Understanding the impact of elexacaftor-tezacaftor-ivacaftor treatment on respiratory disease in people with cystic fibrosis:

The change in physiotherapy treatment burden and defining pulmonary exacerbations.

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Abstract

Introduction: Cystic fibrosis (CF) is the most common fatal genetic autosomal recessive disease in Caucasians. Although CF is a multisystem disorder, its respiratory complications account for the majority of morbidity and mortality. The management of lung disease in CF has developed over the years. As people with CF grow older, the amount of treatment required usually increases, and treatment burden is a major issue. Airway clearance techniques (ACTs) and nebulised mucolytics, which play a vital role in CF management, are known to be associated with the highest burden among the different treatments. The introduction of elexacaftor-tezacaftor-ivacaftor (ETI) treatment has likely led to a change in treatment needs. In addition, despite the improvement in respiratory symptoms associated with ETI, pulmonary exacerbation (PEx) remains important clinically. However, there is a lack of consensus on definitions of PEx.

Aims and methods: To understand the changes in treatment burden after ETI, a semi-structured qualitative interview with children, their families, and healthcare professionals were conducted to explore their opinions and attitudes toward ACTs and mucolytic nebulisers. In addition, a retrospective analysis of the data from Great North Children's Hospital (GNCH) was performed to analyse the change in physiotherapy treatment and other clinical outcomes after one year of ETI. Finally, to investigate the definitions reported for PEx, a scoping review of the literature were performed.

Results: Quality of life, simplifying treatment – hopes and fears, and 'Kaftrio is a game-changer" were three themes developed from the interviews which capture participants' experiences. From the retrospective study, a statistically significant decline in the use of ACTs and nebulised mucolytics and an improvement in exercise capacity were found. In addition, lung function and weight showed a statistically significant improvement. From the scoping review analyses, two themes were developed which highlight the PEx definitions reported in the literature. The first theme is objective – based on criteria, and the second theme is subjective- based on the clinician's judgment.

Conclusion: These findings provide a comprehensive understanding of the changes after ETI in physiotherapy treatment, including ACTs, nebulised mucolytics, and exercise using multimethod designs. In addition, the scoping review findings highlighted the heterogeneity in definitions reported in the literature and helped understand the components used to define them.

Dedication:

To my Mum, Latifah Alabdulqader, who waited all these years for her prayer to come true.

To my dear husband, Mosaab – whom I owe so much: the love, compassion, and for putting up with a long-distance marriage.

To my daughters, Seba and Lama, who found themselves in a battle they did not choose.

You were all part of this.

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My thanks go to my family, the real treasure of my life.
Thank you to my mum Latifah. There are no words to describe my love and gratitude for you. Your sacrifices, both big and small, have shaped me into the person I am today.

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This journey would not have been accomplished without the support of my friends. Being away from my home country and family was a challenge. However, I am blessed that Allah granted me a second family.

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Last and foremost, a huge thanks to my beloved country, Saudi Arabia, for the fully funded scholarship, which allows me to pursue my dream.

To everyone who believes in me and supports me, I say thank you!

Declaration

This thesis is submitted for the degree of Doctor of Philosophy to Newcastle University. I declare that the work presented in this thesis is my own, and I was responsible for the data collection, analysis, and interpretation under the supervision of my PhD supervisors.

Academic achievements during this PhD

Publication directly related to my PhD project:

Almulhem, M., Harnett, N., Graham, S., Haq, I., Visram, S., Ward, C. and 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', British Medical Journal Open Respiratory Research, 9(1), pp. e001420.

Poster presentations:

Almulhem, M., Ward, C., Harnett, N., Graham, S., Visram, S. and Brodlie, M., 2022. P69 The impact of elexacaftor-tezacaftor-ivacaftor (ETI, Kaftrio) treatment on the opinions of children and young people with cystic fibrosis about physiotherapy and nebulised treatment: a qualitative study.

Won a prize for the following poster presentation at NUTCRI live 2022 at Newcastle University:

A qualitative study to explore the impact of Ivacaftor-tezacaftor-elexacaftor (Kaftrio) treatment on the opinions of children and young people with cystic fibrosis about physiotherapy and nebulised treatment: the TEMPO study.

Oral presentation

Present the previous qualitative paper in European Cystic Fibrosis Society- Exercise working group – online journal club.

Publication not directly related to my PhD project:

Haq, I., Almulhem, M., Soars, S., Poulton, D. and Brodlie, M. (2022) 'Precision medicine based on CFTR genotype for people with cystic fibrosis', *Pharmacogenomics and Personalized Medicine,* 15, pp. 91–104.

Workshops attended:

1. 5-day course Oxford Qualitative Course: Introduction to Qualitative Research Methods Course.
2. A systematic review workshop.
3. How to search in different databases workshop.
4. NVIVO training.

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ACPT	Active cycle of breathing techniques
ACTs	Airway clearance techniques
ASL	Airway surface liquid
B. cepacia	Burkholderia cepacia
BMI	Body mass index
CF	Cystic fibrosis
CFF	Cf foundation
CFFPR	Cystic fibrosis Foundation Patient Registry
CFTR	Cystic *fibrosis transmembrane conductance regulator*
CFQ	CF Questionnaire-revised
Cl^-	Chloride
cwCF	Children with CF
ECFS	European CF society
EMA	European medicines agency
EPIC	Early pseudomonas infection control
ESCF	Epidemiologic Study of Cystic Fibrosis
ETI	Elexacaftor-tezacaftor-ivacaftor
FDA	Food and Drug Administration
FEV1	Forced expiratory volume in the first second
FVC	Forced vital capacity
GLI	Global lung function initiative
GNCH	Great north children's hospital
HCPs	Healthcare professionals
HEMT	Highly effective modulator therapy
H. influenzae	*Haemophilus influenzae*
HRQoL	Health-Related Quality of Life
IPA	Interpretative phenomenological analysis
IQR	Interquartile ranges
ISWT	Incremental shuttle walk test
IQR	Interquartile ranges
IV	Intravenous

MDT	Multidisciplinary team
MRSA	Methicillin-resistant Staphylococcus aureus
MSAS	Memorial symptom assessment scale
MST	Modified shuttle test
MSSA	Methicillin-sensitive Staphylococcus aureus
NHS	National health service
NIV	Non-invasive ventilation
NTM	Nontuberculous mycobacterium
P. aeruginosa	*Pseudomonas aeruginosa*
PEP	Positive expiratory pressure
PES	Pulmonary exacerbation score
PEx	Pulmonary exacerbations
PIS	Patient information sheet
ppFEV1	Percent-predicted forced expiratory volume in 1 second
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
pwCF	People with CF
RCTs	Randomised controlled trials
R&D	Research and development
S. aureus	*Staphylococcus aureus*
SD	Standard deviation
S. maltophilia	Stenotrophomonas maltophilia
SPEX	Seattle pulmonary exacerbation score
SpO_2	Oxygen saturations
SPSS	Statistical Package for the Social Sciences
TA	Thematic analysis
VO2 peak	Peak oxygen consumption
WHO	World health organisation
6MWT	Six-minute walk test

COVID-19 statement.

I started my PhD program six months before the pandemic, which impacted my original aims and objectives. Originally, my objectives were as follows:

1. Complete a scoping review of the definitions of a 'pulmonary exacerbation' in people with CF used in the scientific literature

2. To develop a standardised definition of pulmonary exacerbation in relevant age groups for use in future clinical research and practice

3. To investigate the feasibility of MR ventilation imaging in young people (adolescents) with CF in Newcastle for research use

4. To describe MR ventilation properties (percentage lung ventilated volume, spatial distribution of ventilation defects) in a selected sample of young people with cystic fibrosis

5. To generate pilot data to investigate the effect of airway clearance techniques on MR ventilation findings in young people with CF (measuring the change in lung ventilated volume and distribution of ventilation defects following airway clearance techniques).

Despite the restriction of COVID-19, I was able to continue working on the scoping review and, at the same time, preparing the protocol and other documents to apply for ethical approval for the MRI study. Unfortunately, after the third lockdown, which was announced in January 2021 (my 2nd year), and constraints on clinical research and uncertainty of the upcoming lockdowns, I decided to change the project to something deliverable despite COVID-19 and the associated uncertainties about the future impact of COVID-19. With help and guidance from my supervisor, I changed it to the current aim, and I started again preparing the second protocol and other relevant documents for ethical approval.

The scoping review objective was planned to be followed by a collaboration with the European Cystic Fibrosis Society- pulmonary exacerbation group (ECFS) to develop definitions using a Delphi survey targeting practitioners, patients, and families. Again, due to COVID-19 and the changes accompanying the introduction of elexacaftor-tezacaftor-ivacaftor, ECFS's priorities changed at that moment, and they decided to postpone this work.

Chapter 1. Introduction

1.1 Overview

This chapter lays the necessary foundation for this thesis as a whole. It starts with a review of the literature and then highlights the gaps in the existing literature. Following this, the aims and objectives of this thesis are stated. Finally, the structure of the thesis is outlined, providing a brief overview of each of the following chapters.

1.2 What is cystic fibrosis?

Cystic fibrosis (CF) is an autosomal, recessive, genetic disease affecting multiple body systems (Shteinberg, Haq, Polineni and Davies, 2021). CF is most common in Caucasian populations, although it affects all races and ethnicities. It is the most common fatal, genetic, autosomal, recessive disease in Caucasians (Scotet, L'Hostis and Férec, 2020). The precise number of people with CF (pwCF) worldwide is unknown. In the UK, CF affects almost 11,000 people, and 1 out of 25 is a carrier for a *cystic fibrosis transmembrane conductance regulator* (*CFTR*) variant (Cystic Fibrosis Trust, 2023b; European Cystic Fibrosis Society, 2021). Major improvements in therapeutic development, advances in care, and early diagnosis have significantly altered the life expectancy of pwCF. As a result, previously, CF was a childhood disease, but the latest registry data shows that 54% of pwCF in Europe are adults (European Cystic Fibrosis Society, 2021). In particular, the predicted median survival age in the UK has increased to 56.1 years versus 43.5 years in 2011 (Cystic Fibrosis Trust, 2023a). According to a recent study, it is expected that the median survival for pwCF treated with elexacaftor-tezacaftor-ivacaftor (ETI) will increase to 71.6 years; while for those who initiated ETI between the ages of 12 and 17 the projected median survival rate is estimated to reach 82.5 years (Lopez *et al.*, 2023).

1.3 The basic defect in cystic fibrosis – genetics and pathophysiology

CF is caused by a variant in the CFTR gene located on chromosome 7. This gene is responsible for encoding the CFTR protein, which is expressed by epithelial cells in several organs (Haq *et al.*, 2022; Zielenski *et al.*, 1991). Therefore, a variant in this gene will affect multiple organ systems such as the sweat gland, respiratory, pancreas, and reproductive systems. The CFTR protein functions as an ion channel for chloride (Cl^-) and bicarbonate that controls water secretion and absorption at the apical surface of epithelial cells. *CFTR* variants will cause a

dysfunction in this ion transportation. This movement is essential to maintain water homeostasis and preserve the normal viscosity of mucus (Haq *et al.*, 2022; Sheppard and Welsh, 1999). In the lung, the disrupted ion movement affects the homeostasis of airway surface liquid (ASL), which is essential to support ciliary stability and functioning. The consequence is a thick, mucopurulent mucus and decreased mucociliary transport, resulting in infection and inflammation (Button *et al.*, 2012; Shteinberg, Haq, Polineni and Davies, 2021).

While a relatively short list of well-defined *CFTR* variants are known to cause CF disease, more than 2,000 variants have been identified *('Clinical and Functional Translation of CFTR,' 2023*). Individuals with CF can have different *CFTR* variants on each allele, resulting in thousands of potential CFTR genotype combinations. Most recognised variants fall under the six classes categorised based on their cellular phenotype, as described in **Table 1** and **Figure 1** (Haq *et al.*, 2022).

Table 1. Classes of CFTR disease-causing variants.

Variant class	Description of defect	Examples
Class I	Characterised by nonsense, frameshift or abnormal splicing of mRNA which leads to no protein synthesis.	G542X W1282X R553X
Class II	Characterised by folding or maturation defects resulting in a near-absence of mature CFTR protein at the apical cell membrane.	F508del N1303K I507del
Class III	Affects the Cl^- channel gating/regulation as a result of ineffectual binding of nucleotide.	G551D, S549R G1349D
Class IV	Conductance defect where the channels are open but a reduced Cl^- current is generated.	R117H D1152H R347P
Class V	The amount of produced protein is diminished due to transcriptional regulation limitation.	3272-26A→G, 3849+10 kg C→T
Class VI	Stability defects at the channel surface leading to a reduction of the CFTR protein.	C 120del123, rPhe580del

Class I, II, and III variants are associated with a classical and more severe phenotype and pwCF with two copies of these variants usually have almost no residual CFTR function. In class II, F508del, also known as ΔF508, is the most common mutation in pwCF, accounting for two-thirds of all *CFTR* variants (Bobadilla, Macek, Fine and Farrell, 2002). In contrast, class IV, V, and VI variants are associated with milder disease and may have some residual CFTR function (Lopes-Pacheco, 2020).

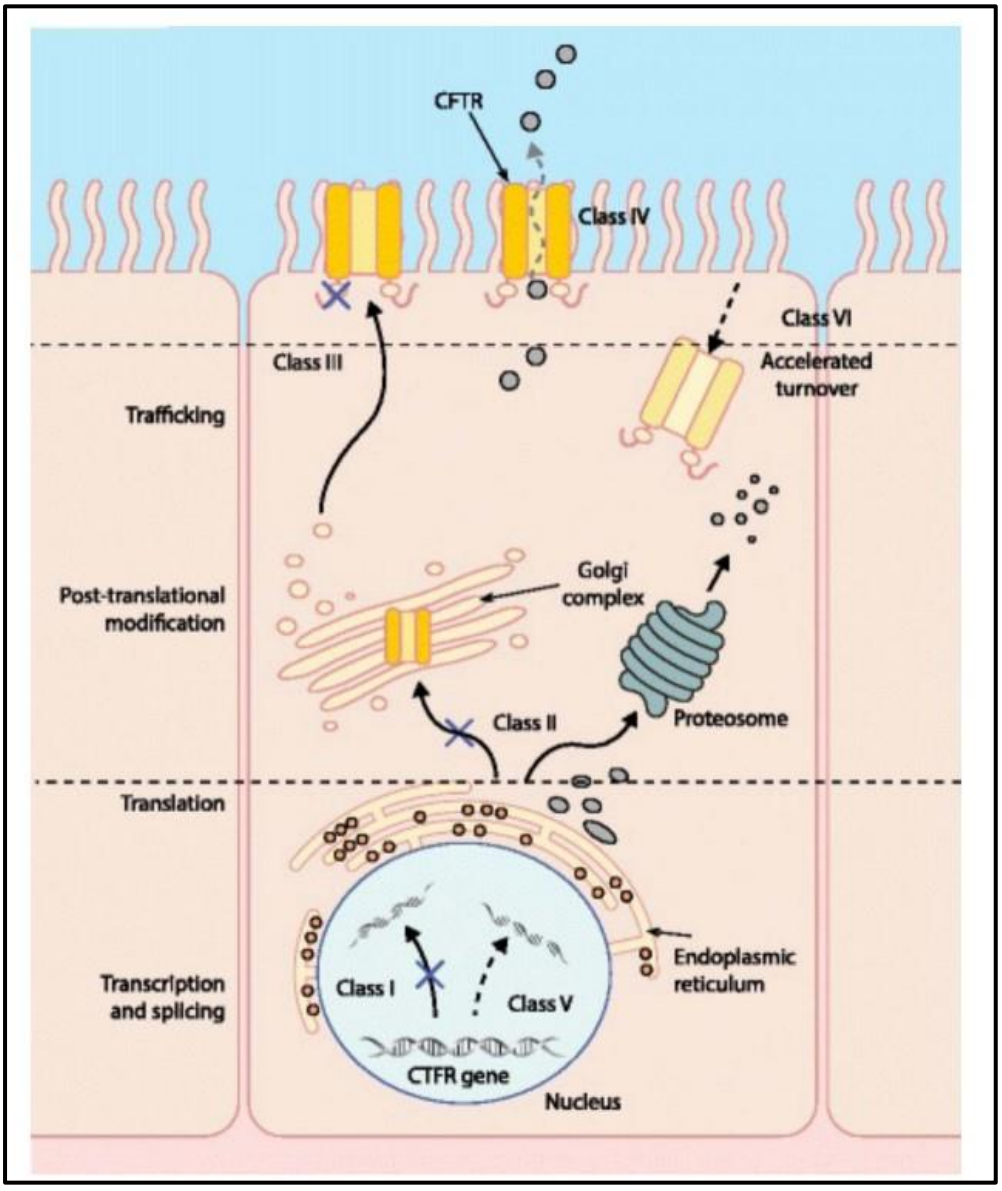


Figure 1. Schematic diagram of different CFTR variants classes

Resource (Haq *et al.*, 2022).

1.4 Diagnostic testing

Diagnostic criteria for CF include disease-related clinical signs and symptoms and objective evidence of CFTR dysfunction (Farrell *et al.*, 2017).

The diagnosis of CF via newborn screening is usually made shortly after birth and is now in place in 26 countries, including the UK (Castellani *et al.*, 2009). Most newborn screening methods include the measurement of immunoreactive trypsinogen (IRT) from a blood spot, followed by DNA testing for CFTR variants (Cystic Fibrosis Trust, 2023a).

A sweat test is performed to confirm the diagnosis once an individual presents with a positive result of two variants. CF is caused by dysfunction of CFTR and the reabsorption of electrolytes into sweat ducts is disrupted. As a result, the chloride and sodium levels in sweat are increased. A sweat test analysing chloride levels in sweat is the primary diagnostic test for CF and has established guidelines (Farrell *et al.*, 2017). Chloride levels above 60 mmol/L are considered elevated and confirm a diagnosis of CF. If the level of chloride is between 30 and 59 mmol/L, it is considered intermediate, which requires further measurement and follow up (Farrell *et al.*, 2017).

1.5 Clinical features of cystic fibrosis

Symptoms associated with CF are present throughout life, with common features between patients but also individual variation in phenotype. The variability in clinical presentation and disease progression can be attributed to the variants in the *CFTR* gene, which lead to a range of protein dysfunction, but also other genetic and environmental factors (Sepahzad, Morris-Rosendahl and Davies, 2021). Although CF is a multisystem disorder, its respiratory complications are responsible for most morbidity and mortality in pwCF (Cystic Fibrosis Trust, 2023a).

