by many which was described by P6 as *"the worst part of it... the constant trying to like keep my weight down"*. The increase in body mass was viewed as a negative as *"seeing your body change was a bit of a shock"*. P7 explained*, "I've been used to being that skinny person, that person who could eat everything and wear all the size 8 and the size 10 and now it's like a squeeze".* P8 agreed, mentioning, "*I'm the heaviest I've ever been at the moment, ever"*. This had led to issues with body image amongst the female participants especially, with P6 saying, *"I don't recognise myself in the mirror, I don't like myself".* Although, the male participants shared they *"put on quite a lot of weight".*

This led to many of the participants adjusting their diet as it was felt by P7 *"you*

have to change the way you are with food". However, this has been a challenge, as pre-Kaftrio:

> *"We've been encouraged to have a high-calorie diet, basically eat what you want, because we don't put weight on easily and I never really have. I've always been able to eat what I want but maintain like a normal, quite okay weight."* (P8)

However, in order to lose that weight, their diet had to change. P2 explained *"it is very difficult to mentally get yourself out of a place where you've eaten enormous portions for 25 years".*

> *"The reality is that it's just weight management is something that I've never had to had to think about from a perspective of the controlled calories and fat which before was the opposite. If anything, weight management it was more calories and more fat. So, it's like a complete U-turn. So yeah, that's just ongoing."* (P3)

Therefore, adjusting diet had been an ongoing struggle, with participants still *"having to watch what I eat".*

Psychological Impact

4.3.9 Improved psychological well-being

Kaftrio helped to improve psychological well-being for some of the participants as *"outlook on life is better"*. Pre-Kaftrio, there was significant anxiety and worry, with P8 worried about *"leaving people behind and obviously dying a lot sooner".* In contrast, post-Kaftrio, they experienced less worry and anxiety.

> *"I could experience periods of feeling quite down, feeling quite worried, quite panicked. Whereas, because my health is more stable now, it's just there's no need for those those worries, because I'm not worried about my future."* (P3)

Starting Kaftrio was described as *"an instant sigh of relief"* and allowed the participants to feel more hopeful.

4.4 Negative impact on emotions

Although, many experienced positive psychological impacts, there were some negative experiences. Feelings of guilt and anxiety were experienced, with P1 voicing, *"I feel a bit guilty for feeling well, for like my friends and family and stuff, cause that was like- that was basically who I was and now it's not who I am anymore".* Mood was also impacted, with reports of feeling *"impatient"* and *"more short-fused".* However, P6 expressed, *"I'll take that any day over the other mental impacts I was dealing with"*.

Relationships

4.4.1 Clinical team

The majority of participants felt they had been supported by their clinical team since starting Kaftrio and that they were understanding.

> *"My team are quite supportive with stuff like that. I mean I know that I'm not the only one going through it. So, they've had like loads and loads of different people having the same issues and the same worries."* (P1)

It is also pertinent to note that, although there were nutritional problems as a result of Kaftrio, the nutritional teams have been *"really helpful"* and *"non-judgemental".*

It was highlighted that clinical teams were still *"learning"*. P6 stated, *"every time I speak to them, I feel like they're a bit more useful like cause they are learning as well"* but did report that *"it is unnerving"*. When asked if there was any more that could be done by the clinical team, there was various areas participants felt could require further support, ranging from providing more guidance, to providing psychological support.

> *"It would be heart breaking for someone if they'd started it and have loads of side effects and then that would be it for them. So, I think they would need to definitely offer as much support as possible in regards to mental health."* (P8)

4.4.2 Friends and family

Kaftrio was also reported to have indirectly influenced friends and family with them noticing a difference in the participants, which, in some cases, they hadn't even noticed in themselves. P9 explained, *"my wife always says to me, the one thing that she noticed massively is like, I don't cough".* P1 highlighted family and friend's reaction as *"everyone's just a bit over the moon for me and how improved I am"*. In addition to that, family were suggested to be less anxious and worried for the participants now that their health was more stable. P3 explains when initially starting Kaftrio, *"my mum was so anxious that I'd be going back to where I was before Kaftrio"*, whereas now *"they don't worry about me being unwell".*

Advice

"Don't miss your doses" was the key piece of advice shared by the participants when asked about what they would say to younger children starting Kaftrio. This was to ensure *"they can stay really well".* Another piece of advice was to *"go for it"* as the participants felt Kaftrio gave them *"a normal life"*.

4.4 Discussion – Study 2

The aim of this study was to assess the longer-term effects of Kaftrio in adults with Cystic Fibrosis (CF). Overall, many expectations of Kaftrio were met, with Kaftrio resulting in several benefits, specifically to quality-of-life and lung function, and bringing hope for the future. Nonetheless, there were still some negatives that should be considered, including adverse effects, influence on body mass and image, and concerns surrounding the sustainability of the benefits of Kaftrio. Those receiving Kaftrio noted the impact it has indirectly had on those close to them and spoke of the support they had received from their clinical team. There was a general perception that their care teams were still learning about Kaftrio, it's effects and the changing needs of the CF population and that this could be unnerving at times. These findings provided

an insight into the lived experiences of adults receiving Kaftrio, many of whom had previously had to make major modifications to their lifestyles and expectations. Whilst many raised the weight of expectation caused by the widespread reference to Kaftrio as a “miracle drug” as being associated with unrealistic hopes, the general perception was still that Kaftrio had had immeasurable effects for those with CF.

4.5.1 Expectations

Kaftrio met, and even exceeded, many of the expectations held by participants. These expectations were largely formed on the basis of clinical trials which reported Kaftrio elicited significant improvements in lung function and quality-of-life. The potential limited generalisability of these early clinical trials to real-world settings stem from inclusion criteria which limited the participants to those of stable health. However, some participants had to readjust their expectations to be more realistic due to the term ‘miracle drug’ leading to high expectations that were not met. This is exemplified by the changes in lung function typically observed; whilst clinical trials suggested that Kaftrio was associated with a 10 percentage-point improvement in forced expiratory volume in 1 second (FEV_1; Heijerman et al., 2019; Middleton et al., 2019), smaller improvements were reported by some. FEV_1 assesses the amount of air a person can exhale forcefully in one second, thereby measuring the effectiveness of the lungs and representing an important indicator into the impact of Kaftrio. Patient expectations regarding new treatments are difficult to manage with marketing and media hype potentially causing high and unrealistic expectations (Keitz et al., 2007). However, such patient perceptions and expectations are important to consider as they impact treatment adherence, with treatments considered to have a benefit to quality-of-life being more closely followed (Arias Llorente et al., 2008). This is reflected in treatments such as nebulized therapies and airway clearance being associated with a low adherence as they are perceived to have a negative impact upon quality-of-life (Sawicki et al., 2009), highlighting the positive

perceptions of Kaftrio being key to adherence and thus the realisation of treatment benefits.

4.5.2 Benefits

An increased quality-of-life was experienced by the participants, which corroborates with previous phase-three studies that highlighted an increased respiratory-related quality-of-life (Heijerman et al., 2019; Middleton et al., 2019). Specifically, the current participants cited that the increase was in relation to their CF being more manageable, their ability to do more, and an increase in physical activity (PA) and energy levels. Importantly, these benefits are likely to have further positive impacts due to the widespread multi-systemic benefits of PA for physical and mental health (Bradley et al., 2006). Specifically, the increase in PA could be implied to have led to further benefits to health and on quality-of-life due to the impact of PA on pulmonary function, airway clearance, and energy levels in addition to the benefits to the general population (Hurley et al., 2021). These findings are in accord with those of Aspinall et al. (2022) who focused on the short-term impacts of Kaftrio, suggesting that an increased quality-of-life could be a potential longer-term benefit of Kaftrio.

CF was considered more manageable due to reduced symptoms, improvements in health, and a reduced treatment burden. These effects are supported by Martin et al. (2021), who found Kaftrio to positively affect symptoms and well-being, and Aspinall et al. (2022) who reported a perceived reduction in symptoms. Kaftrio also led to the current participants experiencing a reduction in hospital stays and intravenous therapies (IVs), which was also shown as an initial effect by Aspinall et al. (2022). Similarly, Choyce et al. (2022) saw a reduction in the prescription of IV antibiotics since 2019 (with Kaftrio being approved in 2020 for adults in the UK) and less inpatient therapy. The reduction in symptoms led to treatment being less burdensome, with some participants even reducing treatment. Such findings are congruent with Brown et al. (2022) who noted a request for a reduction in inhaled therapy due to improved well-being. This effect on treatment requirements is a significant

benefit for those with CF given the (previously) extremely high treatment burden (Gifford et al., 2020). Indeed, treatment was generally considered as being costly and time-consuming, requiring more than three hours per day on average (Angelis et al., 2015; Sawicki et al., 2009). Therefore, a reduction in time spent on treatment was viewed as a huge patient benefit. Furthermore, on an economic level, reduced treatment requirements also have potential cost-saving implications, particularly in terms of medication and hospital admission and stays. However, it is pertinent to note that Kaftrio is an expensive drug which offsets those reduced costs (Balfour-Lynn & King, 2022). Spending less time on treatments and having better health also led to participants returning to work, lessening the economic burden of CF due to prior impacts such as job loss (Angelis et al., 2015). Indeed, working is an important factor of psycho-social functioning, providing social interaction, and helping people to integrate within society; unemployment is conversely suggested to damage health (Angelis et al., 2015). Therefore, CF being more manageable led to several improvements in day-to-day life, positively impacting upon participant's quality-of-life.

An ability to do more was favourably viewed as an ability to live *"a normal life"*. This has been previously reported by those on other cystic fibrosis transmembrane conductance regulator (*CFTR*) modulator therapies, who described being able to do more normal activities (Kauser et al., 2022). This increased ability provided more freedom for those with CF, with Aspinall et al. (2022) suggesting Kaftrio had given their lives back. Although not a focus of this study, it was highlighted that Kaftrio had led to two of the participants now having children, through pregnancy and adoption. Indeed, Lillis et al. (2021) showed Kaftrio to be associated with an increase in pregnancies in females with CF, with Ivacaftor leading to pregnancies in 7 out of 12 women previously reported to be infertile (Taylor-Cousar, 2020). Greater hope for the future was also reflected post-Kaftrio by women with CF, expressing a greater interest in having families; previously there were concerns surrounding ill-health and ability to care for offspring. The ability to do more, therefore creates more opportunities, though, further research is required to explore the realisation of new possibilities.