1.5.1 Lung disease and complications

Typical lung manifestations involve a persistent, productive cough, hyperinflation of lung fields on chest radiograph, and lung function test findings indicative of obstructive airway disease. As the disease progresses, a repeated cycle of infection and inflammation occurs and bronchiectasis develops (Ong and Ramsey, 2023).

In the paediatric population diagnosed with CF, recurrent respiratory tract infections caused by viral and bacterial pathogens, including *Haemophilus influenzae* (*H. influenzae*) and *Staphylococcus aureus* (*S. aureus*), lead to both direct and indirect damage due to the inflammatory reaction triggered by airway infection (Gilligan, 2014). This cycle of infection and inflammation leads to progressive bronchiectasis. This progresses to infection dominated by *Pseudomonas aeruginosa* (*P. aeruginosa)*, which increases in prevalence with age. Several of these microorganisms are prevalent in the natural surroundings and are only linked to human infection in cases where the individual's immune system is weakened or the protective layer of the host's epithelium is compromised (Parkins and Floto, 2015). Latest registry data from the Cystic Fibrosis Trust (2023a) shows the prevalence of different organism at different ages, as shown in **Figure 2**. Chronic infection and inflammation are associated with a deterioration in lung function, as evidenced by a reduction in the forced expiratory volume in the first second (FEV1) and forced vital capacity (FVC) (Döring and Hoiby, 2004). According to the latest report from the UK CF registry, these pulmonary complications are responsible for about 53.3% of CF-related deaths in the UK (Cystic Fibrosis Trust, 2023a).

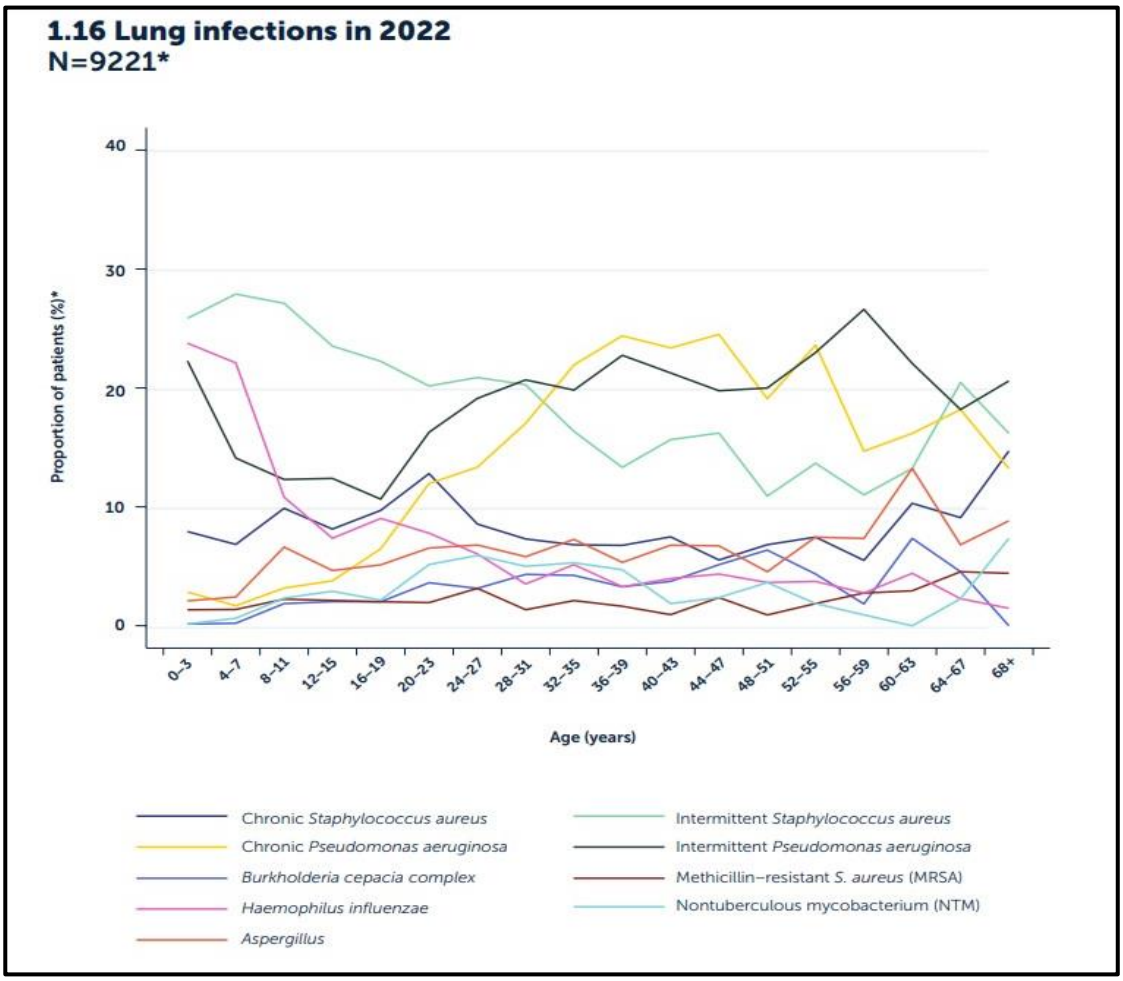


Figure 2. Organism prevalence in different age

Resource (Cystic Fibrosis Trust, 2023a).

1.5.1.1 Pulmonary exacerbations

CF lung disease is characterised by episodes of worsening pulmonary signs and symptoms, particularly cough and sputum production that require treatment, known as pulmonary exacerbations (PEx) (Goss and Burns, 2007). PEx are associated with dyspnoea, fatigue, decreased exercise tolerance, and systemic symptoms of an acute-phase inflammatory response (Abbott *et al.*, 2009; Abbott *et al.*, 2012). The pathophysiology of CF PEx has not been fully elucidated, although they are associated with increased airway infection and inflammation (Ferkol, Rosenfeld and Milla, 2006). Episodes of PEx usually develop over several days and are treated with antibiotics and increased airway clearance techniques (ACTs) (Flume *et al.*, 2009a).

1.5.1.1.1 Clinical importance of pulmonary exacerbations

Exacerbations have been proven to reduce lung function acutely, and many patients fail to recover to baseline lung function despite treatment ((Sanders *et al.*, 2010a; Sanders *et al.*, 2010b). Increases in exacerbation rates affect CF patients' survival (Liou *et al.*, 2001). Additionally, PEx have been associated with decreased quality of life in both psychosocial and physical domains (Britto *et al.*, 2002; Flume *et al.*, 2019). In terms of economic aspects, exacerbations increase healthcare costs due to the need for intravenous (IV) treatment and hospitalisation (Rubin *et al.*, 2017). PEx necessitating hospitalisation impose a significant burden on parents and carers in terms of loss of work productivity, social impact, and low mental health (Suthoff *et al.*, 2019).

Due to the clinical importance of PEx, reduction in PEx rate has been recognised as a significant clinical efficacy endpoint for CF therapy trials (VanDevanter and Konstan, 2012). PEx served as a key outcome measure in CF clinical trials for treatments such as dornase alfa (Fuchs *et al.*, 1994), tobramycin (Ramsey *et al.*, 1999), azithromycin (Saiman *et al.*, 2003), hypertonic saline (Elkins *et al.*, 2006), and CFTR modulators (Heijerman *et al.*, 2019; Middleton *et al.*, 2019).

1.5.1.1.2 Pulmonary exacerbation definitions

Despite this significance, a universally standardised definition is currently absent, leading to a lack of consensus among clinicians and heterogeneity between studies. There is a lack of consensus on what clinical presentations define PEx, what thresholds require interventions, and what those interventions might be. Using standardised and valid criteria holds significant importance in ensuring the accuracy of diagnosing a PEx, assessing its severity and comparing results between different clinical trials (Ellaffi *et al.*, 2005). This is crucial as it enables tracking changes in the disease epidemiology and allows meta-analysis of results.

Awareness of establishing PEx definitions to be universally used in clinical trials is not recent, having first been described in 1994 by the CF Foundation (CFF) (Ramsey and Boat, 1994). Although PEx play a critical role in both research and the clinical treatment areas of CF, a single definition is not likely to fit across different ages of pwCF. For this reason, formulating a standardised definition for each age group by reviewing the definitions used in research and then undertaking a consensus process will be valuable for future research and practice.

The formulation of a precise exacerbation definition is impacted by several factors, including the fluctuation of daily symptoms, the limited correlation between biomarkers and clinical outcomes, and the variations in hospital admission and antibiotic administration protocols among CF centres and healthcare facilities (Rubin *et al.*, 2017).

CFTR modulators have led to a significant reduction in the rate of PEx (Heijerman *et al.*, 2019; Middleton *et al.*, 2019). However, pwCF still experience episodes of PEx in addition to those untreated with CFTR modulators. There is renewed interest regarding what defines a PEx in the era of CFTR modulators.

1.6 Approach to treatment

CF is a multisystem condition, which makes it a complex disease to treat. A multidisciplinary team including physicians, nurses, physiotherapists, dietitians, psychologists, and social workers is recommended to monitor disease progression and deliver effective care for this life-long condition (Conway *et al.*, 2014). Annual screening, monitoring for comorbidities, and measuring the trends in nutrition status, lung health, and PEx are all parts of CF care (Conway *et al.*, 2014).

The treatment approach has evolved dramatically over the years. Previously, treatment focused solely on reducing the symptoms caused by CFTR dysfunction. This included various treatments such as ACTs and mucociliary clearance drugs for mucus obstructions, antibiotics for infections, and pancreatic enzyme replacement therapy for malabsorption (Flume *et al.*, 2009b). All of these treatments incrementally improved life expectancy and overall quality of life. However, following the discovery of the *CFTR* gene in 1989, scientists worked on finding a therapy targeting the underlying cause of CF and improving the function of the mutated CFTR protein (Kreindler, 2010). This led to the development of CFTR modulators which changed the care for pwCF who are eligible for them. **Figure 3** shows an overview of the approach to lung treatment.

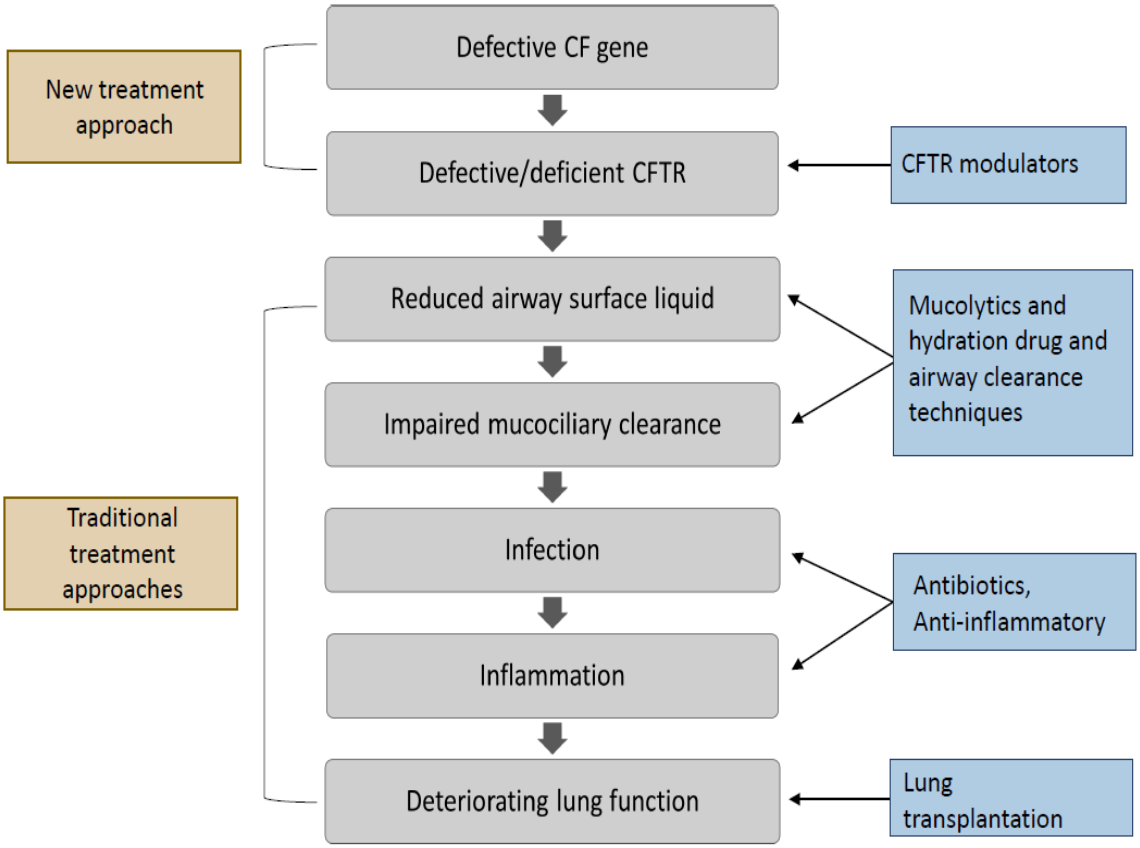


Figure 3. Overview of lung treatment approach.

Adapted from: (Agent and Parrott, 2015)

1.6.1 Symptomatic treatment of the lung disease.

Managing lung disease in CF involves a proactive approach to deal with acute symptoms such as cough and sputum production and to maintain lung health by preventing infection and optimising airway clearance (Chin, Aaron and Bell, 2017).

1.6.1.1 Physical therapy

ACTs are one of the key pulmonary management techniques used in pwCF, and the treatment starts early, after the CF diagnosis, and continues for the rest of the patient's life (Cystic Fibrosis Trust, 2020a). These techniques target the mucus and enhance mucociliary function to help move it upwards and expectorate it from the airways by coughing. Numerous modalities of ACTs can be used based on age and preference, such as breathing techniques, positive expiratory pressure (PEP) devices, oscillatory devices, external percussion and vibration, or non-invasive ventilation (NIV). Although ACTs have been widely used in the management of CF, few randomised clinical trials support their use or compare the efficacy of one method over another. According to the CFF guidelines (Flume *et al.*, 2009b) and the latest Cystic Fibrosis Trust (2020a), ACTs are recommended for regular use in all ages. However, they do not recommend one modality over another, instead it should be personalised. During illness and PEx, the frequency of ACTs should be increased to maintain lung health (Castellani *et al.*, 2018).

In addition to using ACTs for sputum expectoration, mucolytic and hydration therapies are used to alter the viscosity of the sputum and facilitate its expectoration (Chin, Aaron and Bell, 2017). Dornase alfa is a mucolytic treatment that helps to degrade the DNA strands into shorter ones, which makes the sputum less viscous. Dornase alfa has been shown to improve lung function and reduce PEx regardless of disease severity (Yang and Montgomery, 2021). It is recommended as part of maintenance therapy in conjunction with ACTs (Castellani *et al.*, 2018; Mogayzel *et al.*, 2013).

Hypertonic saline and mannitol are inhaled hydration therapies that help rehydrate viscous sputum to facilitate expectoration. Some studies have proved the efficacy of regular use of hypertonic saline in increasing lung function and reducing exacerbation in CF patients 12 years old and over (Elkins *et al.*, 2006; Wark and McDonald, 2018), while other studies in infants and children with CF (cwCF) who are younger than 6 years old show no differences in lung function

and PEx (Rosenfeld *et al.*, 2012). Using hypertonic saline is recommended as part of maintenance therapy in conjunction with ACTs and is supported by guidelines (Castellani *et al.*, 2018; Mogayzel *et al.*, 2013). Mannitol is another alternative hydration therapy available in dry powder, improving adult lung function (Nevitt, Thornton, Murray and Dwyer, 2020). Hydration therapy may irritate the airways and may require pre-treatment with a bronchodilator and initial tolerability testing. According to the latest Cystic Fibrosis Trust (2020a) guidelines, it is recommended for pwCF who have clinical evidence of lung disease to start with dornase alfa as the first choice of mucoactive agent. If a clinical evaluation indicates an insufficient response to dornase alfa, both dornase alfa and hypertonic saline or hypertonic saline alone is recommended.

In addition, regular exercise and physical activity are encouraged and should be part of physiotherapy management in pwCF, irrespective of age and disease severity (Cystic Fibrosis Trust, 2020a; Radtke *et al.*, 2022). Regular physical activity has notable physical benefits, which include a slower rate of lung function decline (Schneiderman-Walker *et al.*, 2000), enhanced airway clearance (Dwyer *et al.*, 2019) and exercise capacity (Hebestreit *et al.*, 2010), and improved quality of life (Klijn *et al.*, 2004).

1.6.1.2 Antibiotic therapy

Airway infection in CF can be classified into early, intermittent, and chronic infection. Antibiotic therapy aims to prevent, eradicate, or control airway infection. There are several antibiotic treatments, and the choice of drug depends on the pathogen found in the lung. Many types of bacteria, like *S. aureus*, *H. influenzae, P. aeruginosa, and Burkholderia complex*, are possible infection causes. The most common pathogen found in cwCF is *S. aureus*, while *P. aeruginosa* is more common in adults (Cystic Fibrosis Trust, 2023a).

Prophylactic treatment aims to decrease the prevalence of infection and prevent secondary bacterial infection. *S. aureus* prophylaxis, flucloxacillin, is often used in the early childhood stage (Castellani *et al.*, 2018). An ongoing trial in the UK aims to identify the potential association between long-term anti-staphylococcal prophylaxis and risk of developing *P. aeruginosa* infection (CF START, no date).

It is recommended that respiratory samples be collected for bacterial culture analysis from pwCF during their routine appointments and the appropriate treatment prescribed if needed

(Cystic Fibrosis Trust, 2009). Once *P. aeruginosa* is found in a respiratory culture, an early eradication regimen is recommended. Early infection with *P. aeruginosa* is a major predictor of mortality and associated with lower FEV1, increased risk of continued *P. aeruginosa* infection, and increased hospitalisation for acute PEx (Emerson *et al.*, 2002). Anti-pseudomonal treatment can be administered via inhaled, oral, or IV routes. There is insufficient evidence to differentiate between the best combinations, dosage, or length of treatment courses (Castellani *et al.*, 2018; Hewer and Smyth, 2017; Hewer *et al.*, 2020).
Once eradication fails and chronic infection with *P. aeruginosa* develops, long-term inhaled suppressive treatment is recommended to prevent the progression of exacerbation and lung damage. These inhaled antibiotics are typically cycled to reduce selective pressure for antibiotic resistance (Nichols *et al.*, 2019). Inhaled anti-pseudomonal antibiotics have been shown to improve lung function and reduce exacerbations (Smith and Rowbotham, 2022).