An increase in PA was reported by the participants, although it is important to note the potential recall bias due to self-report (Prince et al., 2008). No studies to date have investigated the effect of Kaftrio on PA levels, but Kauser et al. (2022) found that other *CFTR* modulators led to improved daily functioning and ability to walk up the stairs, which was also mentioned by the current participants. Participants in this study also reported being able to build up their fitness, which is also in accord with those of Causer et al. (2022), although the different age populations should be noted. The increased PA reported likely relates to the increase in energy experienced, with a reduction in tiredness amongst the participants, which in turn enables them to do more and removes some of the barriers previously experienced, such as low energy, time and confidence (Hurley et al., 2021). Indeed, Aspinall et al. (2022) found that Kaftrio was associated with an increase in energy and ability to complete daily tasks. This suggests that Kaftrio can result in a sustained increase in energy and ability to engage in PA, although further research using device-based measures would enable further conclusions to be drawn.

An increase in lung function was experienced by the participants which then remained stable for the majority. An initial increase was expected due to the global studies, suggesting a 10% increase in lung function (Heijerman et al., 2019; Middleton et al., 2019), which was exceeded by some of the current participants. However, in the longer-term, it was found that some may experience a subsequent decrease in lung function as occurred in three participants from the current study, albeit not to pre-Kaftrio levels, and some participants experienced a subsequent increase again. This decrease may be expected due to the decline in lung function conventionally observed over time for those with CF (Begum et al., 2022). Why this is still manifesting in some, but not others, is beyond the scope of the current study. Further studies are thus required to investigate the trajectory of change in lung function prior to, and following the initiation of Kaftrio therapy and the factors that mediate and moderate these trajectories.

A positive impact on the future was hoped for by many participants. Mathews and Kirby (2022) also found this but that having to plan for the future, such as

work, retirement, and family, were considerations that were unexpected. In contrast, in this study, participants were looking forward to going back to work and starting their own family, although it was noted it could be difficult. This perception was consistent with the findings of Kauser et al. (2022), in which participants described the impact on the future caused by *CFTR* modulator therapies as *"welcomed challenges"*. The hope for an increased lifespan was shared by many of the current participants. There is no data to date as to whether this hope will be realised for those on Kaftrio; Ivacaftor has been suggested to be associated with 18 years improvement in life expectancy, and it was indicated this could be the same, or exceeded, by Kaftrio (Balfour-Lynn & King, 2022). Similar to the advances in modulator therapies over the past decade, it was highlighted by the current participants that Kaftrio brings hope for further advances in treatments, in accord with Aspinall et al. (2022). Indeed, participants in Cabral et al.'s (2022) study went as far as to suggest that, in the near future, it is possible that *CFTR* modulators therapies may be able to successfully treat CF. Despite this positivity, there was also a feeling that the future remains uncertain with limited knowledge surrounding the long-term effects of Kaftrio. It is vital that clinical care teams and those supporting people with CF are cognisant of these ongoing fears which may exert increasing pressure as time passes.

4.5.3 Negatives

Initial side effects were experienced by most participants, which was to be expected given that 93% of participants experienced adverse effects in phase-three clinical trials (Middleton et al., 2019). Fortunately, the majority of these side effects were mild and resolved over time, which is consistent with Middleton et al. (2019), and many participants stated that even if their symptoms had persisted, they would not have stopped Kaftrio. It is pertinent to note that, for some participants, a lower dose of Kaftrio was able to resolve the side effects experienced which was considered preferable to ceasing Kaftrio. This highlights that further research is required to ascertain who is likely to experience more severe side effects, why some people are likely to have such experiences, and the dose-response relationship of Kaftrio in the short- and long-term to allow its appropriate titration over the patient's lifespan.

Indeed, in accordance with the current study, Dooney and Saba (2022) found that significant benefits of Kaftrio remain at a lower dose. However, continuing Kaftrio is not feasible for all; Aspinall et al. (2022) highlighted that some people had a truly negative experience with Kaftrio which led to discontinuation. Given the potential resistance to discontinuing Kaftrio due to improvements in lung function and symptoms (Heo et al., 2022), those that have to discontinue likely need psychological support in order to overcome such a setback, especially as the expectations of Kaftrio were so high. This may result in a widening of the health gap over time with some potentially feeling 'left-behind' (Allen et al., 2023). This could also be the case for those on a lower dose, given that although they may still receive some benefits, it may not be to the extent they had been led to believe. Although side effects did not lead to discontinuation amongst the participants, it highlighted the need for clinical teams to focus on these negative effects in order to avoid the risk of discontinuation and ensure the benefits of Kaftrio are maintained in the future.

Congruent with Aspinall et al. (2022) and Almulhem et al. (2022), concerns regarding whether the benefits of Kaftrio would last were cited. This is understandable due to the unknown future of Kaftrio given its infancy for those with CF. CF will continue to progress and is suspected to become more difficult to monitor due to reduced disease progression, with asymptomatic patients, in addition to infections, which do not fully clear, and persistent airway inflammation, which may also cause concern for those with CF (Allen et al., 2023). When starting a new treatment, patients have a need for more specific information, with many doubts and concerns being left unresolved (Horne et al., 2013; Kaae et al., 2016). As concerns about treatment are associated with non-adherence, it is important for these concerns to be addressed (Horne et al., 2013). Although it was shared by the current participants that, over time, these concerns should lessen, it emphasises the need for continued research to provide clarity on the long-term effects and help reduce those worries.

An increased appetite led to weight gain amongst some of the participants, a finding previously reported by others (Aspinall et al., 2022; Petersen et al., 2022). The potential for such changes to occur was evident with earlier single

and double modulator therapies which were reported to lead to an increase in body mass, and subsequent concern regarding overweight and obesity among CF populations (Bailey et al., 2021; Egan et al., 2022). Specifically, Ivacaftor led to the proportion of overweight adults with CF, increasing from 16% to 25% (Bailey et al., 2022). Whilst there is limited data available regarding Kaftrio, Gur et al. (2023) found a 2.5 kg increase in body mass, on average, amongst participants. Despite an increased body mass potentially being clinically beneficial due to the relationship between lung function and body mass index (BMI; Gur et al., 2023), there were concerns regarding body image shared by the current female participants, in accord with Martin et al. (2021). Females with CF tend to overestimate their weight, whilst males tend to underestimate, which may be a result of societal influences (Walters, 2001). Therefore, males were expected to have a more positive reaction to the gain in weight, though male participants in the current study had already begun to alter their diet to counteract the weight gain. It is, however, important to note the small number of males included in the present study. Such influences on body mass are critical, given that nutrition may lead to discontinuation of Kaftrio (Aspinall et al., 2022). Changes to diet, exercise and behaviour were suggested by Gabel et al. (2022) to maintain a healthy weight. While some participants were already making such changes, it is important to note the difficulty involved in implementing these. Specifically, changing diet has been a difficult adjustment, as mentioned by the participants, due to being advised to eat a high-fat, high-calorie diet throughout their life (Egan et al., 2022). However, even for the general population, changes to diet are difficult due to having to change established behaviours and habits (Kapur, 2008). In addition, weight loss is difficult to achieve and maintain amongst the general population and, as health is associated with BMI, those with CF may not be encouraged to lose weight (Gur et al., 2023; Kruger et al., 2006).Therefore, it is recommended that clinical teams ensure there is ample nutritional and psychological support to help those with CF with this change and to prevent discontinuation of Kaftrio.

4.5.4 Psychological Impact

The positive impact on psychological well-being, reducing anxiety and worry, stemmed from being healthier and improving their *"outlook on life"*. Indeed Kauser et al. (2022) highlighted that CF-related health complications resulted in increased anxiety or depression. Aspinall et al. (2022) also reported an initial positive impact on psychological well-being. Despite these positive impacts, there were also contrasting views, with some participants sharing negative impacts on psychological well-being. Specifically, Kaftrio had affected mood and resulted in feelings of guilt and anxiety. A development or worsening of depression and anxiety has been highlighted as a potential result of Kaftrio in previous studies with concern the effect is a result of drug-drug interactions with serotonin reuptake inhibitors (Dagenais et al., 2021; Tindell, 2020). Importantly, Zhang et al. (2022) discussed that mood and anxiety could be impacted by Kaftrio, however changes were mitigated by medication. This contrasts the relief in anxiety felt by some of the participants and highlights Kaftrio can impact anxiety, however it cannot be concluded from this study whether Kaftrio leads to a positive or negative impact. This emphasizes the importance of further research being warranted into the psychological impacts of Kaftrio.

4.5.5 Relationships

For the participants, their relationship with their clinical teams were generally positive, with the care teams regarded as being highly supportive in relation to Kaftrio. Converse to Aspinall et al. (2022), in which individuals did not feel heard, participants in the present study felt understood by their team. However, the participants did feel particular clinical areas could be improved; although this varied due to their own personal experiences, it was expressed that this was due to the changing landscape of CF. This was congruent with Aspinall et al. (2022), in which participants required further support to meet their needs. It is pertinent to note that further resources are needed for CF care amongst adults and it is clear that Kaftrio has changed the needs of CF care with clinical teams still learning and adapting (Madge et al., 2017). Thus,

some areas needed further improvement in order to provide the right support and prevent discontinuation of Kaftrio.

The impact Kaftrio had on friends and family was also highlighted. This effect was positive, with families feeling less concern and being able to see a noticeable difference in the participants. This impact has not been explored amongst current research; however, it is important due to the negative effect CF can have on carers and those close to individuals with CF (Bell et al., 2020). This is due to the burden of care and stress relating to CF the family experiences, therefore starting Kaftrio and the benefits to health could have helped relieve this burden (Bell et al., 2020; Berge & Patterson, 2004).This suggests Kaftrio impacts upon those close to the individual in addition to the individual themselves.

Advice for those just starting Kaftrio was also discussed and reflected the individual's own personal experience making it important to be understood. This allowed the individuals to highlight how important adherence to Kaftrio is to ensure the continued benefit to health. Adherence to treatment is very important especially for those with a lifelong disease such as CF. Therefore, adhering to Kaftrio is important but in addition, Hine et al. (2022) encouraged people with CF to continue with all treatments. Furthermore, the advice showed the opportunities Kaftrio had created for those with CF to live a "normal life", with Kauser et al. (2022) highlighting the positive outlook for the future. This advice is important when considering the huge impact Kaftrio had on the lived experience as it encompasses the positive perceptions of Kaftrio and the importance it now has on the lives of those with CF.