Airway inflammation is part of CF pulmonary disease, and anti-inflammatory therapy aims to reduce airway inflammation and airway damage. Although several anti-inflammatory treatments have been examined, including ibuprofen, oral and inhaled corticosteroids, and leukotriene antagonists, few are used routinely (Castellani *et al.*, 2018).

The antibiotic azithromycin, which has anti-inflammatory properties although not directly antipseudomonal, is also sometimes prescribed (Castellani *et al.*, 2018). Chronic use of azithromycin in adults with CF has been found to reduce the frequency of PEx, rate of decline in lung function, and improve quality of life in those with chronic *P. aeruginosa* infection (Nichols *et al.*, 2020; Saiman *et al.*, 2003; Wolter *et al.*, 2002).

1.6.2 Cystic fibrosis transmembrane conductance regulator modulator therapy

CF care has entered a new era with the development of CFTR modulator therapies. These small-molecule drugs target the underlying cause of CF and enhance CFTR protein function, thereby improving key clinical outcomes (Flume *et al.*, 2012; Heijerman *et al.*, 2019).

There are two classes of approved modulators, and depending on the targeted defect, they have different modes of action (Haq *et al.*, 2022). **Potentiators** are molecules capable of enhancing or restoring *CFTR* channel gating; hence, they are effective in class III and IV variants that cause gating defects. *CFTR* **correctors** target *CFTR* protein folding and trafficking

to the cell membrane (Haq *et al.*, 2022). In the UK, there are four modulators and combined modulators approved for patients depending on the type of CFTR variant they have:

1. Kalydeco (ivacaftor) was the first potentiator approved by the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), and the national health service (NHS) has now approved it for pwCF aged 4 months and older who are heterozygous for R117H and nine gating variants (NHS England, 2021).
2. Orkambi (lumacaftor-ivacaftor) was initially approved by the FDA and the EMA for pwCF aged 12 years and above, and then they extended it to cover pwCF aged 1 year or older with two copies of the F508del variant (European Medicines Agency, 2023a; Orkambi, 2023). In the UK, it is approved for pwCF over the age of 6 months (Cystic Fibrosis Trust, no date-b).
3. Symkevi (tezacaftor-ivacaftor) was initially approved by the FDA, EMA, and the NHS for pwCF aged 12 years or older and then extended to pwCF aged 6 years and older with homozygous F508del or heterozygous F508del with residual function variant (European Medicines Agency, 2023b; NHS England, 2021; Symdeko, no date).
4. Kaftrio (elexacaftor-tezacaftor-ivacaftor), known as 'triple therapy' was approved by the FDA, EMA, and NHS for pwCF 12 years and older with at least one copy of F508del and later extended to pwCF aged 6 years and older (Cystic Fibrosis Trust, no date-a). Recently, the FDA approved it for cwCF aged 2 through 5 years (Cystic Fibrosis Foundation, 2023).

Figure 4 shows the timeline of the approved CFTR modulators.

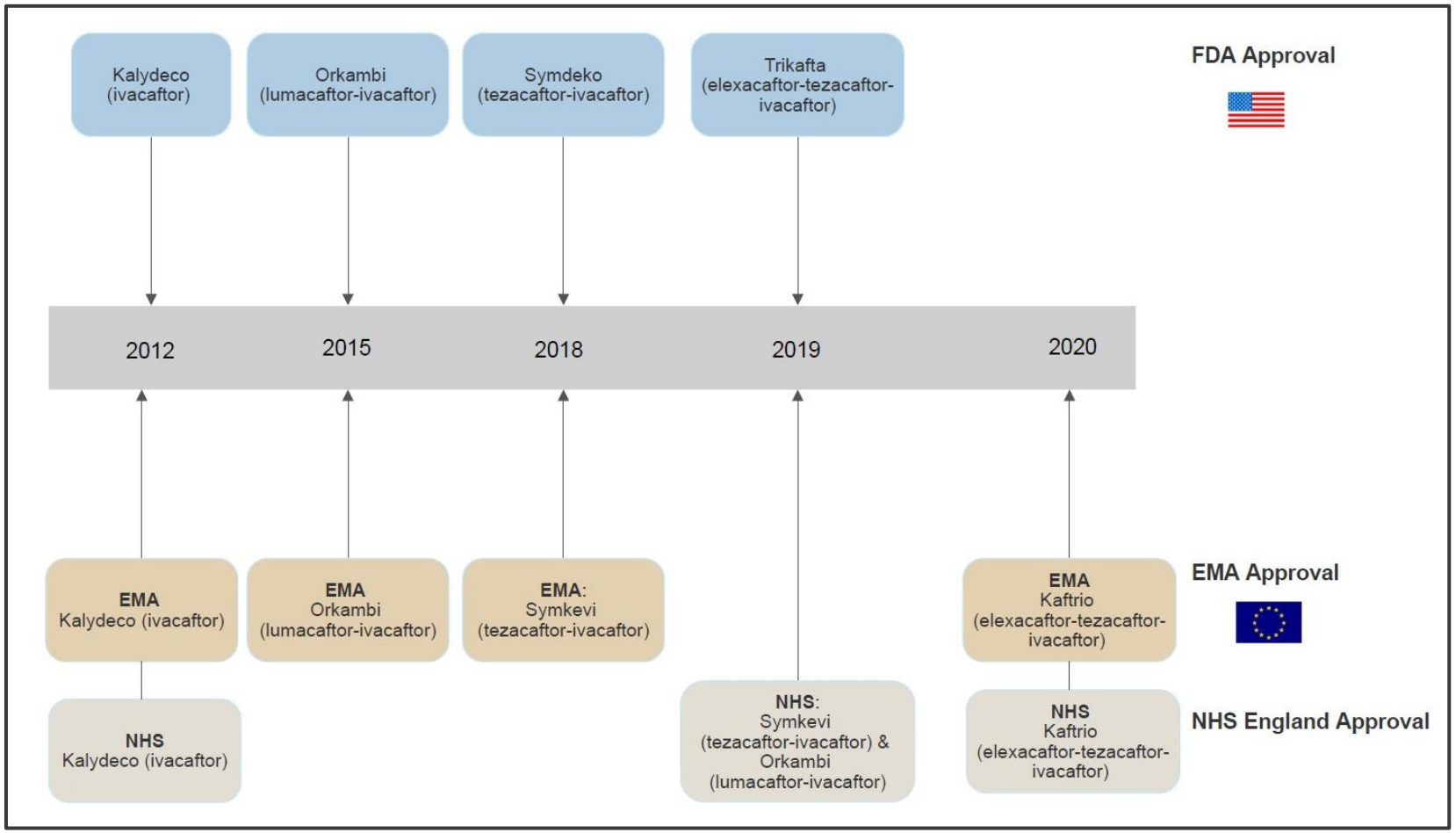


Figure 4. CFTR modulator therapies approval timeline.

EMA: European Medicines Agency; FDA: Food and Drug Administration; NHS: National Health Service

1.6.2.1 Clinical studies

Since the introduction of CFTR modulators, several studies have investigated the safety and efficacy of these drugs. They examined the effect on different outcomes such as lung function, PEx, hospitalisations, respiratory symptoms, nutritional status, BMI, quality of life, and any reported adverse events experienced in individuals with CF.

1.6.2.1.1 Ivacaftor (Kalydeco)

The first approved generation of modulator therapies was ivacaftor, a potentiator that increases the flow of Cl^- ions through the CFTR channel. The safety and efficacy of ivacaftor for patients was tested in randomised, double-blind, placebo-controlled trials at different phases and age groups for patients with gating defects variants.

The first phase 3 randomised, double-blind, placebo-controlled, clinical trial included pwCF ≥ 12 years with at least one G551D over 48 weeks. The treated group showed improvement in ppFEV1, risk of PEx, patient-reported respiratory symptoms, weight, and concentration of sweat Cl^- (Ramsey *et al.*, 2011). Subsequently, younger children aged 6 to 11 years also showed a good response to ivacaftor in decreasing sweat Cl^- concentration and improving lung function and nutritional status in patients carrying at least one gating variant (Davies *et al.*, 2013; De Boeck *et al.*, 2014). Ivacaftor was later found to be efficacious in those aged 2 to 5 years carrying at least one gating variant after proving its safety and efficacy (Davies *et al.*, 2016; Rosenfeld *et al.*, 2018). Lastly, ivacaftor was approved for pwCF aged 4 months and older who are heterozygous for nine selected gating variants and R117H after the data from the ARRIVAL study which demonstrated its safety and efficacy (Davies *et al.*, 2020b).

These clinical trials were crucial in facilitating access to this modulator therapy. However, post-approval observational studies provide essential longitudinal data and may better represent the CF population who were excluded from the clinical trial.

A systematic review of 57 real-world studies was conducted to investigate the longitudinal outcomes of ivacaftor after five years. The findings showed consistency with the well-established safety profile based on clinical trial data. In addition, the included studies supported the consistent and sustained clinical benefit in both pulmonary and non-pulmonary outcomes across various settings, confirming and expanding upon evidence from clinical trials (Duckers *et al.*, 2021). However, a recently published study has shown some reduction in the initial benefits in ppFEV1 5 years after commencing ivacaftor in pwCF with the G551D variant and return to the pre-ivacaftor ppFEV1 baseline (Mitchell *et al.*, 2021). Continuous evaluation of lung function and other clinical outcomes is essential, and more longitudinal studies are needed to confirm this result.

1.6.2.1.2 Lumacaftor-Ivacaftor (Orkambi)

Ivacaftor targeted only 4-5% of the CF population with gating variants. The F508del variant is the most common variant among the CF population (Cystic Fibrosis Trust, 2023a). This misfolding variant requires correction to reach the cell surface. Lumacaftor was the first corrector to be developed. However, a randomised clinical trial demonstrated that a potentiator ivacaftor was also required to support channel opening (Boyle *et al.*, 2014; Clancy *et al.*, 2012). A 24-week, randomised, controlled phase 3 trial demonstrated significant positive effects of lumacaftor-ivacaftor, particularly on lung function, BMI, and a reduced frequency of PEx as well as hospitalisations in F508del homozygous patients (Wainwright *et al.*, 2015). Subsequent clinical trials on younger ages between 6 – 11 years were executed and showed improvement in lung function, lung clearance index$_{2.5}$, sweat Cl^-, nutritional status, and health-related quality of life (Milla *et al.*, 2016; Ratjen *et al.*, 2017). This combination was then approved for cwCF ≥ 2 years after the results of clinical trials on this age group which showed the safety and efficacy of maintaining lung function and decreasing sweat Cl^- concentration (Hoppe *et al.*, 2021; McNamara *et al.*, 2019).

A real-world observational study which aimed to explore the adverse events associated with lumacaftor-ivacaftor treatment revealed frequent reported respiratory adverse effects in 51% of participants and drug intolerance, leading to the treatment's discontinuation in 30% of participants (Hubert *et al.*, 2017). A recent, large multi-centre study in France found an

association between lumacaftor-ivacaftor and improvement in lung function and nutrition status and decreased IV courses. Adverse events caused treatment discontinuation in 18% of participants, and they were found to be at high risk of clinical deterioration (Burgel *et al.*, 2020).

1.6.2.1.3 Tezacaftor-Ivacaftor (Symkevi)

The frequent side effects of lumacaftor-ivacaftor led to a focus on another corrector, tezacaftor. A monotherapy of tezacaftor showed some improvement in lung function; however, combined therapy with ivacaftor displayed more effectiveness in sweat Cl^- and ppFEV1 in patients homozygous for F508del (Donaldson *et al.*, 2017). A randomised, double-blind, multi-centre phase 3 trial in patients homozygous for F508del showed an improvement in ppFEV1 and a 35% lower rate of PEx in the tezacaftor-ivacaftor group compared to the placebo (Taylor-Cousar *et al.*, 2017). In addition, there was no increase in adverse respiratory events in the treatment group (Taylor-Cousar *et al.*, 2017). In contrast with lumacaftor-ivacaftor, the combination of tezacaftor-ivacaftor showed efficacy in patients heterozygous for F508del and *G551D* more than patients homozygous for F508del in both sweat Cl^- and ppFEV1 (Donaldson *et al.*, 2017). Another randomised, double-blind, multi-centre phase 3 trial looked at the effectiveness of this combination on 12-year-old patients heterozygous for F508del and residual function variant. It showed improvement in the ppFEV1 and lower concentration of sweat Cl^-. The secondary endpoint, which measures the respiratory domain of the CF Questionnaire-revised (CFQ-R), also showed improvement in the treatment group (Rowe *et al.*, 2017). Most reported adverse events related to tezacaftor-ivacaftor are mild to moderate in severity and vary between respiratory events or other events such as headache, nausea, and fatigue (Donaldson *et al.*, 2017; Rowe *et al.*, 2017; Taylor-Cousar *et al.*, 2017).

The use of tezacaftor-ivacaftor was extended to cwCF between 6 to 11 years who are homozygous or heterozygous for F508del and residual function variants after a randomised clinical trial evaluated the safety and tolerability. This study showed results consistent with the adult studies, which improved the sweat Cl^- level, CFQ-R respiratory domain scores, and ppFEV1 (Walker *et al.*, 2019). A more recent randomised, phase 3 clinical trial evaluated the efficacy and safety of tezacaftor-ivacaftor in participants ≥12 years of age heterozygous for

the F508del, and a minimal function variant did not show a clinically meaningful benefit in lung function but was generally safe and well-tolerated (Munck *et al.*, 2020).

An ongoing, five-year, real-world safety study evaluated clinical outcomes in pwCF ≥ 12 years treated with tezacaftor-ivacaftor. An interim result showed decreased PEx rates and hospitalisations, and increased lung function with no safety concerns (Bower *et al.*, 2021).

1.6.2.1.4 Elexacaftor-Tezacaftor-Ivacaftor (Kaftrio)

Elexacaftor is another *CFTR* corrector that has been used in combination with tezacaftor-ivacaftor. This triple therapy has been tested in a multi-centre, randomised phase 3 trial in pwCF who are F508del homozygous and showed improvement in the primary outcome ppFEV1 by 10 percentage points, and secondary outcomes sweat Cl^- by 45.1 mmol/l, and CFQ-R respiratory domain after four weeks (Heijerman *et al.*, 2019). Another phase 3 multi-centre, randomised clinical trial on 12 years and older patients heterozygous for F508del with minimal-function *CFTR* variant showed lower sweat Cl^- concentration by 40 mmol/l, 13.8 points higher ppFEV1, 63% lower in the PEx score, and 20 points higher in the respiratory domain score on the CFQ-R, with 1% of the treatment group participants showing mild to moderate adverse events after 34 weeks (Middleton *et al.*, 2019).

These results were remarkable because the previous modulator therapies had lower benefits for patients with heterozygous F508del and minimal function variants (Munck *et al.*, 2020). Minimal function variants are those that produce no or very little CFTR protein. They are mostly found in class I–III variants. Patients in this category combined with F508del usually have severe and difficult-to-treat disease, characterised by severe pulmonary symptoms and a progressive decrease in ppFEV1, as well as increased PEx, pancreatic insufficiency, and premature mortality (Lopes-Pacheco, 2020). Based on the clinical trials, ETI was approved for pwCF 12 years and above with at least one F508del variant.

Further, ETI has been assessed in a multi-centre phase 3 clinical trial on pwCF heterozygous for F508del-CFTR with either a gating variant or a residual function variant on the second allele

(Barry *et al.*, 2021). ETI caused an increase in ppFEV1 by 3.7 percentage points compared to the active control group and sweat Cl^- concentration lowered by 23.1 mmol per litre compared to the active group. The change in the CFQ-R respiratory domain was 10.3 points higher after ETI (Barry *et al.*, 2021). After the massive improvement with ETI in pwCF above 12 years old, more clinical trials examined the safety and efficacy of this drug in younger age (6 through 11 years), which showed improvement in lung function, lung clearance $index_{2.5}$, BMI, and CFQ-R score (Mall *et al.*, 2022; Zemanick *et al.*, 2021).

Due to the recent approval of ETI treatment, information regarding its long-term effects in the real world is presently limited and derived from small studies. Nichols *et al.* (2022) in the PROMISE study started enrolling pwCF age 12 and older in late 2019 with at least one F508del variant. It was conducted at 56 CF research centres across the US to understand the broad effects of ETI over 30 months for those starting ETI for the first time. The core outcome measurements are ppFEV1, BMI, sweat Cl^- concentration change, and self-reported respiratory symptoms. Assessments were taken before and at 1, 3, and 6 months after ETI treatment, with additional 18- and 30-month visits planned. Around half of the participants were previously treated with dual therapies before switching to ETI, and 6.7% used ivacaftor consistent with their variant types. They found that after six months, compared to the baseline, the mean ppFEV1 improved by 9.7%, CFQ–R respiratory domain score improved 20.4 points, sweat Cl^- decreased 241.7 mmol/L, and mean BMI increased by 1.2 kg/m2 for adult populations and 0.3 z-score in adolescents. Furthermore, BEGIN (NCT04509050) and RECOVER (NCT04602468) are ongoing separate studies but related to PROMISE, which will focus on children and infants younger than 6 years old to evaluate the biological and clinical effect of the triple therapies on them (Nichols *et al.*, 2021). The findings of these large studies will provide valuable data regarding the long-term effects of ETI in cwCF.

Additional real-world studies which represent CF populations excluded from clinical trials are required to examine the long-term effects of ETI. These studies should include longer time periods and diverse demographic areas across all eligible age groups to establish conclusive evidence.

1.7 Treatment burden

The incremental improvement in survival for pwCF described above has been associated with a steadily increasing burden of daily treatment. In general, this burden increases as pwCF get older. Moreover, treatments such as antibiotics and ACTs typically need to be increased during PEx. A study reported the changes in the treatment pattern from 1995 to 2005, and found a dramatic increase in the use of ACTs (69.9% vs 89.6%), inhaled bronchodilators (72.0% vs 84.0%), dornase alfa (44.8% vs 67.2%), inhaled corticosteroids (16.0% vs 49.3%), inhaled antibiotics (6.5% vs 43.1%), oral nutritional supplements (18.3% vs 24.5%), and insulin/oral hypoglycaemic agents (4.9% vs 10.2%) (Konstan *et al.*, 2010). Using epidemiologic study of cystic fibrosis (ESCF) data, Sawicki *et al.* (2013) developed a treatment complexity score to describe the treatment burden trend over three years in different age groups (child, adolescent, and adult). The treatment burden increased over the years in all age groups. However, it was highest in adults.