4.5 Implications – Study 2

This is one of the first qualitative studies to explore the impacts of Kaftrio on those with CF, and the first exploring this after 12 months, providing an in-depth analysis of individuals' lived experience. It is important that those with CF perspectives' about Kaftrio are considered, as it provides first-hand knowledge of Kaftrio and its impact. Clinical teams would also benefit from this

knowledge so that the participants' needs are understood and can be met. This research could also be beneficial in the development of future, alternative treatments, taking into consideration what needs to be improved upon, in order to provide a suitable treatment for all people with CF, including the 10% without the *F508del* mutations and those who have discontinued treatment due to adverse effects.

Whilst there are numerous strengths associated with this study, there are some limitations, including the relatively small sample size and the majority of participants being female, precluding an in-depth evaluation of sex differences. This is particularly important due to the shorter life expectancy of women with CF (Harness-Brumley et al., 2014). Therefore, there is an urgent need for larger-scale research to facilitate such comparisons. Moreover, further research into the long-term impacts of Kaftrio on the lived experience is warranted.

4.6 Conclusion – Study 2

This research provides a key insight to people with CF's perceptions of Kaftrio and its longer-term impacts. The current research significantly advances our understanding of the lived experience beyond the initial response to starting Kaftrio. This study highlights Kaftrio's positive impact, especially in relation to quality-of-life, although the negative impact of media hype and side effects were raised. There was still significant hope regarding the long-term impacts of Kaftrio, but the fear regarding the ability for the current benefits to be sustained was highlighted.

Chapter 5: Concluding Statements

This thesis provides a key insight into the impact of Kaftrio on the lived experience of those with CF and their carers. It was concluded that Kaftrio had a positive impact on those with CF, in addition to those close to them, with a beneficial effect on quality-of-life, whilst negative impacts such as adverse effects did not influence their decision to take Kaftrio. These findings are highly useful in the development of future treatments and provide valuable insights for clinical teams regarding often unheard patient perspectives.

Given that Kaftrio is a recently approved treatment, there has been limited research to date and this thesis provides important insights in order to understand the patient perspectives and experiences of this new treatment. Key questions raised by the current thesis that warrant further research are the sustainability of Kaftrio-related effects, and the most appropriate strategies to manage the impacts upon well-being associated with changes in appetite. Furthermore, especially in the children aged 6 to 11 years, Kaftrio offers significant hope for the future but further work is urgently required regarding the impact of Kaftrio on morbidity and mortality associated with CF. Specifically, whilst Kaftrio may be significantly altering current health, its long-term effects and the consequences for the prevalence and severity of other morbidities remains to be determined. There is growing concern regarding a potential obesity epidemic in those with CF and its consequences, something that's never previously been of concern.

In conclusion, this thesis explored the impact of Kaftrio amongst adults and children aged 6-11 years with CF and their carers, demonstrating Kaftrio to be greatly beneficial to the lived experience of those with CF and their carers.

Chapter 6: References

Aalbers, B. L., de Winter-de Groot, K. M., Arets, H. G. M., Hofland, R. W., de Kiviet, A. C., van Oirschot-van de Ven, M. M. M., Kruijswijk, M. A., Schotman, S., Michel, S., van der Ent, C. K., & Heijerman, H. G. M. (2020). Clinical effect of lumacaftor/ivacaftor in F508del homozygous CF patients with FEV(1) ≥ 90% predicted at baseline. *J Cyst Fibros*, *19*(4), 654-658. https://doi.org/10.1016/j.jcf.2019.12.015

Abbott, J., Hart, A., Morton, A., Gee, L., & Conway, S. (2008). Health-related quality of life in adults with cystic fibrosis: The role of coping. *Journal of Psychosomatic Research*, *64*(2), 149-157. https://doi.org/https://doi.org/10.1016/j.jpsychores.2007.08.017

Abbott, J., Hurley, M. A., Morton, A. M., & Conway, S. P. (2013). Longitudinal association between lung function and health-related quality of life in cystic fibrosis. *Thorax*, *68*(2), 149-154. https://doi.org/10.1136/thoraxjnl-2012-202552

Accurso, F. J., Sontag, M. K., & Wagener, J. S. (2005). Complications associated with symptomatic diagnosis in infants with cystic fibrosis. *The Journal of Pediatrics*, *147*(3, Supplement), S37-S41. https://doi.org/https://doi.org/10.1016/j.jpeds.2005.08.034

Ahmed, M. I., Dayman, N., Madge, J., & Gaillard, E. (2021). The impact of Symkevi (Tezacaftor/Ivacaftor) on exercise capacity in adolescents with CF. *European Respiratory Journal*, *58*(suppl 65), PA2101. https://doi.org/10.1183/13993003.congress-2021.PA2101

Alhojailan, M. I. (2012). Thematic analysis: A critical review of its process and evaluation. *West east journal of social sciences*, *1*(1), 39-47.

Allen, L., Allen, L., Carr, S. B., Davies, G., Downey, D., Egan, M., Forton, J. T., Gray, R., Haworth, C., Horsley, A., Smyth, A. R., Southern, K. W., & Davies, J. C. (2023). Future therapies for cystic fibrosis. *Nature*

Communications, *14*(1), 693. https://doi.org/10.1038/s41467-023-36244-2

Almulhem, M., Harnett, N., Graham, S., Haq, I., Visram, S., Ward, C., & Brodlie, M. (2022). Exploring the impact of elexacaftor-tezacaftor-ivacaftor treatment on opinions regarding airway clearance techniques and nebulisers: TEMPO a qualitative study in children with cystic fibrosis, their families and healthcare professionals. *BMJ Open Respiratory Research*, *9*(1), e001420. https://doi.org/10.1136/bmjresp-2022-001420

Andersen, H. U., Lanng, S., Pressler, T., Laugesen, C. S., & Mathiesen, E. R. (2006). Cystic Fibrosis–Related Diabetes: The presence of microvascular diabetes complications. *Diabetes Care*, *29*(12), 2660-2663. https://doi.org/10.2337/dc06-0654

Angelis, A., Kanavos, P., López-Bastida, J., Linertová, R., Nicod, E., Serrano-Aguilar, P., & Network, B.-R. R. (2015). Social and economic costs and health-related quality of life in non-institutionalised patients with cystic fibrosis in the United Kingdom. *BMC Health Services Research*, *15*(1), 428. https://doi.org/10.1186/s12913-015-1061-3

Archibald, M. M., Ambagtsheer, R. C., Casey, M. G., & Lawless, M. (2019). Using Zoom Videoconferencing for Qualitative Data Collection: Perceptions and Experiences of Researchers and Participants. *International Journal of Qualitative Methods*, *18*, 1609406919874596. https://doi.org/10.1177/1609406919874596

Arias Llorente, R. P., Bousoño García, C., & Díaz Martín, J. J. (2008). Treatment compliance in children and adults with Cystic Fibrosis. *Journal of Cystic Fibrosis*, *7*(5), 359-367. https://doi.org/https://doi.org/10.1016/j.jcf.2008.01.003

Aspinall, S. A., Mackintosh, K. A., Hill, D. M., Cope, B., & McNarry, M. A. (2022). Evaluating the Effect of Kaftrio on Perspectives of Health and Wellbeing in Individuals with Cystic Fibrosis. *International Journal of*

Environmental Research and Public Health, *19*(10), 6114. https://www.mdpi.com/1660-4601/19/10/6114

Bailey, J., Krick, S., & Fontaine, K. R. (2022). The Changing Landscape of Nutrition in Cystic Fibrosis: The Emergence of Overweight and Obesity. *Nutrients*, *14*(6), 1216. https://www.mdpi.com/2072-6643/14/6/1216

Bailey, J., Rozga, M., McDonald, C. M., Bowser, E. K., Farnham, K., Mangus, M., Padula, L., Porco, K., & Alvarez, J. A. (2021). Effect of CFTR Modulators on Anthropometric Parameters in Individuals with Cystic Fibrosis: An Evidence Analysis Center Systematic Review. *Journal of the Academy of Nutrition and Dietetics*, *121*(7), 1364-1378.e1362. https://doi.org/https://doi.org/10.1016/j.jand.2020.03.014

Balfour-Lynn, I. M., & King, J. A. (2022). CFTR modulator therapies – Effect on life expectancy in people with cystic fibrosis. *Paediatric Respiratory Reviews*, *42*, 3-8. https://doi.org/https://doi.org/10.1016/j.prrv.2020.05.002

Barber, J., & Walczak, K. (2009). *Conscience and Critic: Peer Debriefing Strategies in Grounded Theory Research*.

Barriball, K. L., & While, A. (1994). Collecting data using a semi-structured interview: a discussion paper. *Journal of Advanced Nursing-Institutional Subscription*, *19*(2), 328-335.

Barry, P. J., & Taylor-Cousar, J. L. (2021). Triple combination cystic fibrosis transmembrane conductance regulator modulator therapy in the real world – opportunities and challenges. *Current Opinion in Pulmonary Medicine*, *27*(6), 554-566. https://doi.org/10.1097/mcp.0000000000000819

Begum, N., Byrnes, C. A., Cheney, J., Cooper, P. J., Fantino, E., Gailer, N., Grimwood, K., GutierrezCardenas, D., Massie, J., Robertson, C. F., Sly, P. D., Tiddens, H. A. W. M., Wainwright, C. E., & Ware, R. S. (2022). Factors in childhood associated with lung function decline to

adolescence in cystic fibrosis. *Journal of Cystic Fibrosis*, *21*(6), 977-983. https://doi.org/https://doi.org/10.1016/j.jcf.2022.03.008

Bell, S. C., Mall, M. A., Gutierrez, H., Macek, M., Madge, S., Davies, J. C., Burgel, P. R., Tullis, E., Castaños, C., Castellani, C., Byrnes, C. A., Cathcart, F., Chotirmall, S. H., Cosgriff, R., Eichler, I., Fajac, I., Goss, C. H., Drevinek, P., Farrell, P. M., . . . Ratjen, F. (2020). The future of cystic fibrosis care: a global perspective. *Lancet Respir Med*, *8*(1), 65-124. https://doi.org/https://doi.org/10.1016/S2213-2600(19)30337-6.