These notable increases in the use of therapies suggest an increase in the overall treatment burden. A project on adults with CF assessed self-reported daily treatment and perceived treatment burden as measured by the CFQ-R. They concluded that regardless of age or illness severity, pwCF are involved in a high daily treatment activity. In particular, ACTs and the number of nebulised treatments are linked to a higher perceived treatment burden (Sawicki, Sellers and Robinson, 2009). CwCF spent a substantial amount of time daily (74.6 ± 57.0 min) completing their treatment regime (Ziaian *et al.*, 2006). This increase in treatment burden plays a role in adherence level (Quittner *et al.*, 2014b) and increased prevalence of anxiety and depression (Knudsen *et al.*, 2016; Quittner *et al.*, 2014a).

Several studies have used qualitative methods as a valuable tool for deeper exploration of the lived experience of pwCF to understand the challenges that patients face with the treatment burden. The experience of living with CF is multidimensional and unique to each person. However, a shared experience also exists (Badlan, 2006; Gjengedal, Rustøen, Wahl and Hanestad, 2003; Nicolais *et al.*, 2019).

A qualitative study interviewed adolescents and adults to identify self-management barriers and facilitators. They found that 64% identified treatment burden as the most common adherence barrier, reflecting treatments' length, frequency, and complexity (George *et al.*, 2010). A systematic review aimed to describe the experiences and perspectives of children and adolescents with CF. It included 43 qualitative studies and developed multiple themes showing that cwCF demonstrated emotional vulnerability while also demonstrating capacities to develop resilience in dealing with their illness. The chronic treatment regimen significantly limited their lifestyle and independence, leading to increased frustration and resentment towards their illness (Jamieson *et al.*, 2014). These two studies show the negative influence of the treatment burden on pwCF on adherence level, social life, and mental health.

Before the approval of ETI, treatment burden was identified as the top research priority by the James Lind Alliance Priority Setting Partnership (Rowbotham *et al.*, 2018). Following this list, a study by Davies *et al.* (2020a) confirmed that the treatment burden in CF is considerable, and it takes time to do routine daily treatments, impacting daily life. ACTs and nebulised antibiotics were the most burdensome in the opinion of CF patients, relatives or friends, and healthcare professionals (HCPs) (Davies *et al.*, 2020a). The key reasons behind their choice are time consumed, dislike, boredom, conflicts with children to do ACTs, cleaning nebulisers, and lack of immediate evidence of an effect (Davies *et al.*, 2020a).

Parents and carers of cwCF also experience a challenge with the increased treatment burden. Carers have to deal with mental and emotional demands and stresses associated with their own, their partner's, and the family's functioning, in addition to the physical work and time required (Foster *et al.*, 2001; Quittner *et al.*, 1998; Slatter, Francis, Smith and Bush, 2004). For example, a study showed that depression affected approximately 35% of mothers and 29% of school-aged children, which was associated with a lower rate of adherence to ACTs (Smith, Modi, Quittner and Wood, 2010).

1.7.1 Treatment burden in the cystic fibrosis transmembrane conductance regulator modulator era

Several studies have confirmed the treatment burden associated with ACTs and nebulised treatment in pwCF and their carers and the impact of this burden on different aspects of their lives. As described earlier, ETI treatment has been shown to improve clinical outcomes in pwCF and is associated with a step-change improvement in many patients. This will likely lead to more changes in treatment regimes, as pwCF require less frequent or intensive treatment. A recent update on the James Lind Alliance's top 10 priorities for clinical research in CF revealed an interesting shift with treatment burden as the former top priority moving to the eighth priority, indicating a change in this issue following ETI (Rowbotham *et al.*, 2023). Although much is known about the experiences of cwCF and adults with CF, there is very little published research into the experiences of cwCF and their carers after CFTR modulators.

Following the revolution of CFTR modulators and the improvement in clinical outcomes, three qualitative studies investigated pwCF's experience in the CFTR modulator era. The first qualitative study interviewed eight adults with CF to understand the experience of individuals with CF on CFTR modulators other than ETI. They aimed to explore how the introduction of CFTR modulators affected the psychological and social aspects of their lives. Participants described the stability in their physical symptoms and the change in how they identify themselves, their goals, and their hope for the future (Page, Goldenberg and Matthews, 2022). Another qualitative study explored the lived experience of adults with CF and the change in their perception of reality after ETI. PwCF talked about the positive perception of ETI, including quality of life, sense of normality, and improved physical outcomes. The second theme highlighted the negative perceptions, including side effects and loss of identity. The third theme focused on the relationship with the clinical team, emphasising the desire for the HCPs to listen more (Aspinall *et al.*, 2022). The third qualitative study focused on the psychological implications of CFTR modulators. Twenty adult participants were interviewed and expressed their appreciation of normal life after CFTR modulators and, with enhancement in physical and psychological symptoms, the need to provide adequate support to promote healthy lifestyle choices (Keyte, Kauser, Mantzios and Egan, 2022). These three studies focused on adults with CF, yet none investigated the associated treatment burden.

In addition to exploring the experience of cwCF with ACTs and nebulised treatment, it is also important to evaluate the longitudinal changes in the burden of physiotherapy treatments, including ACTs, nebulised mucolytics, and exercise. Some studies have examined the effect of ETI on the use of inhaled nebulisers (Nichols *et al.*, 2022; Olivier *et al.*, 2023; Song *et al.*, 2022). Nichols *et al.* (2022) and Song *et al.* (2022) found a decrease in the use of dornase alfa and hypertonic saline after six months of ETI. In contrast, Olivier *et al.* (2023) found no changes in dornase alfa and hypertonic saline use after six months of ETI. There is an ongoing clinical study in the UK (CFSTORM) looking into the effect of discontinuing mucoactive nebulised treatment (hypertonic saline, dornase alfa, or both) on the change in ppFEV1 at 12 months on six years and older CF patients (Southern, 2021).

In addition, only one abstract was found in the literature on the changes in ACTs after ETI in adults with CF (Faulkner *et al.*, 2022). Faulkner *et al*. (2022) concluded there was a self-reported decline in adherence to daily ACTs after 12 months of ETI. On the other hand, no studies showed the impact on exercise activities, which suggests that this area has not been well-investigated.

1.8 Conclusions and gaps in the existing literature.

This literature review points to some gaps in existing knowledge. In general, research on the effects of ETI on pwCF is expanding. However, there is still a need to comprehensively understand the longitudinal effects of ETI on clinical outcomes in general and physiotherapy regimes in particular.

One of the limitations of the existing literature is the limited understanding of the changes in physiotherapy treatment burden, including ACTs, nebulised mucolytics, and exercise, after ETI. Prior to this thesis, there has been no published study exploring the experience of cwCF, their families, and HCPs toward the burden of ACTs and nebulised mucolytic treatments after ETI. Most qualitative studies in the literature are directed at the adult experience, focusing more on the psychological and social aspects (Aspinall *et al.*, 2022; Keyte, Kauser, Mantzios and Egan, 2022; Page, Goldenberg and Matthews, 2022). A qualitative approach can provide a rich understanding of the lived experiences of cwCF and their carers after ETI. It can also

provide insights into how ETI has affected their experience with ACTs, nebulised mucolytics need, and their outlook on the future.

In addition, little work has been published on the real-world evidence of long-term changes in ACTs, nebulised mucolytics, and exercise in cwCF who have been prescribed ETI (Faulkner *et al.*, 2022; Nichols *et al.*, 2022). A quantitative approach can be used to quantify the effects of ETI on physiotherapy regimes. This data can assist in identifying the specific areas of physiotherapy affected by ETI and in understanding the long-term effects on other clinical outcomes. Qualitative and quantitative approaches will provide a comprehensive understanding of the changes in ACTs, nebulised mucolytics, and exercise after ETI.

Another key limitation of existing literature primarily concerns the lack of consensus on definitions of PEx. Despite the improvement in lung symptoms associated with ETI, PEx remains a clinically important event in pwCF. This issue may be considered particularly problematic within CF research, as PEx is used as an endpoint outcome to assess different interventions (Elkins *et al.*, 2006; Fuchs *et al.*, 1994; Heijerman *et al.*, 2019; Middleton *et al.*, 2019; Ramsey *et al.*, 1999; Saiman *et al.*, 2003). Using different methods to define PEx makes comparing the results from these studies challenging.

1.9 Aims and objectives.

Therefore, to address these gaps, the aims of this thesis were as follows:

1. To explore the attitudes of cwCF, families, and HCPs toward ACTs and nebulised mucolytics after ETI using a qualitative research approach.
2. To analyse the longitudinal changes in the physiotherapy treatment and clinical outcomes after ETI treatment in cwCF attending the Great North Children's Hospital (GNCH) Regional Paediatric CF Clinic.
3. To perform a scoping review of the definitions of a 'pulmonary exacerbation' in pwCF reported in the medical literature.

The study's objectives were pursued concurrently, not consecutively, which helped to understand this topic comprehensively.

1.10 Thesis structure

This thesis consists of five chapters.

- Chapter 1: presents the literature review, conclusions with gaps in the literature highlighted, aims and objectives, and thesis structure.

In Chapters 2, 3 and 4, the findings of this thesis were presented. Each of these chapters is structured similarly to a manuscript, with an introduction, methods, results, discussion, and conclusion.

- Chapter 2: focuses on the first objective where the attitudes of cwCF, families, and HCPs toward ACTs and nebulised mucolytics were explored using qualitative methods.
- Chapter 3: focuses on the second objective where the medical records of cwCF at the GNCH were reviewed retrospectively to analyse the change in physiotherapy treatment after starting ETI treatment in addition to other clinical outcomes.
- Chapter 4: focuses on the third objective where the literature was reviewed to analyse the definitions used for PEx.
- Chapter 5: presents a general discussion and conclusion of the findings of this thesis and clinical implications along with suggested directions for future research.

Chapter 2. Exploring the Impact of Elexacaftor-Tezacaftor-Ivacaftor Treatment on Opinions Regarding Airway Clearance Techniques and Nebulised Treatment: A Qualitative Study.

Part of the work described in this chapter has been previously published in the form of a full-text article in *BMJ Open Respiratory*. (Almulhem *et al.*, 2022)

2.1 Introduction

CF is a multi-system, life-limiting genetic disorder caused by dysfunction of the CFTR protein (Shteinberg, Haq, Polineni and Davies, 2021). CF primarily affects the lungs, where epithelial cells' reduced Cl^- and bicarbonate secretion causes abnormal ASL homeostasis (Haq *et al.*, 2016). The hydration and clearance of mucus are impaired, and endobronchial infection and inflammation result in progressive bronchiectasis.

Treatments for cwCF have historically targeted downstream symptoms, including ACTs and nebulised mucolytics to increase airway clearance and antibiotics to prevent or treat infections. These treatments are required twice daily and are part of a time-consuming regime. Children frequently report feeling overwhelmed by treatment as they grow older and that it impacts on their life and opportunities (Knudsen *et al.*, 2018; Sawicki *et al.*, 2013). In 2018, a James Lind Alliance Priority Setting Partnership identified simplifying the treatment burden as the top research priority in CF (Rowbotham *et al.*, 2018). ACTs and nebulised treatment are rated as the most burdensome for pwCF (Davies *et al.*, 2020a).

The development of CFTR modulators has heralded a new era of precision medicine in CF. These small-molecule drugs target the underlying defect and improve CFTR function (Haq *et al.*, 2022). ETI, along with ivacaftor, a potentiator monotherapy that has been available since 2012 for 5% of the CF population with gating defects, is often referred to as 'highly effective modulator therapy' (HEMT). In August 2020 ETI was approved for patients over the age of 12 years in England and most recently, in November 2023, for those ≥2 years of age. The James Lind Alliance Priority Setting Partnership has recently revised the top 10 research priorities in light of the recent development of CFTR therapies. This update reflects a notable change in the prioritisation of treatment simplification, which has shifted from being the highest priority to now being number eight in the list of top priorities (Rowbotham *et al.*, 2023).

Considering this step-change improvement in treatment outcomes associated with ETI, the continued need for ACTs and nebulised mucolytics or antibiotics has been questioned. A survey of pwCF in the HEMT-era in the US confirmed that reducing treatment burden is a priority (Cameron *et al.*) and that ACTs and nebulised antibiotics are the treatments they wish

to simplify the most (Gifford, Mayer-Hamblett, Pearson and Nichols, 2020). Lived experience pre-ETI was described as challenging by many with individuals striving for equality and expressing a wish to be able to access the same opportunities as healthy people (Knudsen *et al.*, 2018). A survey of HCPs involved in CF care found that the majority supported the idea of a trial of replacing ACTs with exercise (Rowbotham *et al.*, 2020). Another study in Australia found that 43% of adults with CF believed exercise could substitute for ACTs, with 44% having done so in the previous three months (Ward, Stiller and Holland, 2019). While the clinical trial evidence of benefits with ETI is impressive, there is little work published that explores the lived experience of cwCF, their families, and HCPs.

2.2 Aims

This study aimed to understand the impact of ETI on the lives of cwCF and their carers and their attitudes towards ACTs and nebulised treatments. The opinions of multidisciplinary HCPs were also explored around implications for future clinical practice.

2.3 Methodology and methods

2.3.1 Overview

This section presents an overview of the methodological standpoint and the research methods employed to enable the reader to understand the research context. The first section provides an overview of the research methodology, highlighting how this shaped the methods' selection. Secondly, details about the research methods and a rationale for adopting thematic analysis are discussed. Following this, there is a description of the recruitment process, data collection, and analysis strategy. Finally, the measurement of the research quality is presented.

2.3.2 Research methodology

A qualitative design was employed to explore the perspective and experiences of cwCF, their families, and HCPs after the introduction of ETI. This design facilitated the exploration of areas that may not have been adequately explored through alternative designs.

Qualitative research has two main approaches that structure it, which can be categorised into experiential and critical (Braun and Clarke, 2022, pp. 158-160). The experiential approach investigates the data's meanings, viewpoints, attitudes, and experiences, while the critical approach questions the patterns expressed in the data and uses them to understand the implications of these patterns. This research adopted an experiential approach where participants share their feelings and attitudes toward the impact of ETI to help the researcher understand their experiences. This approach was underpinned by my ontological and epistemological beliefs.

Defining the researcher's ontological and epistemological position in qualitative research is critical because it determines the methodology used to investigate the topic. Ontology concerns what reality is like (Bryman, 2016, p. 32). Each researcher has a specific assumption about the nature of reality. Realism, sometimes called ‘naïve’, presumes the truth can be discovered independently of our minds as a researcher. Relativism believes there are multiple versions of reality, and it is constructed by human interpretation and knowledge. Critical realism is a combination of realism and relativism ontology. It identifies the truth and reality and recognises the influence of human practice to provide access to the underlying data. However, because people's views of reality are subjective, socially affected, and prone to

change over time, this reality can only be accessed partially (Braun and Clarke, 2022, pp. 167-174). Critical realism was adopted in the current research, which acknowledges one reality and emphasises individual experiences in interpretation.

Epistemology reflects assumptions about what constitutes meaningful and valid knowledge and how this knowledge is generated (Bryman, 2016, p. 27). It is deeply connected to ontology. There are three main epistemologies, as described by Braun and Clarke (2022, pp. 177-183): positivism, constructionism, and contextualism. Positivism is the dominant framework in scientific research, which captures objective knowledge following a scientific method. Constructionism is founded on the premise that research practices produce rather than reveal evidence. The middle position, contextualism, sees knowledge and the individuals who developed it as contextually situated, partial, and perspectival. A contextualist standpoint was adopted for this study. In conclusion, a critical realist, contextualist methodology was used to investigate individuals' perspectives of the influence of ETI on their treatment and lives.

2.3.3 Research methods

2.3.3.1 Rationale for reflexive thematic analysis

Thematic analysis (TA) and interpretative phenomenological analysis (IPA) were considered as analysis methods for achieving the research objective because of their exploratory nature. Both methods have advantages and disadvantages. Therefore, an informed choice can be made about the best fit between the study's aims and the method. IPA focuses on discovering in detail how participants are making sense of their lived world and understanding what it is like, from the participants' point of view (Larkin, Flowers and Smith, 2021, p. 53). TA is a method for identifying, analysing, and reporting patterns within data to provide insights into participants' experiences (Braun and Clarke, 2006).

While both IPA and TA might offer insightful information about the lives of pwCF, reflexive TA was chosen as the most suitable strategy to answer the research questions. This choice was made based on the study's aim to describe the pattern in participants' experiences rather than understand how they interpret their experiences.

In contrast to IPA, TA is suitable for heterogenous sample sizes, which is another benefit of using the method (Braun and Clarke, 2013, p. 56; Larkin, Flowers and Smith, 2021, p. 56).

Additionally, TA is not bound by a pre-existing theoretical framework, allowing flexibility and freedom (Braun and Clarke, 2022, pp. 162-163). This flexibility can be utilised to answer this study's critical realist research question. According to Braun and Clarke (2013, pp. 42-45), this method is a more effective starting point for qualitative researchers than other intensive qualitative methods. Furthermore, TA is best suited to explore the nature of the relatively understudied phenomenon. Thus, TA aligns with the current study's goal of understanding participants' perspectives following the administration of ETI.

Endorsing TA involves three decisions that must be addressed before starting the analysis process (Braun and Clarke, 2006). A decision on what is considered to be a theme, inductive versus deductive analysis, and semantic or latent analysis must be made. A theme represents a pattern or meaning within the data set and captures something important about the data related to the research question.

These themes can be identified in two ways. First, an inductive method implies that the themes directly relate to the data. The researcher's unconscious bias, knowledge, and personal viewpoint influence the analysis. Second, a deductive method generates themes based on the researcher's theoretical interest. The inductive method places less emphasis on the need to generalise data than deductive. An inductive approach was more appropriate since the research focuses on a relatively new area.

The level at which themes are identified – semantic or latent – must also be decided. When using a semantic method, the researcher mainly looks at what a participant has said or written, and themes are found in the data's explicit or surface meaning. A latent TA goes beyond the semantic content of the data and discovers or examines the underlying ideas, assumptions, conceptualisations, and ideologies that are thought to be defining or informing the semantic content of the data. This study identified themes at a semantic level to maintain a close relationship with the participants' voice and highlight the significance of patterns and the data's broader meanings and implications.

2.3.3.2 Participants and recruitment

2.3.3.2.1 Inclusion and exclusion criteria

This study explored the perspective of cwCF, their families, and HCPs toward the impact of ETI on their lives and their attitude toward ACTs and nebulised treatment. The inclusion criteria were as follows:

1. CwCF between the age of 12 and 18 years and a minimum of 6 months of taking ETI to allow time for the participants to have a lived experience after ETI. In addition, children must have been clinically stable and doing ACTs and/or prescribed nebulised treatment.
2. The parent(s) or guardian(s) of a clinically stable cwCF who had taken ETI for at least six months and been prescribed nebulisers and/or ACTs.
3. HCPs who had experience caring for children and young people included in this study.

The exclusion criteria for participants were as follows:

1. Mental health disorders that may impact being able to take part in qualitative interviews in an age-appropriate way or give informed consent.
2. Language barrier. There were no resources to accommodate individuals who did not speak English as part of this study, and, therefore, these individuals were excluded because they would not be able to communicate with the researcher.

Participants for this research project were recruited using the purposive criterion sampling method in which individuals who met the inclusion criteria were invited to participate (Bryman, 2016, p. 418).

2.3.3.2.2 Sample size

Methods for measuring sample size in qualitative research are controversial. Several criteria, such as what the researcher wants to know, the research objective, what will be valuable, what will have credibility, and what can be accomplished within the available time and resources, might influence the sample size (Braun and Clarke, 2021). The claim of data saturation is widely used in qualitative studies, but it is not the only criterion. Data saturation, defined as no new codes, was determined during data collection and from data analysis. Instead, some recommend using the 'information power' concept, which reflects the richness of the data related to the aim of the study (Braun and Clarke, 2021; Malterud, Siersma and Guassora, 2015). Due to the qualitative nature of this study, the sample size must be large enough to provide an in-depth insight into the participants' perspectives yet small enough to generate a high-quality analysis efficiently

Each group of participants was treated as a distinct entity, and the sample size for each group was calculated independently based on the information power. This approach ensures that the sample size aligns with each participant group's unique informational richness and relevance, thereby enhancing the study's ability to achieve its research objectives with sufficient depth and detail.

When the analysis reached 10 children, 7 carers, and 10 HCPs , I stopped recruiting. This number of interviews was considered appropriate to 'tell a rich story' (Braun and Clarke, 2013, pp. 55-56), impacted by my perception of the quality of the dialogue and information power (Malterud, Siersma and Guassora, 2015; Braun and Clarke, 2021).

2.3.3.2.3 Recruitment

Participants were recruited from a regional CF clinic at the GNCH in the north-east of England. Recruitment was arranged via the Consultant Paediatrician, Dr Malcolm Brodlie (MB), and physiotherapist Nuala Harnett (NH). Participants were enrolled from a single CF centre.

Dr MB, who is involved in the participants' clinical care at GNCH, identified potential participants according to the criteria outlined above through a review of clinic lists and patient medical records. Potential participants were approached in two ways. During their regular clinic, which takes place every six–eight weeks, MB or NH approached the potential participants (n = 22), explained the nature of the research, distributed the patient information

sheet (PIS) (see Appendix A), and asked them to sign the consent-to-contact form (See Appendix B) if willing to participate. They were given at least 24 hours before I called them to answer their questions and inquire their willingness to participate.

The second recruitment method involved the physiotherapist (NH) calling potential participants. She explained the project to them and asked for their agreement to send the invitation letter (Appendix C), consent-to-contact, and the PIS by mail. I then sent an invitation letter and PIS to those who initially agreed to participate (n = 6). Interested patients were advised that they could contact the researcher by email or text should they wish to participate or learn more about the study or complete the consent-to-contact form and return it using a stamped-addressed return envelope.

Potential participants were given a month to contact the researcher or return the consent-to-contact form. If they did not contact the researcher, NH contacted the family to remind them about the study. Potential participants were informed that if they did not respond within a week of this reminder, it would be assumed that they did not wish to participate and they would not be approached about the study again.

The HCPs who are part of the CF multidisciplinary team (MDT), such as paediatricians, physiotherapists, specialist nurses, and dietitians, were approached by Dr MB, who is part of this team. An invitation email was sent to all members of the CF MDT, along with the information sheet and consent-to-contact form, which asked if they were interested in participating. I received a list of HCPs who agreed to participate and then contacted them to arrange a meeting.

Where possible, all cwCF, carers, and HCPs who were eligible to participate were invited to do so until an appropriate number with quality information was reached. See **Figure 5** for a flow chart of the recruitment process for cwCF and their carers.

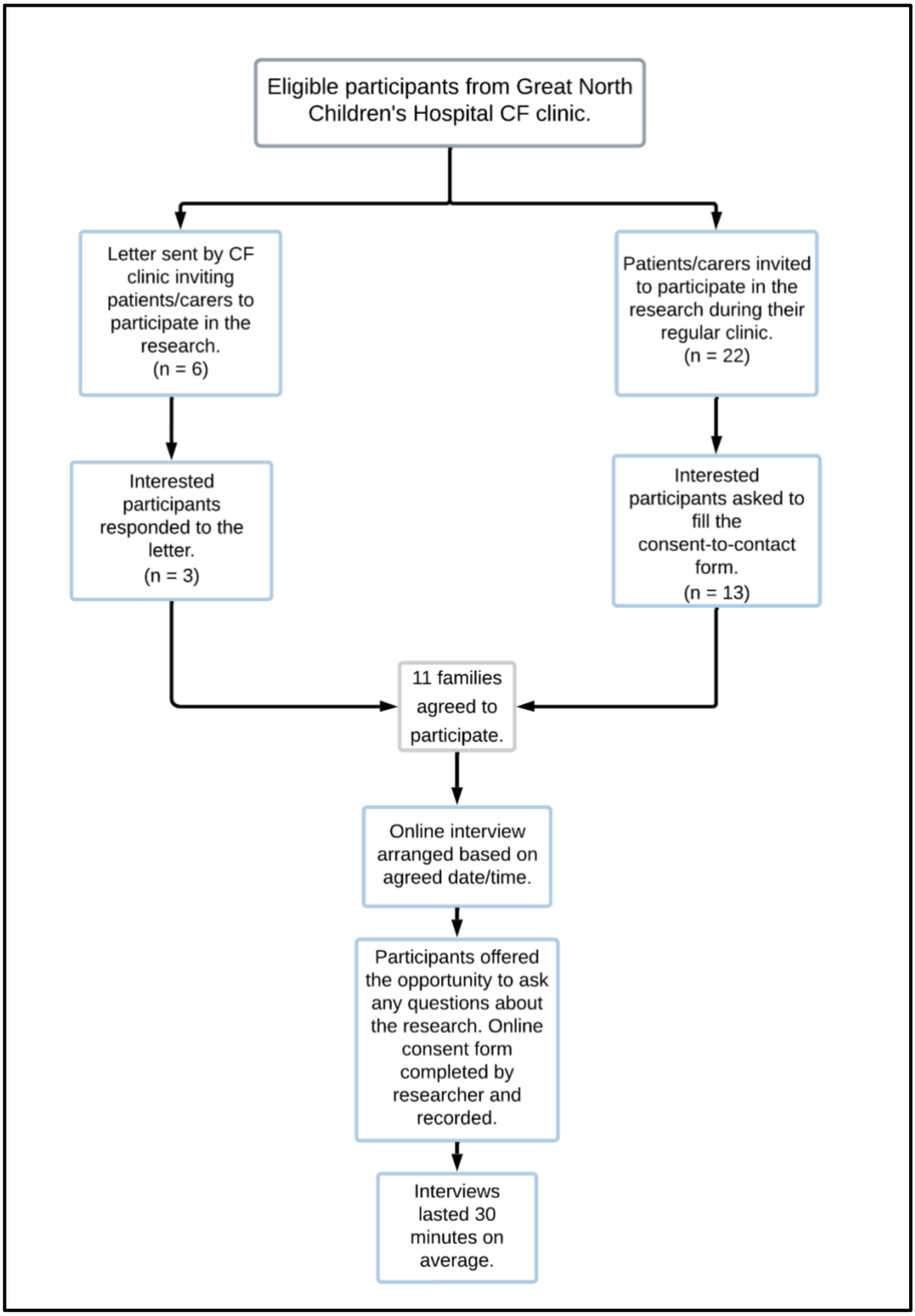


Figure 5. Flow chart of the recruitment and interview process for children with cystic fibrosis and carers.

CF: cystic fibrosis.

2.3.3.2.4 Participant consent and withdrawal

Informed consent was sought verbally and recorded from all participants via a consent form (Appendix D) before starting the interview. Participants were informed of their right to skip questions or withdraw prior to data analysis without consequence. This was detailed in the information sheet, reiterated in the consent form, and stated before the start of the interview. If the call disconnected, an attempt was made to call again to not lose participants due to a temporary loss of signal or Internet; however, so as not to harass anyone who chose to terminate the interview and did not wish to be contacted further, only one attempt was made.

2.3.3.3 Data collection

2.3.3.3.1 Interviewing process

After the cwCF or their carers agreed to participate, I contacted them by phone to obtain consent after discussing the study, answering any questions, and arranging a convenient date and time for the interview. Consent was taken verbally (recorded) as per the pro forma in telephone or video-call interviews. A range of ages and gender of cwCF were contacted.

HCP participants were given a choice between online or in-person interviews. All HCP interviews were conducted face-to-face in a private room in the hospital, except one interview, which was conducted online using Microsoft Teams.

All interviews with cwCF and parents were conducted online as instructed by the ethics committee. Some families chose to have an interview together with the cwCF (n = 4), whereas the rest of the participants were interviewed independently (n = 8). The interviews took place between January and May 2022 and ranged in length from 15 to 55 minutes (a mean of 30 minutes).

At the beginning of each meeting, the participant, and their parent (if they were under 16 years) reviewed the PIS and raised any questions or concerns. They were reminded that the interview would be recorded and last approximately an hour. After the interview, I stopped the audio recording, and the participants were given time to reflect on their involvement in the research and offer feedback.

The original copy of the consent form was preserved for the site file, and a copy was made for the patient's medical records.

2.3.3.3.2 Interview schedule

A semi-structured interview guideline was developed to direct the interview (see Appendix E). The questions were open-ended and broad since the research was exploratory and intended to enable participants to discuss their experiences in a non-directive manner. Thus, this allowed participants to address concerns that may not have been expected or covered in the interview guide. This is especially crucial when studying a new subject. The interview agenda served as a focus-keeping tool and ensured the questions were relevant to the research topics. The interview was flexible regarding the questions, wording, follow-up, and how participants were probed for further information. Reviewing relevant literature and the study's objectives shaped the interview questions. It was an iterative process in which the questions were modified as interviews were conducted and the research progressed.

To ensure the quality of the interview questions and meet the study aims, I sent the guideline questions to two HCPs and one qualitative researcher for counsel. Additionally, I performed a pilot interview with a colleague to ensure that the questions would lead to a 'natural' conversation and to gain experience conducting in-depth, semi-structured interviews before committing to an official study interview (Majid *et al.*, 2017). A second pilot interview was subsequently held with an HCP to test whether the suggested questions would investigate their intended subjects, to catch any problem in the wording of the questions and interview technique, and to give me some early feedback. The data from this pilot interview were included in the data analysis.

Interviewees were asked if they had any comments about the questions to gain additional feedback. The interview schedule was modified based on the pilot participant's feedback and additional discussions between the research team.

The guideline covered five areas: the time before ETI treatment, time after ETI, treatment burden, simplifying treatment, and future research. The first part of the interview questioned the steps involved in and their feelings toward their previous treatment routine. The questions started at the time before ETI to allow participants to compare the changes in their conditions. Next, I asked about ETI's positive and negative impact on their everyday lives, followed by specific aspects – such as treatment routine, social life, and concerns. The following section

involved questions relating to their thoughts about simplifying ACTs and nebulised therapy after ETI. The final section surveyed the future research studies participants would like to be addressed after ETI. Lastly, the participant received a summary of the interview's main themes and was given a chance to bring up any additional issues or offer information.

2.3.3.4 Data analysis

2.3.3.4.1 Transcription

The interviews were recorded and then transcribed verbatim by a professional transcriber (UK Transcription Ltd). They were subsequently anonymised to ensure the confidentiality of participants. I assigned participants a pseudonym. Any identifying information (such as age, location, and profession) was removed from the interview transcript or substituted with generic alternatives. A confidentiality agreement was obtained before submitting the data to the professional transcriber. I checked the transcripts to ensure accuracy. This thesis contains direct quotations, which are fundamental to the methods employed and support the desire to represent participants' voices. Only short quotations, no more than a few sentences, were used so that individuals would not be identifiable by their story.

2.3.3.4.2 Approach to thematic analysis – the analysis processes

Both electronic and hard copies of the data were used during the analysis. NVivo (QSR International) software Version 1.6.1 and Microsoft Word (Microsoft 365 MSO) were used for coding and data management. The data were analysed using inductive TA, emphasising broad thematic patterns across the data, and identifying semantic meanings. The six phases of reflexive TA are well-defined yet iterative **(Figure 6)**. The reflexive feature of this approach to TA requires continual movements between the phases with an attitude of inquiry and interpretation (Braun and Clarke, 2022, pp. 34-36). I read the transcripts twice for familiarisation. Initially, notes and comments were made alongside two transcripts using Microsoft Word (Appendix F). Then, I read with a focus on the broad changes after ETI. Through the process of data familiarisation, I was able to locate many points of possible analytical interest (Appendix G).

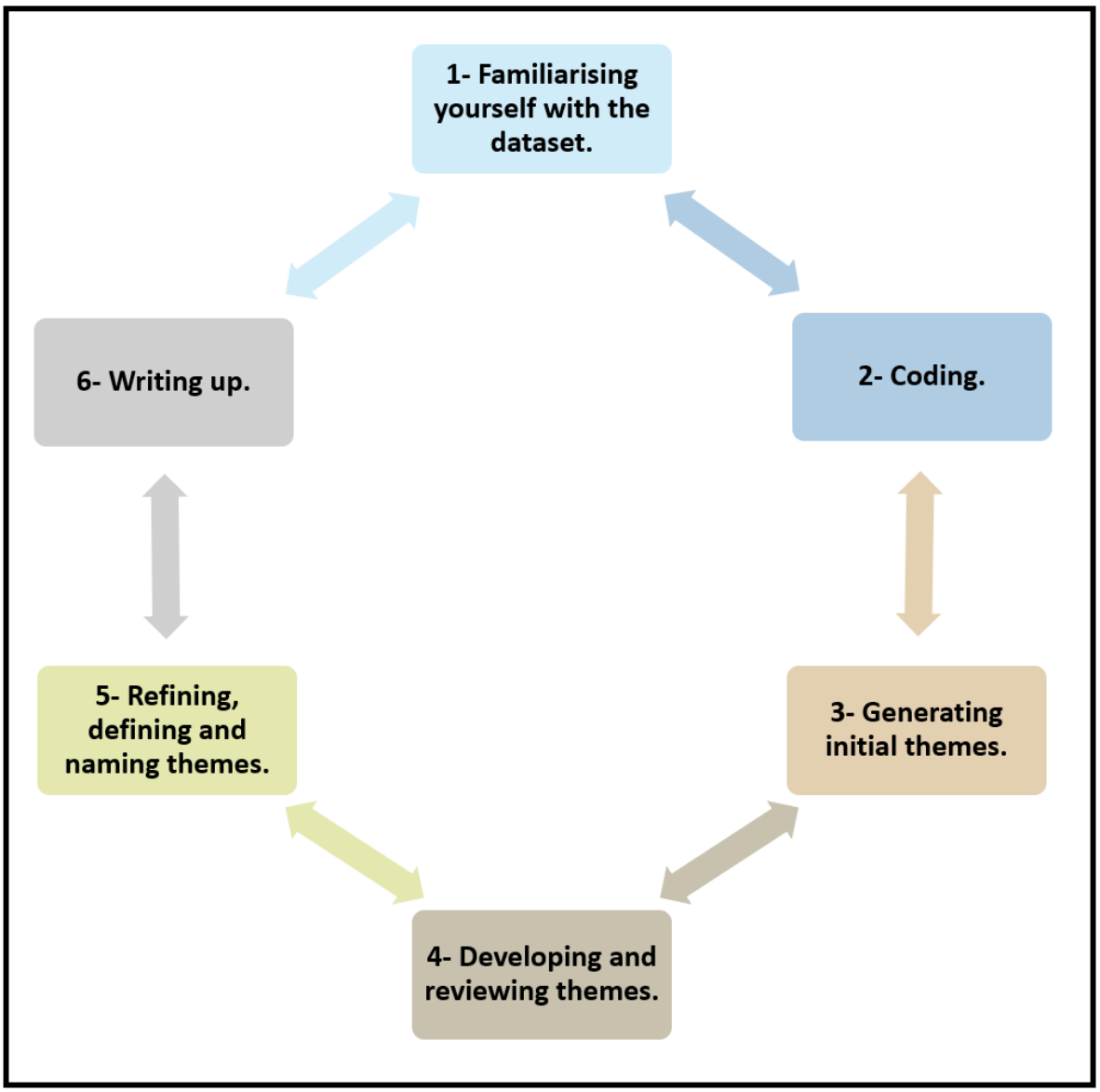


Figure 6. Phases of reflexive thematic analysis .

The first coding generated a few hundred codes, but these frequently identified micro-information in the data. Clustering made it simple to reduce this number to a more manageable level. Interesting features were grouped systematically, and all data relating to a specific theme were gathered into six potential broad patterns of meaning. These initial themes were reviewed and discussed with my supervisor (**Figure 7** shows the initial thematic map). To fit the data well, themes were mapped, edited, and modified using NVIVO software (**Appendix H**). In the subsequent analysis phase, I focused on the data connected to lifestyle, treatment, and practice changes and confirmed that themes accurately reflected the whole data set. Within this phase, I clearly defined each theme and its story. The final theme nomenclature was reached after several discussions with my supervisor.

Due to the lack of qualitative data in the literature detailing the changes after ETI in cwCF, I began with a contextual discussion of lifestyle change. Then, I report on two themes concerning simplifying treatment, and change in practice. The themes were encapsulated under the overarching theme 'I still can't get my head around how three tablets can do what Kaftrio done', highlighting the vast changes participants experienced after ETI's introduction. The quotes have not been proofread for misspellings and grammatical errors.