Berge, J. M., & Patterson, J. M. (2004). Cystic fibrosis and the family: A review and critique of the literature. *Families, Systems, & Health*, *22*, 74-100. https://doi.org/10.1037/1091-7527.22.1.74

Bessonova, L., Volkova, N., Higgins, M., Bengtsson, L., Tian, S., Simard, C., Konstan, M. W., Sawicki, G. S., Sewall, A., Nyangoma, S., Elbert, A., Marshall, B. C., & Bilton, D. (2018). Data from the US and UK cystic fibrosis registries support disease modification by CFTR modulation with ivacaftor. *Thorax*, *73*(8), 731-740. https://doi.org/10.1136/thoraxjnl-2017-210394

Bieniek, J. M., Lapin, C. D., & Jarvi, K. A. (2021). Genetics of CFTR and male infertility. *Transl Androl Urol*, *10*(3), 1391-1400. https://doi.org/10.21037/tau.2020.04.05

Blackwell, L. S., & Quittner, A. L. (2015). Daily pain in adolescents with CF: Effects on adherence, psychological symptoms, and health-related quality of life. *Pediatric Pulmonology*, *50*(3), 244-251. https://doi.org/https://doi.org/10.1002/ppul.23091

Boyle, M. P., Bell, S. C., Konstan, M. W., McColley, S. A., Rowe, S. M., Rietschel, E., Huang, X. H., Waltz, D., Patel, N. R., Rodman, D., & Grp, V. X. S. (2014). A CFTR corrector (lumacaftor) and a CFTR potentiator (ivacaftor) for treatment of patients with cystic fibrosis who have a phe508del CFTR mutation: a phase 2 randomised controlled trial.

Lancet Respiratory Medicine, *2*(7), 527-538. https://doi.org/10.1016/s2213-2600(14)70132-8

Bradley, J. M., Moran, F. M., & Stuart Elborn, J. (2006). Evidence for physical therapies (airway clearance and physical training) in cystic fibrosis: An overview of five Cochrane systematic reviews. *Respiratory Medicine*, *100*(2), 191-201. https://doi.org/https://doi.org/10.1016/j.rmed.2005.11.028

Braun, V., & Clarke, V. (2014). What can “thematic analysis” offer health and wellbeing researchers? *International Journal of Qualitative Studies on Health and Well-being*, *9*(1), 26152. https://doi.org/10.3402/qhw.v9.26152

Brown, C., Ahitan, B., Carrolan, V., Choyce, J., Jones, L., Hanif, N., MacDonald-Johns, R., Patel, N., Pond, J., Poole, J., Rashid, R., & Whitehouse, J. L. (2022). P226 Our evolving prescribing practice: inhaled medication prescription changes over 5 years at the West Midlands Adult Cystic Fibrosis Centre. *Journal of Cystic Fibrosis*, *21*, S129-S130. https://doi.org/https://doi.org/10.1016/S1569-1993(22)00555-0

Buchbinder, E. (2011). Beyond Checking:Experiences of the Validation Interview. *Qualitative Social Work*, *10*(1), 106-122. https://doi.org/10.1177/1473325010370189

Bucks, R. S., Hawkins, K., Skinner, T. C., Horn, S., Seddon, P., & Horne, R. (2009). Adherence to Treatment in Adolescents with Cystic Fibrosis: The Role of Illness Perceptions and Treatment Beliefs. *Journal of Pediatric Psychology*, *34*(8), 893-902. https://doi.org/10.1093/jpepsy/jsn135

Burgel, P.-R., Durieu, I., Chiron, R., Ramel, S., Danner-Boucher, I., Prevotat, A., Grenet, D., Marguet, C., Reynaud-Gaubert, M., Macey, J., Mely, L., Fanton, A., Quetant, S., Lemonnier, L., Paillasseur, J.-L., Silva, J. D., & Martin, C. (2021). Rapid Improvement after Starting Elexacaftor–

Tezacaftor–Ivacaftor in Patients with Cystic Fibrosis and Advanced Pulmonary Disease. *American Journal of Respiratory and Critical Care Medicine*, *204*(1), 64-73. https://doi.org/10.1164/rccm.202011-4153OC

Burgel, P. R., Munck, A., Durieu, I., Chiron, R., Mely, L., Prevotat, A., Murris-Espin, M., Porzio, M., Abely, M., Reix, P., Marguet, C., Macey, J., Sermet-Gaudelus, I., Corvol, H., Bui, S., Lemonnier, L., Dehillotte, C., Da Silva, J., Paillasseur, J. L., & Hubert, D. (2020). Real-Life Safety and Effectiveness of Lumacaftor-Ivacaftor in Patients with Cystic Fibrosis. *Am J Respir Crit Care Med*, *201*(2), 188-197. https://doi.org/10.1164/rccm.201906-1227OC

Button, B. M., Edgeworth, D., Finlayson, F., Fantidis, M., Wilson, L., Talbot, A., Keating, D., Williams, E., Clark, D., Tierney, A. C., Kotsimbos, T., & Wilson, J. W. (2015). WS09.5 Effect of ivacaftor on wellness, quality of life and cognitive function in adults with cystic fibrosis and G551D mutation. *Journal of Cystic Fibrosis*, *14*, S18. https://doi.org/https://doi.org/10.1016/S1569-1993(15)30056-4

Cabral, B., Terlizzi, V., Laselva, O., Conte Filho, C., & Mota, F. (2022). Anticipating New Treatments for Cystic Fibrosis: A Global Survey of Researchers. *Journal of Clinical Medicine*, *11*(5), 1283. https://www.mdpi.com/2077-0383/11/5/1283

Candela, A. G. (2019). Exploring the Function of Member Checking. *The Qualitative Report*, *24*(3), 619-628. https://www.proquest.com/scholarly-journals/exploring-function-member-checking/docview/2213787326/se-2?accountid=14680

Capurro, V., Tomati, V., Sondo, E., Renda, M., Borrelli, A., Pastorino, C., Guidone, D., Venturini, A., Giraudo, A., Mandrup Bertozzi, S., Musante, I., Bertozzi, F., Bandiera, T., Zara, F., Galietta, L. J. V., & Pedemonte, N. (2021). Partial Rescue of F508del-CFTR Stability and Trafficking Defects by Double Corrector Treatment. *International Journal of*

Molecular Sciences, *22*(10), 5262. https://www.mdpi.com/1422-0067/22/10/5262

Carter, N., Bryant-Lukosius, D., DiCenso, A., Blythe, J., & Neville, A. J. (2014). The use of triangulation in qualitative research. *Oncol Nurs Forum*, *41*(5), 545-547. https://doi.org/10.1188/14.Onf.545-547

Castellani, C., & Assael, B. M. (2017). Cystic fibrosis: a clinical view. *Cellular and Molecular Life Sciences*, *74*(1), 129-140. https://doi.org/10.1007/s00018-016-2393-9

Causer, A. J., Shute, J. K., Cummings, M. H., Shepherd, A. I., Wallbanks, S. R., Pulsford, R. M., Bright, V., Connett, G., & Saynor, Z. L. (2022). Elexacaftor–Tezacaftor–Ivacaftor improves exercise capacity in adolescents with cystic fibrosis. *Pediatric Pulmonology*, *57*(11), 2652-2658. https://doi.org/https://doi.org/10.1002/ppul.26078

Choyce, J., Hanif, N., Ahitan, B., Brown, C., Patel, N., Rashid, R., & Whitehouse, J. (2022). P152 Trends in intravenous antibiotic prescriptions pre- and postintroduction of Kaftrio® in a large UK adult cystic fibrosis centre. *Journal of Cystic Fibrosis*, *21*, S107-S108. https://doi.org/https://doi.org/10.1016/S1569-1993(22)00483-0

Cohen-Cymberknoh, M., Shoseyov, D., & Kerem, E. (2011). Managing Cystic Fibrosis. *American Journal of Respiratory and Critical Care Medicine*, *183*(11), 1463-1471. https://doi.org/10.1164/rccm.201009-1478CI

Colombo, C., Burgel, P.-R., Gartner, S., van Koningsbruggen-Rietschel, S., Naehrlich, L., Sermet-Gaudelus, I., & Southern, K. W. (2020). Impact of COVID-19 on people with cystic fibrosis. *The Lancet Respiratory Medicine*, *8*(5), e35-e36. https://doi.org/10.1016/S2213-2600(20)30177-6

Connelly, L. M. (2016). Trustworthiness in Qualitative Research. *Medsurg Nurs*, *25*(6), 435-436.

Curran, M., Tierney, A. C., Button, B., Collins, L., Kennedy, L., McDonnell, C., Casserly, B., & Cahalan, R. (2022). The effectiveness of exercise interventions to increase physical activity in Cystic Fibrosis: A systematic review. *Journal of Cystic Fibrosis*, *21*(2), 272-281. https://doi.org/https://doi.org/10.1016/j.jcf.2021.10.008

Cystic Fibrosis Trust. (2020). *Kaftrio (Trikafta in the US)- Triple combination therapy*. Retrieved April 19 from https://www.cysticfibrosis.org.uk/the-work-we-do/campaigning-hard/life-saving-drugs/triple-combination-therapy

Cystic Fibrosis Trust. (2022). *Kaftrio now approved for 6-11 year olds across the UK*. Retrieved November 2nd from https://www.cysticfibrosis.org.uk/news/kaftrio-now-approved-for-6-11-year-olds-across-the-uk

Dagenais, R. V. E., Su, V. C., & Quon, B. S. (2021). Real-World Safety of CFTR Modulators in the Treatment of Cystic Fibrosis: A Systematic Review. *Journal of Clinical Medicine*, *10*(1), 23. https://www.mdpi.com/2077-0383/10/1/23

Davies, J. C., Sermet-Gaudelus, I., Naehrlich, L., Harris, R. S., Campbell, D., Ahluwalia, N., Short, C., Haseltine, E., Panorchan, P., Saunders, C., Owen, C. A., & Wainwright, C. E. (2021). A phase 3, double-blind, parallel-group study to evaluate the efficacy and safety of tezacaftor in combination with ivacaftor in participants 6 through 11 years of age with cystic fibrosis homozygous for F508del or heterozygous for the F508del-CFTR mutation and a residual function mutation. *J Cyst Fibros*, *20*(1), 68-77. https://doi.org/10.1016/j.jcf.2020.07.023

Davies, J. C., Wainwright, C. E., Canny, G. J., Chilvers, M. A., Howenstine, M. S., Munck, A., Mainz, J. G., Rodriguez, S., Li, H., Yen, K., Ordoñez, C. L., & Ahrens, R. (2013). Efficacy and Safety of Ivacaftor in Patients Aged 6 to 11 Years with Cystic Fibrosis with a G551D Mutation. *American Journal of Respiratory and Critical Care Medicine*, *187*(11),

1219-1225. https://www.proquest.com/scholarly-journals/efficacy-safety-ivacaftor-patients-aged-6-11/docview/1439827531/se-2

Davis, P. B., Yasothan, U., & Kirkpatrick, P. (2012). Ivacaftor [Drug overview]. *Nature Reviews Drug Discovery*, *11*, 349+. https://link.gale.com/apps/doc/A289835459/AONE?u=anon~46aa755d&sid=googleScholar&xid=cd893624

Donnelley, M., Parsons, D., & Prichard, I. (2023). Perceptions of airway gene therapy for cystic fibrosis. *Expert Opinion on Biological Therapy*, *23*(1), 103-113. https://doi.org/10.1080/14712598.2022.2150544

Dooney, M. K., & Saba, T. (2022). P082 Reduced-dose Kaftrio® can significantly improve respiratory health for those intolerant of the recommended dosing schedule. *Journal of Cystic Fibrosis*, *21*, S85. https://doi.org/https://doi.org/10.1016/S1569-1993(22)00415-5

Dworkin, S. L. (2012). Sample Size Policy for Qualitative Studies Using In-Depth Interviews. *Archives of Sexual Behavior*, *41*(6), 1319-1320. https://doi.org/10.1007/s10508-012-0016-6

Egan, H., Keyte, R., & Mantzios, M. (2022). The Challenges of Eating Well for People Living with Cystic Fibrosis: an Interview Study Exploring the Use of Mindful Eating Approaches and Behaviours to Support Optimal Nutritional Status. *International Journal of Behavioral Medicine*. https://doi.org/10.1007/s12529-022-10057-x

Elborn, J. S. (2016). Cystic fibrosis. *Lancet*, *388*(10059), 2519-2531. https://doi.org/10.1016/s0140-6736(16)00576-6

Emmanuelle, B., Alexandra, P., Michaela, S., Anita, G., Kate, H., Benoit, C., Farouk, B., Guillaume, P., Alexandre, H., Christine, G.-P., Iwona, P., & Isabelle, S.-G. (2021). Modulators of CFTR. Updates on clinical development and future directions. *European Journal of Medicinal Chemistry*, *213*, 113195. https://doi.org/https://doi.org/10.1016/j.ejmech.2021.113195

Fairweather, N. H., Jones, F. W., Harris, S. A., Deiros Collado, M., & Shayle, A. (2021). Thriving alongside cystic fibrosis: Developing a grounded theory of empowerment in children and young people with cystic fibrosis during key life transitions. *Child: Care, Health and Development*, *47*(4), 484-493. https://doi.org/https://doi.org/10.1111/cch.12860

Farmer, T., Robinson, K., Elliott, S. J., & Eyles, J. (2006). Developing and implementing a triangulation protocol for qualitative health research. *Qualitative health research*, *16*(3), 377-394.

Ferrera, L., Capurro, V., Delpiano, L., Gianotti, A., & Moran, O. (2021). The Application of Bicarbonate Recovers the Chemical-Physical Properties of Airway Surface Liquid in Cystic Fibrosis Epithelia Models. *Biology*, *10*(4), 278. https://www.mdpi.com/2079-7737/10/4/278

Fitzgerald, C., George, S., Somerville, R., Linnane, B., & Fitzpatrick, P. (2018). Caregiver burden of parents of young children with cystic fibrosis. *Journal of Cystic Fibrosis*, *17*(1), 125-131. https://doi.org/https://doi.org/10.1016/j.jcf.2017.08.016

Flume, P. A., Biner, R. F., Downey, D. G., Brown, C., Jain, M., Fischer, R., De Boeck, K., Sawicki, G. S., Chang, P., Paz-Diaz, H., Rubin, J. L., Yang, Y., Hu, X., Pasta, D. J., Millar, S. J., Campbell, D., Wang, X., Ahluwalia, N., Owen, C. A., . . . Gilljam, M. (2021). Long-term safety and efficacy of tezacaftor–ivacaftor in individuals with cystic fibrosis aged 12 years or older who are homozygous or heterozygous for Phe508del CFTR (EXTEND): an open-label extension study. *The Lancet Respiratory Medicine*, *9*(7), 733-746. https://doi.org/https://doi.org/10.1016/S2213-2600(20)30510-5

Fogarty, A., Hubbard, R., & Britton, J. (2000). International Comparison of Median Age at Death From Cystic Fibrosis. *Chest*, *117*(6), 1656-1660. https://doi.org/https://doi.org/10.1378/chest.117.6.1656

Gabel, M. E., Fox, C. K., Grimes, R. A., Lowman, J. D., McDonald, C. M., Stallings, V. A., & Michel, S. H. (2022). Overweight and cystic fibrosis:

An unexpected challenge. *Pediatric Pulmonology*, *57*(S1), S40-S49. https://doi.org/https://doi.org/10.1002/ppul.25748

Gifford, A. H., Mayer-Hamblett, N., Pearson, K., & Nichols, D. P. (2020). Answering the call to address cystic fibrosis treatment burden in the era of highly effective CFTR modulator therapy. *Journal of Cystic Fibrosis*, *19*(5), 762-767. https://doi.org/https://doi.org/10.1016/j.jcf.2019.11.007

Goetz, D. M., & Savant, A. P. (2021). Review of CFTR modulators 2020. *Pediatric Pulmonology*, *56*(12), 3595-3606. https://doi.org/https://doi.org/10.1002/ppul.25627

Goss, C. H., Edwards, T. C., Ramsey, B. W., Aitken, M. L., & Patrick, D. L. (2009). Patient-reported respiratory symptoms in cystic fibrosis. *Journal of Cystic Fibrosis*, *8*(4), 245-252. https://doi.org/https://doi.org/10.1016/j.jcf.2009.04.003

Gray, L. M., Wong-Wylie, G., Rempel, G. R., & Cook, K. (2020). Expanding qualitative research interviewing strategies: Zoom video communications. *The Qualitative Report*, *25*(5), 1292-1301.

Griese, M., Costa, S., Linnemann, R. W., Mall, M. A., McKone, E. F., Polineni, D., Quon, B. S., Ringshausen, F. C., Taylor-Cousar, J. L., Withers, N. J., Moskowitz, S. M., & Daines, C. L. (2021). Safety and Efficacy of Elexacaftor/Tezacaftor/Ivacaftor for 24 Weeks or Longer in People with Cystic Fibrosis and One or More F508del Alleles: Interim Results of an Open-Label Phase 3 Clinical Trial. *American Journal of Respiratory and Critical Care Medicine*, *203*(3), 381-385. https://doi.org/10.1164/rccm.202008-3176LE

Gur, M., Bar–Yoseph, R., Hanna, M., Abboud, D., Keidar, Z., Palchan, T., Toukan, Y., Masarweh, K., Alisha, I., Zuckerman-Levin, N., & Bentur, L. (2023). Effect of Trikafta on bone density, body composition and exercise capacity in CF: A pilot study. *Pediatric Pulmonology*, *58*(2), 577-584. https://doi.org/https://doi.org/10.1002/ppul.26243

Harness-Brumley, C. L., Elliott, A. C., Rosenbluth, D. B., Raghavan, D., & Jain, R. (2014). Gender Differences in Outcomes of Patients with Cystic Fibrosis. *Journal of Women's Health*, *23*(12), 1012-1020. https://doi.org/10.1089/jwh.2014.4985

Heijerman, H. G. M., McKone, E. F., Downey, D. G., Van Braeckel, E., Rowe, S. M., Tullis, E., Mall, M. A., Welter, J. J., Ramsey, B. W., McKee, C. M., Marigowda, G., Moskowitz, S. M., Waltz, D., Sosnay, P. R., Simard, C., Ahluwalia, N., Xuan, F., Zhang, Y., Taylor-Cousar, J. L., . . . Majoor, C. (2019). Efficacy and safety of the elexacaftor plus tezacaftor plus ivacaftor combination regimen in people with cystic fibrosis homozygous for the F508del mutation: a double-blind, randomised, phase 3 trial. *The Lancet*, *394*(10212), 1940-1948. https://doi.org/10.1016/S0140-6736(19)32597-8

Heo, S., Young, D. C., Safirstein, J., Bourque, B., Antell, M. H., Diloreto, S., & Rotolo, S. M. (2022). Mental status changes during elexacaftor/tezacaftor / ivacaftor therapy. *Journal of Cystic Fibrosis*, *21*(2), 339-343. https://doi.org/https://doi.org/10.1016/j.jcf.2021.10.002

Hillian, A. D., Londono, D., Dunn, J. M., Goddard, K. A. B., Pace, R. G., Knowles, M. R., & Drumm, M. L. (2008). Modulation of cystic fibrosis lung disease by variants in interleukin-8. *Genes & Immunity*, *9*(6), 501-508. https://doi.org/10.1038/gene.2008.42

Hine, C., Nagakumar, P., & Desai, M. (2022). Small molecule drugs in cystic fibrosis. *Archives of disease in childhood - Education & practice edition*, *107*(5), 379-382. https://doi.org/10.1136/archdischild-2020-319009

Horne, R., Chapman, S. C. E., Parham, R., Freemantle, N., Forbes, A., & Cooper, V. (2013). Understanding Patients' Adherence-Related Beliefs about Medicines Prescribed for Long-Term Conditions: A Meta-Analytic Review of the Necessity-Concerns Framework. *PLOS ONE*, *8*(12), e80633. https://doi.org/10.1371/journal.pone.0080633

Horsley, A., Cunningham S., & Innes, A. J. . (2015). *Cystic Fibrosis* (A. Horsley, Cunningham S., & Innes, A. J. , Ed. 2nd ed.). Oxford University Press.