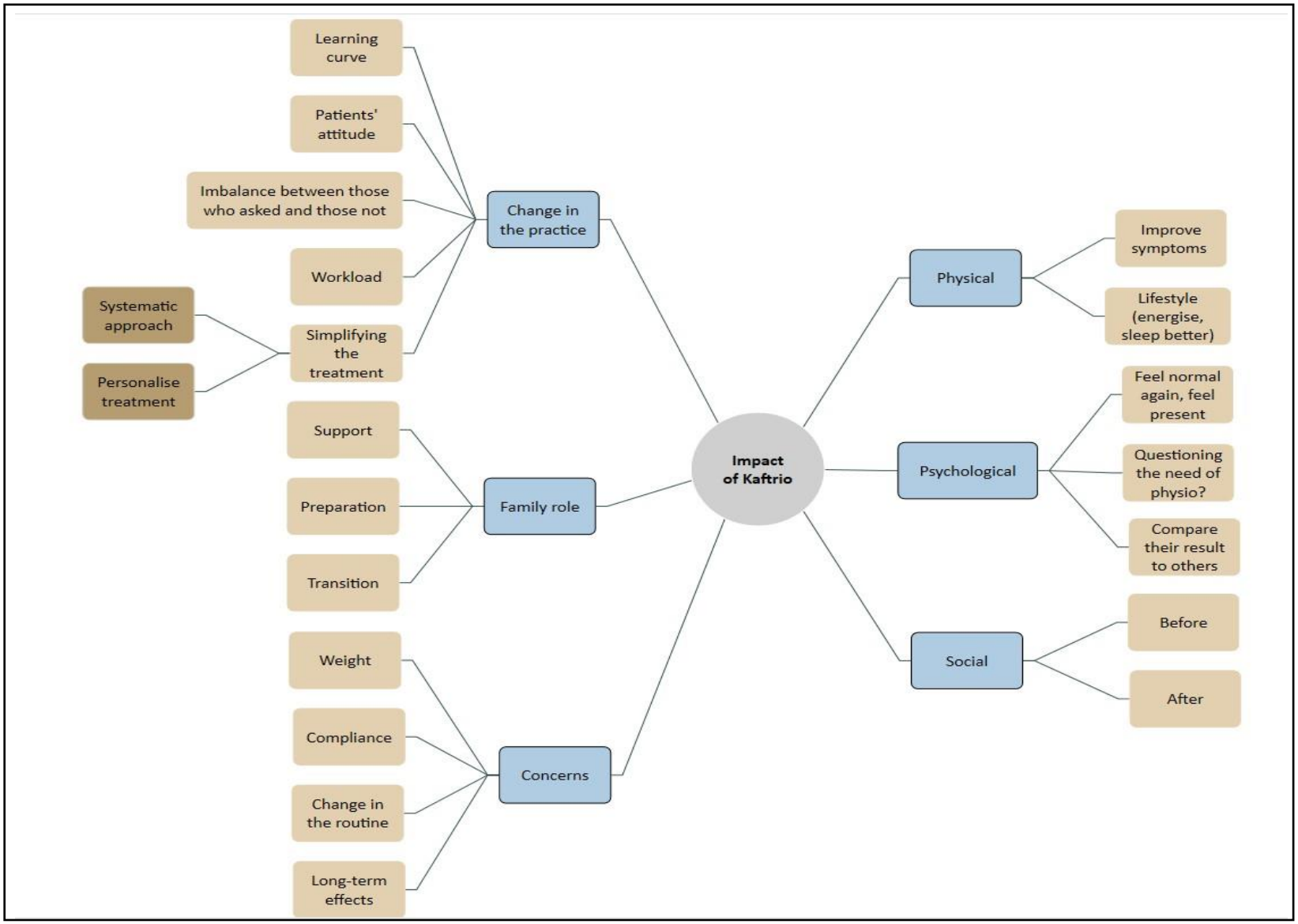


Figure 7. Early-stage of thematic mind map.

2.3.3.5 Research quality

Quality assurance in a qualitative study is controversial, and a wide variety of evaluation tools exist. Unlike a quantitative study, no universal criteria are agreed on for judging the quality of qualitative studies. According to Braun and Clarke (2022, pp. 268-269), the key to quality in TA is understanding good practices and problems you can recognise and avoid. As presented in **Table 2**, a 15-point checklist for good reflexive TA was followed in this study to ensure quality across each stage within the TA phases (Braun and Clarke, 2022, p. 269). Various alternative criteria could have been used to inform qualitative research quality (Tracy, 2010; Yardley, 2000). However, reflexive TA checklists were chosen because they are simple, practical, and comprehensive models that fit the researcher's methods used.

Table 2. Fifteen-point checklist for good reflexive thematic analysis .

Process	Criteria	Application of criteria in this research
Transcription	1. The data have been transcribed with an appropriate level of detail, and the transcripts have been checked against the tapes for "accuracy".	A professional transcriber transcribed the interviews verbatim, and subsequently, I checked it against the audio for accuracy.
Coding	2. Each data item has been given thorough and repeated attention in the coding process.	Each transcript had a rigorous review during the coding process, and each data item received equal consideration. The coding process was thorough, inclusive, and comprehensive. Microsoft Word and NVivo were utilised to code and manage the data, providing quick access to extracts under different themes. The themes were derived from numerous participant data examples. Once the themes were developed, they were compared to the original dataset to confirm that they accurately represented what had been expressed. Additionally, themes were compared to confirm that they were distinct. For internal coherence and consistency, the entire data set was
	3. The coding process has been thorough, inclusive, and comprehensive. Themes have not been generated from a few vivid examples (an anecdotal approach).	
	4. All relevant extracts for each theme have been collated.	
	5. Candidate themes have been checked against coded data and the original dataset.	
	6. Themes are internally coherent, consistent, and distinctive; each theme contains a well-defined central organisation concept; any	

Process	Criteria	Application of criteria in this research
	subthemes share the central organising concept of the theme.	evaluated to ensure that it matched to the theme.
Analysis and interpretation – written	7. Data have been analysed – interpreted, made sense of – rather than just paraphrased or described.	The results section outlines the effects of ETI implementation on cwCF, their families, and HCPs. The participant quotations presented in the findings section were matched and supported by the analysis. The data analysis was not merely summarised or explained; instead, a deeper insight was conducted. This is demonstrated in the discussion, which has been identified through data analysis.
	8. Analysis and data match each other – the extracts illustrate the analytical claims.	
	9. Analysis tells a convincing and well-organised story about the data and topic.	
	10. An appropriate balance between analytical narrative and data extracts is provided.	
Overall	11. Enough time has been allocated to adequately complete all phases of the analysis without rushing a phase or giving it a once-over lightly.	I gave sufficient time for each phase to analyse and reflect on the data generated.
Written report	12. The specific approach to thematic analysis, and particulars of the approach, including theoretical positions and assumptions, are clearly explained.	Construction of the themes through an iterative and systematic process indicates my active position. I avoid phrases like 'theme emerge', instead referring to the themes as 'identified'.
	13. There is a good fit between what was claimed and what was done (i.e. described method and reported analysis are consistent).	The reported thematic analysis used in this report is consistent with the analysis carried out. As indicated previously, the epistemological and ontological approach selected for this study was a critical realist contextualist approach. The language used in the results and discussion reflects the belief in one reality, 'truth'. It also understands that access to information is limited since people's perceptions of reality are subjective, socially determined, and changeable.
	14. The language and concepts used in the report are consistent with the epistemological position of the analysis.	
	15. The researcher is positioned as active in the research process; themes do not just 'emerge'.	

Source (Braun and Clarke, 2022, p. 269).

2.3.3.5.1 Reflexivity and positionality

Reflexivity is crucial to good quality research through acknowledging your biases (Braun and Clarke, 2022, pp. 13-19). Reflexivity is an ongoing process which involves routinely reflecting on your assumptions, expectations, choices, and actions throughout your research process. This means a researcher needs to be aware of their theoretical assumptions and work accordingly. Researchers advise keeping a reflexive journal for the research process. An example of my reflective notes is in **Figure 8.**

Interview with participant 7 and 8.

The interview was online using Zoom. I had a sound issue at the beginning, and it was fixed after a couple of minutes. The interview was after school time, which was challenging for me as a mother to fit the time before the time to pick up my kids. The mum seemed relaxed, and the boy was shy and refused to show his face to the camera. The mum helped me a lot, especially with the hard accent of the boy. She was elaborating on his answers. The boy was upset when we talked about the changes after Kaftrio and started comparing his results with others, while the mum saw the opposite. It was exciting to hear different opinions from the mother and her son.

- **What I need to do for next time:**

1- check the technical part first

2- add more questions about the family role after changing the routine.

Figure 8. Example from my reflective diary.

Also, it is vital to acknowledge your positioning within the research process, such as professional knowledge, gender, culture, age, ability, experience, and other factors and understand how these may have shaped your interaction with participants and influenced the production of knowledge within research.

My position as a non-native English speaker influenced the interview process. Speaking English as a second language made it sometimes challenging to comprehend the participant's response. However, this allowed me to seek clarification, probe deeper, and give the participants more time to discuss the point. I used simple language to resolve this obstacle and make myself clear, and I used a recorder to ensure I could fully comprehend the responses.

Additionally, as a respiratory therapist from a different culture, I have little experience working with pwCF, although I have worked with other chronic respiratory diseases such as chronic obstructive pulmonary diseases (COPD) and asthma. However, the severity of CF and its effect on patients' lives differs. In addition, having no direct personal experience with pwCF may impact how I view and understand the experience of carers and children. Acknowledging these positions, which could influence the interpretation of the data, is part of ensuring good research quality.

2.3.4 Ethical consideration

2.3.4.1 Ethics and registration

Full NHS ethical approval was granted for this study on 4th October 2021 by the East Midlands – Leicester Central Research Ethics Committee (Ref: 21/EM/0210; see Appendix I). Newcastle Joint Research Office granted research sponsorship and insurance. I prepared all the necessary documents required for the ethical approval under the supervision of my supervisor.

2.3.4.2 Patient safety and wellbeing

Although this study aimed not to discuss sensitive topics, and the discussed areas are regarded as 'good news stories', a guideline was developed in the event of any experienced distress (see Appendix J).

2.3.4.3 Data management

A password-protected audio recording device (Sony ICD-UX570 Digital MP3/LPCM Dictaphone) was used to record interviews. The audio data were moved from the encrypted recording device to password-protected drives at Newcastle University. The original recordings were retained throughout the analysis phase to allow reviewing of the data for verification purposes if needed. The online interview transcripts were securely stored in a password-protected drive at Newcastle University. The printed transcripts were locked in storage that was only accessible to the research team.

2.4 Results

2.4.1 Sample demographics

Twenty-seven individuals participated in the study (ten cwCF, seven parents, and ten HCPs). Characteristics are summarised in **Table 3, Table 4** and **Table 5**. For confidentiality purposes, all participants have been given a pseudonym. Interviews ranged from 15 to 55 minutes (mean duration 30 minutes).

Table 3. Characteristics of children with cystic fibrosis.

Pseudonyms	**Gender**	**Age (years)**	**Time on elexacaftor-tezacaftor-ivacaftor (months)**	**Latest lung function result (ppFEV1, %)**
Rose	Female	16	16	91
Elisa	Female	17	15	104
Anna	Female	15	6	92
Maggie	Female	16	15	103
Arthur	Male	15	17	103
Pippa	Female	16	18	102
David	Male	13	18	98
Sonny	Male	14	18	110
Ruby	Female	13	11	88
Elizabeth	Female	14	16	106

ppFEV1: percent-predicted forced expiratory volume in 1 second

Table 4. Characteristics of parents/guardians.

Pseudonyms	Gender	Age of child (years)
Amy	Female	17
Martha	Female	15
Olivia	Female	13
Helen	Female	14
Rob	Male	13
Peter	Male	14
John	Male	14

Table 5. Characteristics of healthcare professional.

Pseudonyms	Role	Length of experience in cystic fibrosis care (years)
Sarah	Physiotherapist	>20
Laura	Nurse Specialist	10–15
Joan	Respiratory Physiologist	10–15
Kate	Physiotherapist	1–4
Jade	Consultant	10–15
Linda	Dietician	1–4
Emma	Nurse Specialist	>20
Mary	Physiotherapist	10–15
Julie	Physiotherapist	1–4
Suzi	Physiotherapist	5–9

2.4.2 Thematic map

Following the analysis of the data, an overall thematic map was created, integrating perspectives from all groups to formulate a comprehensive narrative. While the specific sample sizes were tailored to each group's distinct characteristics, the overarching goal of the thematic map was to merge and convey a coherent storyline that captures the collective essence of the study. Numerous insights were provided by participants about the impact of ETI, along with personal anecdotes and opinions. Commonalities in experience and some dissimilarities were identified. An overarching theme with three associated and interconnected themes were described, as summarised in **Figure 9,** that encapsulated the perspectives of cwCF, their careers, and HCPs.

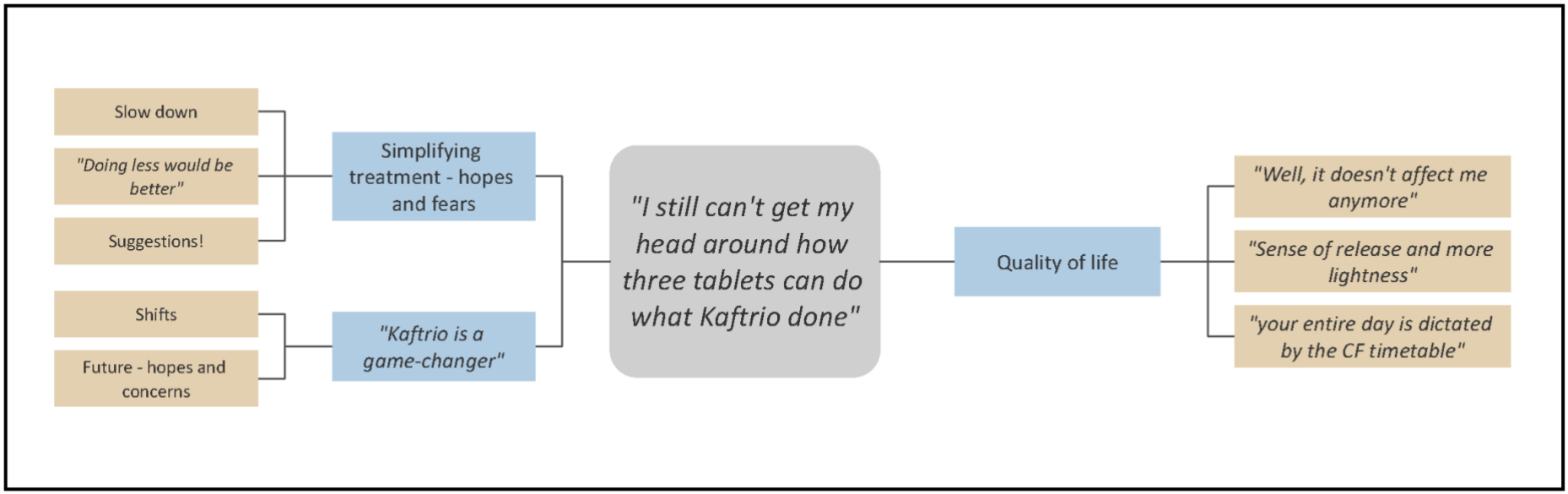


Figure 9. Thematic map of all participants.

2.4.3 Overarching theme. 'I still can't get my head around how three tablets can do what Kaftrio done'

This quote from a parent illustrates the huge impact ETI has had and summarises the overall experience. Substantial improvements in physical health have led to wider benefits in terms of mental well-being and extended social lives and opportunities for cwCF. In addition, reducing the burden of physiotherapy treatment led to a change in their attitude toward these treatments. The introduction of ETI has also changed the physiotherapy treatment and approaches to multidisciplinary care that are ongoing. The three associated themes are described below in the context of cwCF, their families, and HCPs.

2.4.4 Theme 1. Quality of life

Most participants emphasised the changes in their quality of life after starting ETI and they compared this with the time before taking it. Three subthemes captured the changes in the patients' and their carers' lifestyles.

Subtheme 1.1: 'Well, it doesn't affect me anymore'

This subtheme highlights the change in the physical symptoms cwCF and their carers experienced. As this young man indicated when asked about the difference he experienced after ETI, he described how the symptoms he had experienced as part of having CF had disappeared. He felt that CF does not affect his health any longer. The majority of cwCF interviewed felt that their respiratory symptoms, such as cough and shortness of breath, had reduced and that their lung function had improved. For example, Anna (cwCF aged 12–15 years) said:

> *I would say that it has made my lungs feel better. It's been less coughing overnight, which I appreciate…., and less mucus which I appreciate.*

Change in the frequency of infections was one of the main changes reported in the children's health. The drop in isolating Pseudomonas and the need for antipseudomonal therapy had made the cwCF and their families feel healthier.

Besides the respiratory symptoms, being more active and awake, having more energy, not being tired and sleeping well were all frequently described by children when they talked about the impact of ETI on their health. Maggie (cwCF aged 16–18 years) spoke about her health after ETI:

> *I'd say a bit because it's made me a lot better, more awake … I was really tired before, and I'd have like nine hours of sleep and still be tired and just like I need another nap. Now it's like I can wake up and just have a day and then sleep at the end instead of needing breaks during the day. Which is nice.*

Issues related to adverse events were not particularly prominent in the interview data. There were some negative comments about side effects participants experienced following ETI introduction, such as abdominal pain, headache, back pain, and acne, which lasted for a couple of weeks and then resolved. For example, Elisa (cwCF aged 16–18 years) said:

> *Immediately afterwards, I started getting a really, really sore stomach, but three weeks, that passed, and it's never come back.*

This subtheme emphasised the improvements in physical symptoms that reduce the disease burden on cwCF and their carers.

Subtheme 1.2: 'Sense of release and more lightness'

This subtheme focused on the psychological impact reported by the children and their families. Many participants reported a positive change in their outlook toward their lives due to the relief of respiratory symptoms. Several children relayed how as long as they could remember they had experienced multiple symptoms, and that now they felt incredibly well comparatively. Due to the progressive nature of CF, the idea of further deteriorating concerns cwCF, and experiencing the improvement with ETI had relieved this pressure. This healthy feeling meant for the first time they looked optimistically to the future.