Hubert, D., Chiron, R., Camara, B., Grenet, D., Prévotat, A., Bassinet, L., Dominique, S., Rault, G., Macey, J., Honoré, I., Kanaan, R., Leroy, S., Nadine, & Burgel, P.-R. (2017). Real-life initiation of lumacaftor/ivacaftor combination in adults with cystic fibrosis homozygous for the Phe508del CFTR mutation and severe lung disease. *Journal of Cystic Fibrosis*, *16*(3), 388-391. https://doi.org/https://doi.org/10.1016/j.jcf.2017.03.003

Hughan, K. S., Daley, T., Rayas, M. S., Kelly, A., & Roe, A. (2019). Female reproductive health in cystic fibrosis. *Journal of Cystic Fibrosis*, *18*, S95-S104. https://doi.org/https://doi.org/10.1016/j.jcf.2019.08.024

Hurley, M. N., McKeever, T. M., Prayle, A. P., Fogarty, A. W., & Smyth, A. R. (2014). Rate of improvement of CF life expectancy exceeds that of general population—Observational death registration study. *Journal of Cystic Fibrosis*, *13*(4), 410-415. https://doi.org/https://doi.org/10.1016/j.jcf.2013.12.002

Hurley, N., Moyna, N. M., Kehoe, B., McCaffrey, N., Redmond, K., & Hardcastle, S. J. (2021). Factors influencing physical activity in adults with cystic fibrosis. *BMC Pulmonary Medicine*, *21*(1), 113. https://doi.org/10.1186/s12890-021-01482-x

Jenkins, L., Mills, H., McCaughan, J., Doherty, G., Reid, A., Bell, J., & Keown, K. (2021). P043 A snapshot of respiratory microbiology results pre- and postcommencing Kaftrio&#xae. *Journal of Cystic Fibrosis*, *20*, S51-S52. https://doi.org/10.1016/S1569-1993(21)01070-5

Kaae, S., Dam, P., & Rossing, C. (2016). Evaluation of a pharmacy service helping patients to get a good start in taking their new medications for chronic diseases. *Research in Social and Administrative Pharmacy*,

12(3), 486-495. https://doi.org/https://doi.org/10.1016/j.sapharm.2015.08.002

Kallio, H., Pietilä, A.-M., Johnson, M., & Kangasniemi, M. (2016). Systematic methodological review: developing a framework for a qualitative semi-structured interview guide. *Journal of Advanced Nursing*, *72*(12), 2954-2965. https://doi.org/https://doi.org/10.1111/jan.13031

Kapur, K. K., A. Ramachandran, Shobhana. Mohan, V. Aravind, SR. Badgandi, M. Srishyla, MV. (2008). Barriers to Changing Dietary Behavior. *Journal of Association of Physicians of India 56*(1), 27-32. https://doi.org/http://mdrf-eprints.in/34/

Karimi, M., & Brazier, J. (2016). Health, Health-Related Quality of Life, and Quality of Life: What is the Difference? *PharmacoEconomics*, *34*(7), 645-649. https://doi.org/10.1007/s40273-016-0389-9

Kauser, S., Keyte, R., Mantzios, M., & Egan, H. (2022). A Qualitative Exploration into Experiences and Attitudes Regarding Psychosocial Challenges, Self-compassion, and Mindfulness in a Population of Adults with Cystic Fibrosis. *Journal of Clinical Psychology in Medical Settings*, *29*(4), 898-910. https://doi.org/10.1007/s10880-022-09859-8

Keitz, S. A., Stechuchak, K. M., Grambow, S. C., Koropchak, C. M., & Tulsky, J. A. (2007). Behind Closed Doors: Management of Patient Expectations in Primary Care Practices. *Archives of Internal Medicine*, *167*(5), 445-452. https://doi.org/10.1001/archinte.167.5.445

Keogh, R. H., Szczesniak, R., Taylor-Robinson, D., & Bilton, D. (2018). Up-to-date and projected estimates of survival for people with cystic fibrosis using baseline characteristics: A longitudinal study using UK patient registry data. *Journal of Cystic Fibrosis*, *17*(2), 218-227. https://doi.org/https://doi.org/10.1016/j.jcf.2017.11.019

Kirwan, L., Fletcher, G., Harrington, M., Jeleniewska, P., Zhou, S., Casserly, B., Gallagher, C. G., Greally, P., Gunaratnam, C., Herzig, M., Linnane,

B., McElvaney, N. G., McKone, E. F., McNally, P., Mullane, D., Chróinín, M. N., O'Mahony, M., Plant, B. J., & Jackson, A. D. (2019). Longitudinal Trends in Real-World Outcomes after Initiation of Ivacaftor: A Cohort Study from the Cystic Fibrosis Registry of Ireland. *Annals of the American Thoracic Society*, *16*(2), 209-216. https://doi.org/https://doi.org/10.1513/AnnalsATS.201802-149OC

Klijn, P. H. C., Oudshoorn, A., van der Ent, C. K., van der Net, J., Kimpen, J. L., & Helders, P. J. M. (2004). Effects of Anaerobic Training in Children With Cystic Fibrosis: A Randomized Controlled Study. *Chest*, *125*(4), 1299-1305. https://doi.org/10.1378/chest.125.4.1299

Konstan, M. W., Butler, S. M., Wohl, M. E. B., Stoddard, M., Matousek, R., Wagener, J. S., Johnson, C. A., & Morgan, W. J. (2003). Growth and nutritional indexes in early life predict pulmonary function in cystic fibrosis. *The Journal of Pediatrics*, *142*(6), 624-630. https://doi.org/https://doi.org/10.1067/mpd.2003.152

Konstan, M. W., McKone, E. F., Moss, R. B., Marigowda, G., Tian, S., Waltz, D., Huang, X., Lubarsky, B., Rubin, J., Millar, S. J., Pasta, D. J., Mayer-Hamblett, N., Goss, C. H., Morgan, W., & Sawicki, G. S. (2017). Assessment of safety and efficacy of long-term treatment with combination lumacaftor and ivacaftor therapy in patients with cystic fibrosis homozygous for the F508del-CFTR mutation (PROGRESS): a phase 3, extension study. *The Lancet Respiratory Medicine*, *5*(2), 107-118. https://doi.org/https://doi.org/10.1016/S2213-2600(16)30427-1

Kruger, J., Blanck, H. M., & Gillespie, C. (2006). Dietary and physical activity behaviors among adults successful at weight loss maintenance. *International Journal of Behavioral Nutrition and Physical Activity*, *3*(1), 17. https://doi.org/10.1186/1479-5868-3-17

Lillis, A., Lorca-Mayor, S., Weldon, P., Marsh, E., Collins, S., Lathia, C., Bowman, E., Jones, A., Simmonds, N., Madge, S., & Felton, I. (2021). P203 Fertile ground: pregnancies in a post-Kaftrio® pandemic

era. *Journal of Cystic Fibrosis*, *20*, S101. https://doi.org/10.1016/S1569-1993(21)01228-5

Madge, S., Bell, S. C., Burgel, P.-R., De Rijcke, K., Blasi, F., & Elborn, J. S. (2017). Limitations to providing adult cystic fibrosis care in Europe: Results of a care centre survey. *Journal of Cystic Fibrosis*, *16*(1), 85-88. https://doi.org/https://doi.org/10.1016/j.jcf.2016.07.001

Martin, C., Burnet, E., Ronayette-Preira, A., P, Martin, J., Delmas, L., Prieur, B., & Burgel, P. R. (2021). Patient perspectives following initiation of elexacaftor-tezacaftor-ivacaftor in people with cystic fibrosis and advanced lung disease. *Respiratory Medicine and Research*, *80*, 100829. https://doi.org/https://doi.org/10.1016/j.resmer.2021.100829

Martin, M., McCarrier, K., Suthoff, E. D., & Hodgkins, P. (2016). 27 Impact of treatment with ivacaftor (IVA) among patients with cystic fibrosis (CF): a qualitative study to evaluate patient-perceived changes in aspects of daily life. *Journal of Cystic Fibrosis*, *15*, S58. https://doi.org/10.1016/S1569-1993(16)30267-3

Mathews, C., & Kirby, S. (2022). P244 The experiences of taking Kaftrio® for cystic fibrosis (CF). *Journal of Cystic Fibrosis*, *21*, S135. https://doi.org/https://doi.org/10.1016/S1569-1993(22)00573-2

McClenaghan, E., Cosgriff, R., Brownlee, K., Ahern, S., Burgel, P.-R., Byrnes, C. A., Colombo, C., Corvol, H., Cheng, S. Y., Daneau, G., Elbert, A., Faro, A., Goss, C. H., Gulmans, V., Gutierrez, H., de Monestrol, I., Jung, A., Justus, L. N., Kashirskaya, N., . . . L Whitehouse, J. (2020). The global impact of SARS-CoV-2 in 181 people with cystic fibrosis. *Journal of Cystic Fibrosis*, *19*(6), 868-871. https://doi.org/10.1016/j.jcf.2020.10.003

McCormick, J., Cho, D.-Y., Lampkin, B., Richman, J., Hathorne, H., Rowe, S. M., & Woodworth, B. A. (2019). Ivacaftor improves rhinologic, psychologic, and sleep-related quality of life in G551D cystic fibrosis

patients. *International Forum of Allergy & Rhinology*, *9*(3), 292-297. https://doi.org/https://doi.org/10.1002/alr.22251

McKone, E. F., Borowitz, D., Drevinek, P., Griese, M., Konstan, M. W., Wainwright, C., Ratjen, F., Sermet-Gaudelus, I., Plant, B., Munck, A., Jiang, Y., Gilmartin, G., & Davies, J. C. (2014). Long-term safety and efficacy of ivacaftor in patients with cystic fibrosis who have the Gly551Asp-CFTR mutation: a phase 3, open-label extension study (PERSIST). *The Lancet Respiratory Medicine*, *2*(11), 902-910. https://doi.org/https://doi.org/10.1016/S2213-2600(14)70218-8

Meoli, A., Fainardi, V., Deolmi, M., Chiopris, G., Marinelli, F., Caminiti, C., Esposito, S., & Pisi, G. (2021). State of the Art on Approved Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) Modulators and Triple-Combination Therapy. *Pharmaceuticals*, *14*(9), 928. https://www.mdpi.com/1424-8247/14/9/928

Middleton, P. G., Mall, M. A., Dřevínek, P., Lands, L. C., McKone, E. F., Polineni, D., Ramsey, B. W., Taylor-Cousar, J. L., Tullis, E., Vermeulen, F., Marigowda, G., McKee, C. M., Moskowitz, S. M., Nair, N., Savage, J., Simard, C., Tian, S., Waltz, D., Xuan, F., . . . Jain, R. (2019). Elexacaftor–Tezacaftor–Ivacaftor for Cystic Fibrosis with a Single Phe508del Allele. *New England Journal of Medicine*, *381*(19), 1809-1819. https://doi.org/10.1056/NEJMoa1908639

Milla, C. E., Ratjen, F., Marigowda, G., Liu, F., Waltz, D., & Rosenfeld, M. (2017). Lumacaftor/Ivacaftor in Patients Aged 6-11 Years with Cystic Fibrosis and Homozygous for F508del-CFTR. *American Journal of Respiratory and Critical Care Medicine*, *195*(7), 912-920. https://doi.org/https://doi.org/10.1164/rccm.201608-1754OC