Rose (cwCF aged 16–18 years) talked about her feelings before and after ETI:

> *For such a very, very long time, CF felt like a really untreatable thing, and everything you're doing feels like you're just trying to prolong something that – like prolong a life that might not be as high a quality as a lot of people's. But the Kaftrio has really been the first proper step towards an effective treatment that actually does something more than necessarily prolonging… You feel more like other people, and you feel more like you are healthy, even if you aren't necessarily better properly.*

Several parents also reported the positive impact of ETI on the quality of life of their child. Parenting an older child with CF can be challenging, and arguments about taking medication and doing ACTs are frequent issues. Many parents had previously spent a huge amount of time caring for their children only to see them struggling as they got older due to increasing symptoms compounded by the stress associated with an ever-increasing treatment burden. However, after starting ETI, their child was now much better than previously, which has relieved their stress. It is reassuring for parents to watch their children enjoying their time with friends and living like others in their age group. A common emotion among parents was a feeling of relief once they had confidence that ETI was working and was going to benefit their child.

The following quote from Peter (father of cwCF aged 12–15 years) illustrates the impact of their child's health improving with ETI on their own mental health:

> *Personally, my mental health and my wife's mental health has improved dramatically since this because it's been a long road coming, and it's very draining to have an emotional black space that's there constantly. Anything that lightens that black space up a little bit is a massive relief on your daily life …. That's our bonus, to make sure that she lives as healthy and as normal a life as possible. If she feels that she can do that better on Kaftrio, then that's good enough for us.*

Some cwCF expressed disappointment and frustration that they had not experienced as much benefit as some other people had. Several children compared their results with others who shared positive experiences on social media. For example, Ruby (cwCF aged 12–15 years) talked about her lung function and how she felt about not seeing the huge impact that she had been expecting:

> *I don't think there has been a huge impact. It's probably in the 80s now, which is still good. It's really good, but the difference, probably. I know some people who – well, I don't say I know, I mean like on social media and stuff – that has gone from 30 to 90, like it has been incredible.*

Overall, the improvement they experienced reduced the mental burden associated with CF.

Subtheme 1.3: 'Your entire life is dictated by the CF timetable'

This subtheme was revealed as participants described the burden of treatment and the impact on their life before and after starting ETI. As patients get older, this typically involves adding more treatments to the daily routine. Furthermore, as CF care has advanced over the decades,

developments have typically involved an increase in treatment burden. The introduction of ETI is different and may be associated with a reduction in treatment and withdrawing therapies.

Most children started ACTs from an early age and maintained that routine throughout their lives. This schedule places a constant pressure on families. Children felt that their lives were limited by the treatment. Although they understood the importance of ACTs and nebulisers in their care, they were often seen as a tedious daily process. Specific preparation is needed before they go out, especially if the treatment involves ACT or nebulisers. Most interviewees emphasised the burden of having nebuliser and ACT in their routine, and they see it as the most limiting treatment. The more nebulisers they have, the more restrictions they are placed under. Rob (a father of cwCF aged 12–15 years) discussed the burden of having ACTs and nebuliser:

> *Tablets is a lot easier, and she has got a lot more acceptance and tolerance to that because it's something that's quick and easy, and perhaps even other friends may take tablets and such as part of their general…. Whereas the nebuliser and the physio are certainly a big-ticket item in terms of being something different than others have to do. It takes the time out of everyday activities that need that. That has always been the inconvenience.*

This regime was also a constant reminder twice a day that they have CF making them feel different to their peers. Addressing this issue, Anna (cwCF aged 12–15 year) said:

> *It can be a bit annoying. You know, in your daily routine, it takes time to just organise your life around that, I suppose. It can be time-consuming every now and then, but apart from that, it's good for my health.*

Some cwCF need home IV treatment for infection, which is another restricting medication that requires specific preparation. Although frequent hospitalisation is burdensome and time restrictive for the whole family, some of the family see it as a chance to spend more time together. As Martha (a mother of cwCF aged 12–15 years) explained:

> *It's a bit of a pressure sometimes, as a parent and child. But yes, that one-to-one time is something that's a good side of it.*

The challenge becomes harder during holidays when the daily routine is disturbed, and they must work the treatment around the new timetable. The school usually helps to keep up with the routine, from waking up to sleeping. It becomes even more challenging when they meet with other family members who do not understand the meaning of having CF and its

consequences. Having to go through this conversation every time they socialise with others is an added burden for the family. Helen (a mother of cwCF aged 12–15 years) talked about her experience with her family, saying:

> *We would travel down to my family and stay with different family members, you see, so it regards to that social time. Also, people not understanding. Family members not understanding what had to be done, really, even though they have known it for years. [Laughter] It is just so alien to their world, so if we were going out for the day, having to explain, 'We have to be back for this', 'We have to do this', da, di, da, di, da, and.*

Commenting on the burden on parents or carers, Olivia (a mother of cwCF aged 12–15 years) emphasised the struggle with motivating their children to do their daily treatment properly, saying:

> *That responsibility of having to get everything done all the time. Just, yes, how did we feel? … With the Aerobika or whatever, to saying, 'Blow', 'Blow', 'Count', 'Concentrate', or with nebulisers, 'Are you holding that properly?', 'Are you sucking it up?', 'Are you doing this?', and it is the constant nudging to make sure that it is done in the right way".*

A small number reported they were resigned to their daily routine. They believed that acceptance was the best way to manage the burden and work the treatment around their lives. As Martha (a mother of cwCF aged 12–15 years) revealed:

> *We sort of didn't make it a big deal... You've got to do them but try and do them in a way that doesn't monopolise all of your day.*

Most participants felt that the treatment burden had diminished since starting ETI. Some cwCF stated that it was now easier to manage their treatment without it having an impact on their day. Going to school had become more manageable without needing to wake up early to complete physiotherapy treatment. Children were also now able to engage in more social activities. Sonny (cwCF aged 12–15 years) stated that:

> *I remember when I first started school again after it, I found it ridiculous how fast you can get ready in the morning without it. It took maybe 10, 20 minutes, just to do everything without tons of the stuff in the way.*

Even the children whose treatment routine had not changed after starting ETI felt that it was easier to complete the treatment now with less effort because they have more energy.

When the amount of treatment is reduced and the symptoms are relieved, the parents' 'to-do list' becomes more manageable. There was also evidence of less tension among family members about managing treatment and trying to get everything done within the time frame. Helen (a mother of cwCF aged 12–15 years) expressed the difference she felt in her family because of the reduced burden of treatment:

> *I think sometimes it has caused stress between mum and dad because if medication hasn't been ordered or somebody hasn't picked something up from the pharmacy or the pharmacy have got it wrong, and we have to go and sort it out, then that causes arguments… Now it is different because there aren't the little niggles and the tensions in the way that there used to be to try and get everything done within the time frame. We're a lot more relaxed now about things. And it seems like so much more manageable.*

The time that was freed up was regarded as a welcome bonus and allowed them to enjoy more quality family time. CwCF had more time to explore life with their peers. Parents who have lived their entire life since the diagnosis around managing the treatment and keeping their children healthy get the chance to look after themselves as expressed by Martha (a mother of cwCF aged 12–15 years) who said:

> *It was an extra 15 minutes out of your day, I think, when you get that back, you do suddenly realise that it's quite nice to have that time.*

Another burden parents cited is the preparation and administration of the treatment. Several carers believed their role reduces over time because the children grow older and more independent. The parent's role revolved around preparing the nebulisers, sterilising the equipment, and observing the physiotherapy techniques. After ETI, some of this treatment diminished or was eliminated from the routine, which makes it easier for the children to take on responsibility for their treatment, lightening the parents' burden. As illustrated by Martha (a mother of cwCF aged 12–15 years):

> *I mean, it has got less over time, because he has got more independent, he has got older, and the physio sort of changed.*

As stated in this subtheme, reductions in the treatment burden were associated with improvements in cwCF and their families' quality of life and mental health.

2.4.5 Theme 2. Simplifying treatment – hopes and fears

This theme developed when discussing opinions about the concept of reducing ACTs and nebulised treatment once established on ETI. Due to the considerable clinical improvements associated with ETI in many pwCF, some clinicians have advised reducing conventional treatments such as ACTs or nebulisers. This has been welcomed by most cwCF. However, there is no high-quality evidence to support this practice, and opinions differed amongst HCPs and families.

Subtheme 2.1: Slow down

All HCPs interviewed explained that they start reducing other treatments gradually after seeing an improvement in children's health. These HCPs recognised the importance of ACTs to maintain lung health. The lack of longer-term data has made decision-making difficult. Although HCPs understood how crucial reducing treatment burden is for the quality of life of many cwCF and their families. Suzi (a physiotherapist) commented:

> *They [CFTR modulators] are new, we don't know how long the effects are going to be, if they're going to be sustained or not. That's what makes me anxious.*

Another HCP Laura (a nurse specialist) said:

> *If it's safe for us to do so and we can reduce that load and that burden on them then I am all for it. Because it is a very intense daily schedule that a lot of the kids have to go through, I wouldn't want to do it myself and we're asking them to do it every day, day in day out forever, essentially. Which if there is an option to reduce it down it's going to make their quality of life so much better.*

Like the HCPs view's, most parents expressed their hesitation in changing their child's routine and preferred to take things slowly. From their point of view, it was seen as safer to keep doing ACTs to keep children as healthy as possible. They believed that the routine of doing ACTs was helping their children stay healthy, and changing this idea was hard for some. Most parents had managed this routine for their child's entire life, and some had experienced what could happen if their child did not do ACTs in the past. As a result, some families found it easier to keep the routine rather than disrupt it and risk needing to reintroduce it. This was one reason that made them hesitant to take the step of reducing treatment. Some mentioned they needed a scientific answer and time to see the feasibility of simplifying physiotherapy yet maintaining their child's health.

Amy (a mother of cwCF aged 16–18 years) summarised this as follows:

> *It's really hard because the physio for [child] has – apart from if she's got a cough or cold – it never anything comes out, there's no sputum comes out. So, you might think, 'Well, what's it doing?'... I reckon it is doing something, keeping her lung volumes up. I'm still very firmly of a mind that she must do it; she must do it to absolutely the best of her ability… I would rather just do it absolutely maximally and then know you've done everything you can, and then that's just in the hands of whatever happens.*

Only a small number of cwCF themselves mentioned uncertainty about reducing treatment being the right thing to do. Arthur's (cwCF aged 12–15 years) comment illustrates this:

> *They offered me the chance, last time we were at clinic, to drop one physio completely. But I didn't want to …. In case I started coughing again.*

Subtheme 2.2: 'Doing less would be better'

Contrary to the HCPs and carers' views, most children expressed enthusiasm about taking this step and thought that reducing physiotherapy would improve their lives and lessen the treatment burden. It was clear that the majority were keen to reduce their treatment as soon as possible, whereas parents were more reluctant. Some children explained that they had been willing to take the step and try stopping some ACTs or nebuliser treatment and see what happened. There was a sense of eagerness among some individuals who had already reduced some physiotherapy to move on to the next level and do none. For example Elizabeth (cwCF aged 12–15 years) said:

> *I'd rather try a break, because if you don't try it you're not going to know. Even if it does go wrong, you can just go back to it.*

Subtheme 2.3: Suggestions

Participants were asked to put forward suggestions about what should happen to ACTs and nebulised treatments following health improvements with ETI. Several children and parents proposed that ACTs should become 'as required' rather than daily. This would mean that they would feel more empowered and be able to contribute to the decision about when to introduce ACTs based on their judgment.

Helen (a mother of cwCF aged 12–15 years) said:

> *I think, depending on how you feel, it should be the patient's decision. It's their health, so they should be able to determine whether they need to or not with the guidance of the doctors.*

Several HCPs advocated for a shift in treatment protocols where approaches are more personalised and tailored to the individual patient's needs. Although they were generally supportive of this change, they highlighted the need to have a structured process and the need to track progress and accurately document any changes in the clinical record. This is crucial to identify the medications required, the starting point for simplifying treatment, and identifying the point of deterioration where treatment must be reintroduced.

This was summarised in this quote:

> *I think we need to come up with a plan of how to do that. I think we need more of a structure of how we're going to simplify it and how we monitor that. And what our objective measures will be on that. So we can decide if they're managing with the lesser reduction or the simplification of physio and things like that, whether that's working well. And what we then put as a threshold to then restart things or increase physio again or add nebulisers back in. I think it just needs a bit more structure.* ***(Sarah, a physiotherapist)***

Another suggestion was to encourage children to do more exercise as ACTs are reduced. Several participants mentioned that they believe that exercise could be an alternative option to ACTs that helps maintain physical health and provides a 'safety net' when simplifying ACTs. As Mary (a physiotherapist) commented:

> *I also think that my advice about exercise is becoming more important, because I suspect that people's – and this is the way I'll sell it to them – is that their ticket out of doing routine airway clearance or day-to-day physio is probably to move more. So, 'I would be happy to reduce your airway clearance to once a day, if you do some exercise.'*

A patient perspective on this was as Maggie (cwCF aged 16–18 years) stated:

> *I think you sort of need exercise still and everything like that … Because although the Kaftrio helps, I feel like you need something with it, so they work hand in hand, I think you still need them both.*

2.4.6 Theme 3. 'Kaftrio is a game changer'

The final theme was the change in CF clinical practice that has developed and is still evolving in the HEMT-era. It can be summarised by the quote from one of the HCPs describing ETI as a 'game changer'. This theme could be grouped into two subthemes: 'shift' and 'future-hopes and concerns'.

Subtheme 3.1: Shift

The majority of HCPs describe this era as a learning time and a challenging one. The changes that happened in a relatively short time were new and had never been experienced in CF practice. The CF treatment has been established over the years and it is challenging for them to change what they have been used to. These changes in patients' health impacted practice at a fast pace. Although excited about these positive effects, HCPs are hesitant and have no definite answer about the right steps. As Kate (a physiotherapist) said:

> *We have been waiting for it, but it has happened so quickly that we haven't necessarily – As CF in general, I don't think we'd got a plan of how we were going to de-escalate, what we stop first, and how long we wait until we stop the next thing.*

Some practitioners believe that honesty with the cwCF and their carers about this era's unpredictability is crucial to engage them more in the treatment plan. This idea is illustrated by Joan (a respiratory physiologist):

> *Almost trying to get them to understand we're learning as we're going along. I think that's been a big thing to let them know that we're still learning. We don't know yet what we need to stop, what we need to slow down and what we change, if anything. Just bear with us as we go along as well.*

A common view amongst participants was that a shift was noticed in practice after ETI was introduced. One of the changes that HCPs reported was a shift in the attitudes of children and families towards ACTs after starting ETI, especially in those who experienced significant health benefits.

There was a sense of growing confidence in individuals to decide on their own treatment. Some participants questioned the need for ACTs. After starting on ETI, some children have felt much healthier and, along with parents, voiced that they may not need to do ACTs, especially those who had no secretions.

As Joan (a physiotherapist) summarised:

> *I think some of the families and patients have almost voted with their feet a little bit, stopped things and then come and told us.*

Helen, (a mother of a cwCF aged 14 years) commented that:

> *He's not producing thick mucus with the drug. So, if he's not producing thick mucus, and he can cough things up himself, or he doesn't have a cough, then he doesn't need physio …. Or if it maybe potentially- I don't know.*

Another reported issue was a shift in the level of adherence with other treatments after starting ETI. Several HCPs felt that treatment adherence had deteriorated after the introduction of ETI because children and families felt they could miss some sessions without any harm. However, some HCPs argued that simplifying treatment had helped patients be more focused and committed to ACTs and to have the energy to do it.

As Mary (a physiotherapist) put it about adherence issues:

> *Think the challenges are still there and they're still the same, but they have been exaggerated, if you like. So, adherence has got a lot worse, because actually, they feel great.*

Another opinion about adherence from Laura (a nurse) is that:

> *The simpler we can make their treatment, the better, because they're more likely to do it.*

'Good luck getting me to do it again' (Sonny, a cwCF aged 12–15 years). This was how one of the children expressed his feeling about doing physiotherapy again after getting used to a simplified treatment regime.

This was a challenge that was also recognised by one of the physiotherapists when a patient experiences an exacerbation or infection and is required to do ACTs and use nebulisers:

> *Because I think they've almost had a taste of the good life, whereby they're doing less. I think it's very hard to then build back up again. (Mary, a physiotherapist)*

Another shift HCPs described was a change in the workload. Historically, physiotherapists mainly concentrated on ACTs, while after ETI, they focused more on promoting exercise and a healthy lifestyle. As a result of the health improvement, the load lies toward outpatient clinics compared with inpatient ones.

As Kate (a physiotherapist) stated:

> *I think, now, we probably do more outpatient stuff, but that's almost because they're more well, so we're able to maintain them at home. And it might be that we're doing a check because they've got a bit of a cough and just have an assessment and take a sample, rather than them coming in because they're so unwell and needing to come through A&E, and things like that.*

Some physiotherapists have raised concerns about the clinical role of physiotherapy and the possibility that demand for physiotherapy will diminish over time. As Mary (a physiotherapist) stated:

> *I think there might be less clinical role and maybe reduced frequency in their reviews as well. So, I think there's no doubt that my role will change, but obviously, for a very good reason. Hopefully, we'll always be needed, though.*

Others argued that the necessity for physiotherapy will persist, at least for those cwCF who do not have access to ETI and those who have not experienced a dramatic clinical benefit from the drug. These opinions are summarised by:

> *And maybe we have got the airway clearance there. But I think more emphasis on keeping them healthy, in terms of chest as well as exercise tolerance and lifestyle, will potentially go more towards the exercise side of things.* (Kate, a physiotherapist)

> *There'll still be some that need it because you'll always get the extremes with different kids that have difficulties. You've got the kids with the other genes that don't necessarily get it.* (Suzi, a physiotherapist)

Despite the positive impact of ETI, there are new challenges facing the CF multidisciplinary team. Weight management is a new challenge. In the past, maintaining good nutritional status was a significant focus of CF care. The normalisation of dietary advice for people who had required a high-calorie intake previously is a dramatic new recommendation. This was summarised by Ruby (cwCF aged 12–15 years) as*:*

> *Before Kaftrio, yes, you could eat anything you want because you wouldn't put weight on. Now, there was a period of time where I was getting really upset, because all of a sudden, I had got a lot of weight on.*

Mary (a physiotherapist) commented:

I think one of the other challenges that we're seeing now is not necessarily always physio-related, but I think will have a massive impact on physiotherapy, will be weight.

John (a carer of cwCF aged 12–15 years) summarised that their concentration switched from the CF toward other comorbidities:

The pressure has shifted from her CF – more or less – to the diabetes. Back then, the CF was the forefront. Always that was what was going to cause the problems. It's now that's taken a back seat to other issues that were there anyway.