Mitchell, R. M., Jones, A. M., Stocking, K., Foden, P., & Barry, P. J. (2021). Longitudinal effects of ivacaftor and medicine possession ratio in people with the Gly551Asp mutation: a 5-year study. *Thorax*, *76*(9), 874-879. https://doi.org/https://doi.org/10.1136/thoraxjnl-2020-215556

Modi, A. C., & Quittner, A. L. (2006). Barriers to Treatment Adherence for Children with Cystic Fibrosis and Asthma: What Gets in the Way? *Journal of Pediatric Psychology*, *31*(8), 846-858. https://doi.org/10.1093/jpepsy/jsj096

Moola, F. (2018). The complexities of contagion: The experience of social isolation among children and youth living with cystic fibrosis in Canada. *Journal of Child Health Care*, *22*(4), 631-645. https://doi.org/10.1177/1367493518767784

Morrissy, D., McCarthy, Y., McCarthy, M., Dorgan, J., Fleming, C., Howlett, C., Vagg, T., Twohig, S., Murphy, D., & Plant, B. (2021). P040 Compassionate use triple therapy CFTR modulation (Kaftrio®) in severe disease. Single-centre, real-world clinical outcomes, safety and tolerability. *Journal of Cystic Fibrosis*, *20*, S50-S51. https://doi.org/10.1016/S1569-1993(21)01067-5

NHS. (2018). *Overview Cystic Fibrosis*. Retrieved April 29 from https://www.nhs.uk/conditions/Cystic-fibrosis/

NICE. (2017). *Cystic fibrosis: diagnosis and management*. Retrieved November 2 from https://www.nice.org.uk/guidance/ng78

Noble, H., & Smith, J. (2015). Issues of validity and reliability in qualitative research. *Evid Based Nurs*, *18*(2), 34-35. https://doi.org/10.1136/eb-2015-102054

Paterson, I., Johnson, C., & MacGregor, G. (2021). Tezacaftor-ivacaftor use in routine care of adults with cystic fibrosis: a medicine use evaluation. *European Journal of Hospital Pharmacy*, ejhpharm-2020-002676. https://doi.org/10.1136/ejhpharm-2020-002676

Perez, A., Jue, I.-S. V., Dawson, D., & Kleinhenz, M. E. (2019). Neurocognitive Side Effects Thwart Transition to Tezacaftor/Ivacaftor CFTR Modulator Therapy in Patients with F508del Homozygous Cystic Fibrosis. In *C23. PLEURAL DISEASE, CF, AND OTHER MAGICAL CREATURES* (pp.

A4330-A4330). https://doi.org/10.1164/ajrccm-conference.2019.199.1_MeetingAbstracts.A4330

Petersen, M. C., Begnel, L., Wallendorf, M., & Litvin, M. (2022). Effect of elexacaftor-tezacaftor-ivacaftor on body weight and metabolic parameters in adults with cystic fibrosis. *Journal of Cystic Fibrosis*, *21*(2), 265-271. https://doi.org/https://doi.org/10.1016/j.jcf.2021.11.012

Popli, K., & Stewart, J. (2007). Infertility and its management in men with cystic fibrosis: review of literature and clinical practices in the UK. *Human Fertility*, *10*(4), 217-221. https://doi.org/10.1080/14647270701510033

Prince, S. A., Adamo, K. B., Hamel, M. E., Hardt, J., Gorber, S. C., & Tremblay, M. (2008). A comparison of direct versus self-report measures for assessing physical activity in adults: a systematic review. *International Journal of Behavioral Nutrition and Physical Activity*, *5*(1), 56. https://doi.org/10.1186/1479-5868-5-56

Proesmans, M., Vermeulen, F., & De Boeck, K. (2008). What's new in cystic fibrosis? From treating symptoms to correction of the basic defect. *European Journal of Pediatrics*, *167*(8), 839-849. https://doi.org/10.1007/s00431-008-0693-2

QSR International Pty Ltd. In. (2018). *NVivo* (Version 12) https://www.qsrinternational.com/nvivo-qualitative-data-analysis-software/home?_ga=2.85691231.734172577.1636023757-1945185769.1636023757

Ramsey, B. W., Davies, J., McElvaney, N. G., Tullis, E., Bell, S. C., Dřevínek, P., Griese, M., McKone, E. F., Wainwright, C. E., Konstan, M. W., Moss, R., Ratjen, F., Sermet-Gaudelus, I., Rowe, S. M., Dong, Q., Rodriguez, S., Yen, K., Ordoñez, C., & Elborn, J. S. (2011). A CFTR Potentiator in Patients with Cystic Fibrosis and the G551D Mutation. *New England Journal of Medicine*, *365*(18), 1663-1672. https://doi.org/10.1056/NEJMoa1105185

Rand, S., Hill, L., & Prasad, S. A. (2013). Physiotherapy in cystic fibrosis: optimising techniques to improve outcomes. *Paediatric Respiratory Reviews*, *14*(4), 263-269. https://doi.org/https://doi.org/10.1016/j.prrv.2012.08.006

Rowe, S. M., Daines, C., Ringshausen, F. C., Kerem, E., Wilson, J., Tullis, E., Nair, N., Simard, C., Han, L., Ingenito, E. P., McKee, C., Lekstrom-Himes, J., & Davies, J. C. (2017). Tezacaftor–Ivacaftor in Residual-Function Heterozygotes with Cystic Fibrosis. *New England Journal of Medicine*, *377*(21), 2024-2035. https://doi.org/10.1056/NEJMoa1709847

Santana-Sosa, E., Gonzalez-Saiz, L., Groeneveld, I. F., Villa-Asensi, J. R., Barrio Gómez de Aguero, M. I., Fleck, S. J., López-Mojares, L. M., Pérez, M., & Lucia, A. (2014). Benefits of combining inspiratory muscle with 'whole muscle' training in children with cystic fibrosis: a randomised controlled trial. *British Journal of Sports Medicine*, *48*(20), 1513-1517. https://doi.org/10.1136/bjsports-2012-091892

Sawicki, G. S., Chilvers, M., McNamara, J., Naehrlich, L., Saunders, C., Sermet-Gaudelus, I., Wainwright, C. E., Ahluwalia, N., Campbell, D., Harris, R. S., Paz-Diaz, H., Shih, J. L., & Davies, J. C. (2022). A Phase 3, open-label, 96-week trial to study the safety, tolerability, and efficacy of tezacaftor/ivacaftor in children ≥ 6 years of age homozygous for F508del or heterozygous for F508del and a residual function CFTR variant. *Journal of Cystic Fibrosis*, *21*(4), 675-683. https://doi.org/https://doi.org/10.1016/j.jcf.2022.02.003

Sawicki, G. S., Sellers, D. E., & Robinson, W. M. (2009). High treatment burden in adults with cystic fibrosis: Challenges to disease self-management. *Journal of Cystic Fibrosis*, *8*(2), 91-96. https://doi.org/https://doi.org/10.1016/j.jcf.2008.09.007

Schneider, E. K., Reyes-Ortega, F., Wilson, J. W., Kotsimbos, T., Keating, D., Li, J., & Velkov, T. (2016). Development of HPLC and LC–MS/MS methods for the analysis of ivacaftor, its major metabolites and

lumacaftor in plasma and sputum of cystic fibrosis patients treated with ORKAMBI or KALYDECO. *Journal of Chromatography B*, *1038*, 57-62. https://doi.org/https://doi.org/10.1016/j.jchromb.2016.10.026

Schneiderman-Walker, J., Wilkes, D. L., Strug, L., Lands, L. C., Pollock, S. L., Selvadurai, H. C., Hay, J., Coates, A. L., & Corey, M. (2005). Sex Differences in Habitual Physical Activity and Lung Function Decline in Children with Cystic Fibrosis. *The Journal of Pediatrics*, *147*(3), 321-326. https://doi.org/https://doi.org/10.1016/j.jpeds.2005.03.043

Schneiderman, J. E., Wilkes, D. L., Atenafu, E. G., Nguyen, T., Wells, G. D., Alarie, N., Tullis, E., Lands, L. C., Coates, A. L., Corey, M., & Ratjen, F. (2014). Longitudinal relationship between physical activity and lung health in patients with cystic fibrosis. *European Respiratory Journal*, *43*(3), 817-823. https://doi.org/10.1183/09031936.00055513

Smyth, R. L., & Rayner, O. (2017). Oral calorie supplements for cystic fibrosis. *Cochrane Database of Systematic Reviews*(5). https://doi.org/10.1002/14651858.CD000406.pub5

Sotiriadou, P., Brouwers, J., & Le, A. (2014). Choosing a qualitative data analysis tool: A comparison of NVivo and Leximancer. *Annals of Leisure Research*, *17*, 218-234. https://doi.org/10.1080/11745398.2014.902292

Southern, K. W., Patel, S., Sinha, I. P., & Nevitt, S. J. (2018). Correctors (specific therapies for class II CFTR mutations) for cystic fibrosis. *Cochrane Database of Systematic Reviews*(8). https://doi.org/10.1002/14651858.CD010966.pub2

Steinkamp, G., & Wiedemann, B. (2002). Relationship between nutritional status and lung function in cystic fibrosis: cross sectional and longitudinal analyses from the German CF quality assurance (CFQA) project. *Thorax*, *57*(7), 596-601. https://doi.org/10.1136/thorax.57.7.596

Sutton, S., Rosenbluth, D., Raghavan, D., Zheng, J., & Jain, R. (2014). Effects of puberty on cystic fibrosis related pulmonary exacerbations in women versus men. *Pediatric Pulmonology*, *49*(1), 28-35. https://doi.org/https://doi.org/10.1002/ppul.22767

Taylor-Cousar, J. L. (2020). CFTR Modulators: Impact on Fertility, Pregnancy, and Lactation in Women with Cystic Fibrosis. *Journal of Clinical Medicine*, *9*(9), 2706. https://www.mdpi.com/2077-0383/9/9/2706

Taylor-Cousar, J. L., Munck, A., McKone, E. F., van der Ent, C. K., Moeller, A., Simard, C., Wang, L. T., Ingenito, E. P., McKee, C., Lu, Y., Lekstrom-Himes, J., & Elborn, J. S. (2017). Tezacaftor–Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del. *New England Journal of Medicine*, *377*(21), 2013-2023. https://doi.org/10.1056/NEJMoa1709846

Tindell, W., Su, A., Oros, S. M., Rayapati, A. O., & Rakesh, G. . (2020). Trikafta and Psychopathology in Cystic Fibrosis: A Case Report. *Psychosomatics*, *61*(6), 735-738. https://doi.org/https://doi.org/10.1016/j.psym.2020.06.021

Tong, A., Sainsbury, P., & Craig, J. (2007). Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *International Journal for Quality in Health Care*, *19*(6), 349-357. https://doi.org/10.1093/intqhc/mzm042

Troosters, T., Langer, D., Vrijsen, B., Segers, J., Wouters, K., Janssens, W., Gosselink, R., Decramer, M., & Dupont, L. (2009). Skeletal muscle weakness, exercise tolerance and physical activity in adults with cystic fibrosis. *European Respiratory Journal*, *33*(1), 99-106. https://doi.org/10.1183/09031936.00091607

UK Cystic Fibrosis Registry. (2020). *UK Cystic Fibrosis Registry 2020 Annual Data Report*. https://www.cysticfibrosis.org.uk/sites/default/files/2022-05/2020%20Annual%20data%20report%20-%20Version%204.pdf

Vaismoradi, M., Jones, J., Turunen, H., & Snelgrove, S. (2016). Theme development in qualitative content analysis and thematic analysis.

Vallières, E., & Elborn, J. (2014). Cystic fibrosis gene mutations: evaluation and assessment of disease severity. *Advances in Genomics and Genetics*, *4*, 161-172. https://doi.org/https://doi.org/10.2147/AGG.S53768

Veit, G., Roldan, A., Hancock, M. A., Da Fonte, D. F., Xu, H., Hussein, M., Frenkiel, S., Matouk, E., Velkov, T., & Lukacs, G. L. (2020). Allosteric folding correction of F508del and rare CFTR mutants by elexacaftor-tezacaftor-ivacaftor (Trikafta) combination. *JCI Insight*, *5*(18). https://doi.org/10.1172/jci.insight.139983

Vertex Pharmaceuticals. (2020). *How does Trikafta work?* Retrieved April 29 from 10.1164/ajrccm-conference.2019.199.1_MeetingAbstracts.A4330

Wainwright, C. E., Elborn, J. S., Ramsey, B. W., Marigowda, G., Huang, X., Cipolli, M., Colombo, C., Davies, J. C., De Boeck, K., Flume, P. A., Konstan, M. W., McColley, S. A., McCoy, K., McKone, E. F., Munck, A., Ratjen, F., Rowe, S. M., Waltz, D., & Boyle, M. P. (2015). Lumacaftor–Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del CFTR. *New England Journal of Medicine*, *373*(3), 220-231. https://doi.org/10.1056/NEJMoa1409547

Walker, S., Flume, P., McNamara, J., Solomon, M., Chilvers, M., Chmiel, J., Harris, R. S., Haseltine, E., Stiles, D., Li, C., Ahluwalia, N., Zhou, H., Owen, C. A., & Sawicki, G. (2019). A phase 3 study of tezacaftor in combination with ivacaftor in children aged 6 through 11 years with cystic fibrosis. *Journal of Cystic Fibrosis*, *18*(5), 708-713. https://doi.org/10.1016/j.jcf.2019.06.009

Walters, S. (2001). Sex differences in weight perception and nutritional behaviour in adults with cystic fibrosis [https://doi.org/10.1046/j.1365-277X.2001.00274.x]. *Journal of Human Nutrition and Dietetics*, *14*(2),

83-91. https://doi.org/https://doi.org/10.1046/j.1365-277X.2001.00274.x

West, N. E., Kazmerski, T. M., Taylor-Cousar, J. L., Tangpricha, V., Pearson, K., Aitken, M. L., & Jain, R. (2022). Optimizing sexual and reproductive health across the lifespan in people with cystic fibrosis. *Pediatric Pulmonology*, *57*(S1), S89-S100. https://doi.org/https://doi.org/10.1002/ppul.25703

Wilkes, D. L., Schneiderman, J. E., Nguyen, T., Heale, L., Moola, F., Ratjen, F., Coates, A. L., & Wells, G. D. (2009). Exercise and physical activity in children with cystic fibrosis. *Paediatric Respiratory Reviews*, *10*(3), 105-109. https://doi.org/https://doi.org/10.1016/j.prrv.2009.04.001

Zamawe, F. C. (2015). The Implication of Using NVivo Software in Qualitative Data Analysis: Evidence-Based Reflections. *Malawi Med J*, *27*(1), 13-15. https://doi.org/10.4314/mmj.v27i1.4

Zemanick, E. T., Taylor-Cousar, J. L., Davies, J., Gibson, R. L., Mall, M. A., McKone, E. F., McNally, P., Ramsey, B. W., Rayment, J. H., Rowe, S. M., Tullis, E., Ahluwalia, N., Chu, C., Ho, T., Moskowitz, S. M., Noel, S., Tian, S., Waltz, D., Weinstock, T. G., . . . McColley, S. A. (2021). A Phase 3 Open-Label Study of Elexacaftor/Tezacaftor/Ivacaftor in Children 6 through 11 Years of Age with Cystic Fibrosis and at Least One F508del Allele. *American Journal of Respiratory and Critical Care Medicine*, *203*(12), 1522-1532. https://doi.org/10.1164/rccm.202102-0509OC

Zhang, L., Albon, D., Jones, M., & Bruschwein, H. (2022). Impact of elexacaftor/tezacaftor/ivacaftor on depression and anxiety in cystic fibrosis. *Therapeutic Advances in Respiratory Disease*, *16*, 17534666221144211. https://doi.org/10.1177/17534666221144211

Appendices

Appendix A: Parent/Carer Information Sheet

PARENT 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 and their carers

Contact Details:

Bethany Cope (Masters Student)

Email: [redacted]

Dr Melitta McNarry (Supervisor)

Email: [redacted]

Telephone: [redacted]

We would like to invite you and your child 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 and your child. So please read and think about this information sheet very carefully. Our child can take part even if you don't want to do so yourself or don't have the time.

If something isn't clear or you have more questions you can give us a call or email us and we can discuss it with you and your child. If you don't want your child to take part, that is fine! Their 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 are aware of the positive effects the new drug can have on lung function and your child's day to day life, but we want to understand more from yourself and your child's perspective on how this may have changed their life in anyway and how they do things differently on Kaftrio compared to when they were not taking it.

Why have I been chosen?

You and your child have been invited to take part because they are aged 6+ years, have CF and are eligible to take the new Kaftrio medication.

What will happen to me if I take part?

You and your child will be asked if you would like to take part in separate short interviews so we can get an idea of your feelings and emotions about CF and Kaftrio. This interview will be via a video link, like Zoom. As a parent, you are welcome to be there for your child's interview but it is not a requirement for your child to be able to take part in the study. There are no right or wrong answers to the interview, we are just interested what you and your child think!

Then, once your child has started on Kaftrio, we will ask that you both to take part in another interview so we can see how they feel and what you both think as time passes.

The interviews will be done online so you and your child 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 you or your child may become upset when talking about their CF, if this does occur then we have measures in place and specialists on hand to help. Remember, you and your child are free to withdraw at any point and one of you can withdraw whilst the other keeps taking part.

What are the possible benefits of taking part?

The benefits are that you can help the whole CF community understand what to expect on

Kaftrio. For those who have not started or are waiting to start it, they will have a good idea of the good things, the bad things and maybe some things that you and your child did not expect. This research will also help your child's clinical care team to build management strategies for some of the negatives to Kaftrio.

Will my taking part in the study be kept confidential?

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

Data Protection and Confidentiality

You and your child's 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 both will be kept strictly confidential. The 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/assent information will be kept separately from your child's 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 for you and your child to take part in the study your child will be assigned a unique person ID number, thus it will not be possible to identify and remove you and your child's 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 and your child will be unable to withdraw the 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.

You and your child's 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 verbal consent prior to interview.

The legal basis that we will rely on to process you and your child's 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 you and your child's personal information, to object to the processing of you and your child's personal information, to rectify, to erase, to restrict and to port you and your child's 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 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 [redacted]. 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 B: Participant Information Sheet

ADULT CF 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 and their carers

Contact Details:

Bethany Cope
Email:
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 CF 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 (for those under 18). 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 [redacted]. 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 C: Child Information Sheet

Child Information Sheet

(Version 1, 30/08/2021)

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

Contact Details:

Bethany Cope (Masters Student)
Email: [redacted]
Dr Melitta McNarry (Supervisor)
Email: [redacted]
Telephone: [redacted]

Thank you for looking into this project! We would like for you to take part in our study. First there's this sheet for you to read to make sure you are happy to take part so please read it carefully.

If you have any questions make sure to ask! Your parents can contact us using the contact details above.

If you are happy to take part thank you. If you don't want to take part that is fine too.

What is the purpose of the study?

Kaftrio is an exciting new treatment! People have looked into Kaftrio and adults but now children can have Kaftrio. So, we want to know what children 6 years and over think about Kaftrio, what hopes they have for how it might affect their life and how they do things.

What will taking part involve?

If you are happy to take part, we would like for you to take part in a short interview online through Zoom so it can all be done at home! We want to talk to you about your CF and what you think about Kaftrio. Your parents can be there too if you want them to be! Then once you have started taking Kaftrio there will be another interview to see how you feel and if it has changed. Remember this study is all about what you think and so there are no wrong or right answers.

What are the possible disadvantages and/or risks of taking part?

We will be asking you questions about your CF and Kaftrio and you may find that you do not actually like talking about your CF. If this upsets you in any way, we can stop the study and get in touch with some specialists that will be there to help you.

What are the possible benefits of taking part?

You will be able to talk about how you are feeling and see if you feel different after taking Kaftrio. It will also help your doctors know how you feel so they can do a better job. It can also help the whole CF community have a better idea of the good things, the bad things and maybe some things that you didn't know about Kaftrio.

What if I want to stop taking part?

You can stop taking part at any time. Just make sure you or your carer let us know.

Who has reviewed this study?

Studies are looked at by a clever group of people and this study has been approved by the College of Engineering Research Ethics and Governance Committee (approval number: MN22-10-20b)

Will my taking part in the study be kept confidential?

All of your information (like your name) will be kept private with only people that are in charge of the study being able to see it. After the study is done this information will be deleted. You will also be assigned a special number so no one knows which results are yours.

Thank you!