Subtheme 3.2: Future – hopes and concerns

As a result of all the changes that have occurred with the introduction of ETI, some cwCF and their families have questioned, "What is next?". Discussing this issue, many participants voiced their concerns if the benefits gained from ETI would be sustained in the long term and wondered if their health would deteriorate in the future. CwCF and their parents constantly battled different types of infections and had more experience being sick than healthy. For this reason, building the confidence to maintain long-term health is hard for them. As Martha (a mother of cwCF aged 12–15 years) said:

And I think, as time goes on, the healthier he is for longer, then the more confidence you'll have.

Looking to the future with an optimistic scope is another observation noticed by participants. As a result of improvement in symptoms and reduction in the necessity for some treatment, cwCF and their carers feel more optimistic about the future and start recognising the potential influence on life expectancy. However, the anticipated increase in lifespan means they will experience comorbidities like diabetes and liver disease for longer. Peter (a father of cwCF aged 12–15 years) talked about his discussion with a member of the CF team:

They said, 'your life expectancy is a lot different to what it used to be. The problems that you probably wouldn't have faced with your diabetes before are problems you're going to have to think about'. It was a little bit of a light switch in my head that said, 'Wow, this probably is going to make a huge difference to the life expectancy of my daughter'. It was quite emotional to hear it, and that was probably the biggest change and the biggest effect that it had on myself... We feel like she's going to be here to annoy us for quite a long time.

A small number of participants stated that observing the results of ETI raised the expectation of having a genuine cure for CF in the future. Compared with the time before ETI, the idea of having such tablets targeting the underlying issue was far away. Now they are in this era and see the possibility of having a better cure:

> *I guess any parent is looking for a cure rather than managing.* (Rob, a father of cwCF aged 12–15 years)

The hope for the future extended to change in CF practice. Mary (a physiotherapist) describes her view for the future of physiotherapy practice in CF saying:

> *For example, physiotherapy-led CF clinic, rather than a consultant-led CF clinic. So, we would undergo full assessment of all of the systems and all aspects of CF, and manage those accordingly, with our extended roles of a non-medical prescriber. But then signpost back to a consultant if we had any concerns or problems. Or whether we work on a triage system, whereby there would be a general CF clinic and then a post-Kaftrio CF clinic, that would go to a physio, to then manage.*

Participants in general held diverse perspectives; HCPs emphasised long-term data and the next steps for practice, parents oscillated between concerns about potential health deterioration and adjustments in disease management, while cwCF generally maintained an optimistic outlook regarding the future.

Overall, the influence of ETI extends from clinical health variables to a better lifestyle for both cwCF and their parents. These results also impact CF practice and change as this treatment continues.

2.5 Discussion

This study aimed to increase understanding of the experiences of cwCF prescribed ETI and the opinions of their carers and HCPs about its impact. There was a particular focus on treatment burden, especially ACTs and nebulisers. The qualitative approach allowed an in-depth look at the experience of cwCF in this new era of care. Three main themes were identified relating to the improvement in the quality of life of cwCF and their families, their perspectives on approaches to simplifying treatment, and, finally, the shifts in CF clinical practice. The significant changes associated with ETI over a short period were encompassed by one overarching theme.

2.5.1 Theme 1. Quality of life

The findings highlight the major improvements in the health and lives of cwCF following the introduction of ETI. The first theme highlights the switch in the physical health, psychological health, social life, and treatment burden for both cwCF and their family. These results support a previous qualitative study that explored the influence of the older *CFTR* modulators (Orkambi and Kalydeco) on adults' outlook on life outside clinical health variables (Page, Goldenberg and Matthews, 2022). They interviewed eight pwCF in the US aged between 18 and 34 who had been on *CFTR* modulators for at least six months. Participants described the change they noticed in their physical health as improved or stable. They also highlighted the changes in their social lives and mental health where they no longer see CF as their identity compared to the time before the modulator.

There are also similarities between the physical and psychological positive attitudes expressed by adolescents in this study and those described by adults (Keyte, Kauser, Mantzios and Egan, 2022). Keyte, Kauser, Mantzios and Egan (2022) conducted a semi-structured interview with 20 pwCF from different countries to explore how ETI has affected individual lives, including physical and psychological well-being. Participants emphasised that, before ETI, the emotional burden of having CF was more complicated than the physical burden associated with their condition. However, after ETI, the symptoms of CF started to reduce, which reduced the burden of CF on their daily lives. PwCF appreciated the 'normal life' after ETI that comes with improved symptoms and quality of life.

One reported improved symptom in this study was sleep quality. This result is contrary to previous literature before ETI, where cwCF are more likely to experience sleep difficulties due

to physical symptoms, including coughing, wheezing, and gastrointestinal discomfort (Vandeleur *et al.*, 2017b; Vandeleur *et al.*, 2017a).

Similar to the present results, previous studies have demonstrated that beyond the burden of disease, the psychosocial impacts of living with CF for cwCF and their caregivers were profound before the introduction of ETI (Sawicki, Sellers and Robinson, 2008). Sawicki, Sellers and Robinson (2008) conducted a longitudinal study of 303 adults with CF from ten CF centres to describe the overall symptoms burden of CF using the Memorial Symptom Assessment Scale (MSAS). They concluded that adults with CF have a high symptom burden, especially respiratory and psychological symptoms. On the other hand, participants in this study described improved respiratory symptoms and mental health as a result of reducing the disease burden after ETI.

I also explored the possible detrimental effects of ETI. Some participants reported initial adverse effects, including abdominal pain, headaches, and rashes, but these were mild and eventually subsided. These findings support those reported in randomised clinical trials (Heijerman *et al.*, 2019). However, a previous qualitative study on adults on ETI reported severe adverse physical and psychological effects to the extent that they chose to stop ETI (Aspinall *et al.*, 2022). Aspinall *et al.* (2022) recruited 12 pwCF to share their experience of ETI. They reported two themes around the positive perceptions, which included improved quality of life and physical symptoms, and negative perceptions, including the side effects of ETI that impacted their quality of life and led to the cessation of the treatment.

The change in the treatment burden after ETI is another factor contributing to the quality of life, as described by participants. Several studies identified the burden of treatment for cwCF prior to HEMT (Quittner, Saez-Flores and Barton, 2016; Davies *et al.*, 2020a). A substantial amount of time was spent completing treatment daily, and this caused many to feel different from their peers (Ziaian *et al.*, 2006). A previous qualitative study with ten cwCF in the UK aimed to explore adolescents' attitudes toward risky behaviours such as lack of adherence. One of the themes acknowledges that keeping up with treatment is the most challenging aspect of CF for older children and prevents them from engaging in everyday activities (Keyte, Egan and Mantzios, 2019). This treatment burden usually increases as cwCF gets older due to

physical health. This burden has diminished with ETI, as reported by cwCF and their caregivers in this study.

A survey study of pwCF, their families, and their HCPs aimed to seek feedback from these groups about their willingness to stop some treatment. They reported ACTs and nebulised treatment as the most burdensome treatments among the CF community, and they wished to start simplifying the treatment with regards to these (Gifford, Mayer-Hamblett, Pearson and Nichols, 2020). Supporting the previous study, cwCF and their families in this study found the ACTs and mucolytics nebulisers to be the most stressful treatment. They believed that their life had been less burdensome since reducing these treatments.

Physical symptoms, sleep quality, mental health, social life, and treatment burden are all associated with cwCF and their families quality of life (Tomaszek *et al.*, 2019). Tomaszek *et al.* (2019) investigated the factors associated with Health-Related Quality of Life (HRQoL) in adolescents and young adults with CF. The survey was completed by 95 participants and included physical, social, treatment, symptoms, emotional function, future concerns, relationships, body image, and career dimensions. They concluded that anxiety and sleep quality have the broadest impact on HRQoL. Participants in this study reported improvements in their physical and mental health, social life, and reduced the treatment burden, and as a result, their overall quality of life improved. Continuous monitoring of these predictors could contribute to maintaining a high quality of life.

2.5.2 Theme 2. Simplifying treatment – hopes and fears

Following the introduction of HEMT, the call to simplify treatment has increased, and the adherence to some treatments has started to change. A retrospective study looked at treatment patterns, including inhaled antibiotics, dornase alfa, hypertonic saline, chronic oral antibiotics, and supplement feeding after starting ivacaftor. They found that these treatments tended to decrease or remain stable in the treated group compared to the non-ivacaftor group, where they remained stable or increased with time (Granger, Davies and Keogh, 2022). The wish to reduce the treatment burden is shared by all, but the safety of doing this must be ensured (Gifford, Mayer-Hamblett, Pearson and Nichols, 2020; Rowbotham *et al.*, 2018). A recent clinical trial examined the safety of discontinuing hypertonic saline or dornase alfa on ppFEV1 in patients receiving ETI for at least 90 days (Mayer-Hamblett *et al.*, 2021). They

concluded that discontinuing hypertonic saline and dornase alfa was non-inferior to continuing treatment regarding the absolute change in ppFEV1.

Despite the positive outcomes for many to date, there were also worries expressed about the longer term. HCPs, carers, and cwCF articulated concerns about sustaining benefits. Continuous evaluation of 'real-world' data is required to confirm long-term safety and efficacy, and qualitative approaches also provide important insights.

Reflecting this, most carers and HCPs favoured a cautious approach in simplifying treatment in the absence of high-quality clinical evidence to support doing this. HCPs emphasised the need for a structure in the process, monitoring progression, and precisely recording changes in the medical record. This is critical for determining the medications needed, the starting point for easing treatment, and the deterioration point at which treatment must be reintroduced. Contrary to the HCPs, most cwCF expressed a willingness to reduce physiotherapy. This result may be explained by the fact that parents and children have different perceptions of risk and responsibility (South *et al.*, 2023). In addition, adults tend to consider the longer-term consequences and prefer to be cautious. In contrast, adolescents tend to prioritise immediate satisfaction and show a lesser concern for future outcomes (Steinberg *et al.*, 2009).

In addition, this study presents a number of suggestions to simplify treatment and improve the engagement of CF patients. A structured and personalised approach is needed to improve adherence following the call to simplify treatment. Consistent with the literature, this research found that a responsive and personalised approach to physical therapy is likely the most effective solution (Flume *et al.*, 2009b; Rand, Hill and Prasad, 2013). Engagement of cwCF in developing their treatment plan and empowerment to select options based on their preferences with the shared goal of maximising health will be crucial. Children are different in their preference; some cwCF reported that they start doing more exercise after ETI because they see it as fun rather than treatment, while others do not like physical activity and prefer to do ACTs while sitting and watching TV. It is crucial to understand patients' preferences to help them engage and adhere more to the treatment (Flume *et al.*, 2009b). However, monitoring exercise and maintaining adherence levels is challenging, especially in adolescents (Santuzzi *et al.*, 2020).

Encouraging exercise is one of the tools suggested to support physical health by reducing ACTs. Several studies have examined the feasibility of exercise replacing ACTs, but no study has proven its effectiveness (Heinz *et al.*, 2022; Rowbotham *et al.*, 2020). A previous study conducted an online survey of pwCF, their families, and HCPs to collect ACT and exercise strategies data. They found that 54% of pwCF incorporate exercise into ACTs, and almost 50% of pwCF who exercised omitted ACTs (Rowbotham *et al.*, 2020).

In the era of HEMT, exercise adherence may be enhanced due to the reported improvement in respiratory symptoms, increased energy, and personalised treatment (Swisher and Erickson, 2008).

2.5.3 Theme 3. 'Kaftrio is a game changer'

Another important finding was the attitude of cwCF toward ACTs and nebulised treatment has changed, and they have started questioning their need for this treatment. In the pre-HEMT era, Williams, Mukhopadhyay, Dowell and Coyle (2007) explored the difficulties of adhering to ACTs and strategies used by families to overcome these difficulties in cwCF aged 7 – 17 years and their parents. They concluded that cwCF and their parents recognised the importance of ACTs and the benefits for their health which stemmed from personal experience of effect or trust in HCPs. Additionally, they considered visualising the mucus production and improving lung health as a motivation. This could explain the difference in attitude toward ACTs after ETI. Previously, the results of ACTs and nebulised treatment were more immediately apparent through mucus clearance. However, views towards ACTs have changed for many, possibly due to fewer problems with lower airway secretions.

Educating cwCF and their carers about the rationale for ACTs, nebulised treatment, and physical activity has become doubly important in the HEMT-era to improve adherence. Before the introduction of Kaftrio, Sawicki, Heller, Demars and Robinson (2015) interviewed 18 cwCF and their parents to identify the barriers and facilitators of adherence to chronic therapies. Recognising the importance of therapies and the lack of perceived consequences from non-adherence were identified as one of the barriers and facilitators of adherence. Another qualitative study interviewed cwCF and their parents emphasised the role of educating about the importance of ACTs. This education was found to contribute to the perceived benefits and

effectiveness of ACTs among this population (Williams, Mukhopadhyay, Dowell and Coyle, 2007).

Adherence is an ongoing issue reported after ETI. It correlates with multiple factors such as mental health (Quittner, Saez-Flores and Barton, 2016), the burden of treatment (Sawicki *et al.*, 2013), and the energy to do physical activity (Nap-van der Vlist *et al.*, 2021), and we need to look to all these factors to address the adherence issue.

Weight management was one of the new challenges reported in this study. Given the reported weight gain and the call to replace ACTs with exercise, a combination of calorie restriction and increased exercise may be the most appropriate approach rather than solely focusing on weight (Mantzios, Egan and Patchell, 2016).

The literature on CF prior to the introduction of CFTR modulators highlighted the unpredictability of the disease. A previous qualitative study assessed the hopes and fears for the future of young adults with CF. They found that pwCF expressed fear and uncertainty about the future due to the unpredictability of their health and hoped for normality (Higham, Ahmed and Ahmed, 2013). In contrast to previous literature, the participants in the current study expressed anticipation and optimism about their future, which they attributed to the CFTR modulator. Most participants in our study had positive expectations about the benefit of ETI before starting it based on the high-profile experiences of older patients. This finding is similar to the one reported in the adult population, where they expressed their prospect of a brighter future and that future drugs will be on the horizon (Keyte *et al.*, 2022). Equally, it is important to be mindful that some experience greater benefits than others and that for around 10% of the CF population, there is no HEMT option (Kramer-Golinkoff, Camacho, Kramer and Taylor-Cousar, 2022). A recent qualitative study explored the lived experience of pwCF who are not eligible for ETI. They expressed disappointment and conflicting emotions linked to dimmish hope (Milo, Ciciriello, Alghisi and Tabarini, 2023). Ongoing support for these groups is vital as there is genuine anticipation of a much longer and healthier life and reduced treatment burden for many others.

People on HEMT are expected to have an increased lifespan, meaning they will experience comorbidities for longer. Holistic care needs to be addressed, which includes support for

comorbidities, eating behaviours, and quality of life issues related to increased longevity. In addition, pwCF need to be educated about these adjustments. The adult population highlight the role of social workers, who help in planning for the future they did not expect to have (Keyte, Kauser, Mantzios and Egan, 2022).

2.5.4 Limitations and strengths

There were a few limitations to note in this study. One limitation of this study is the sample size which was limited to one centre and did not explore the experience from a different centre or area. In addition, the interviews were conducted after a relatively long time (approximately one year) on ETI, which may have made it hard to remember and compare with the time before ETI. Another potential limitation of this study is the possibility of selection bias, as families of children who experienced positive responses to the intervention may be more inclined to participate. This could lead to an overrepresentation of success stories and potentially skew the findings towards more favourable outcomes.

Furthermore, despite our effort to include all specialities of HCPs, we could not include a social worker and psychologist, who could have added valuable insights. The social worker was on leave during the study's recruitment time, and there was no psychologist in the CF team. The fact that I am a non-native English speaker is another limitation that could provide some difficulties, mainly when communicating with the adolescent participants. Lastly, interviews were conducted online, making establishing rapport with some participants harder.

On the other hand, this research has demonstrated numerous strengths. Most of the current literature has focused on the experience of adults with CF after HEMT. However, limited attention has focused on the experience of young people. This study contributes to an area of literature that has been under-researched and gives an insight into the lived experience of cwCF. Another strength of this study was the heterogeneity of age and gender of the cwCF interviewed with various degrees of severity, which reinforces our findings and represents a balance of views. This study also explored the perspective of a different group, including cwCF, carers, and HCPs, which helps to understand the impact of ETI from a different perspective.

2.6 Conclusion

This study has provided a deep understanding of what cwCF, families, and HCPs have experienced after the introduction of ETI. Introducing HEMT has improved many CF patients' health and quality of life. On the other hand, some cwCF did not experience the expected results and compared their results with others. Patients who are not eligible for CFTR modulator therapy or did not experience the expected outcomes may need support. Before beginning ETI, educating patients about the potential outcomes is essential.

Despite the overall highly positive experiences, new challenges have emerged and must be addressed. The introduction of ETI has prompted a shift from traditional treatment approaches, especially concerning ACTs and nebulised therapy. This offers an opportunity to personalise treatment, but it remains vital to study longer-term effects.

Chapter 3. The Impact of Elexacaftor-Tezacaftor-Ivacaftor on Physiotherapy Treatment and Clinical Outcomes in Children with Cystic Fibrosis: A Single-Centre, Retrospective Study.

3.1 Introduction

ETI is a newly approved CFTR modulator drug that contains two correctors, which correct protein misfolding and trafficking of CFTR to the apical membrane, and one potentiator that works to improve channel gating and increase epithelial Cl^- transport (Haq *et al.*, 2022). Randomised clinical trials have demonstrated ETI to be more efficient in improving lung function, body weight, and quality of life, and in reducing sweat Cl^- and exacerbations (Heijerman *et al.*, 2019; Middleton *et al.*, 2019) than previous dual CFTR modulators (tezacaftor-ivacaftor or lumacaftor-ivacaftor) (Munck *et al.*, 2020; Paterson, Barry and Horsley, 2020). These favourable findings led to the approval of ETI for people with CF (pwCF) aged 12 years and older with ≥ 1 F508del-*CFTR* allele in the UK in late 2019 with access later expanded to individuals aged 6 years and older.

It is important to understand the impact of ETI in real-world clinical settings, along with the results obtained from clinical trials and their open-label extensions, to validate its long-term efficacy and safety. Using real-world data, a recent study of the effect of ETI in the eligible CF population has found that treatment is associated with improved outcomes, including better lung function preservation, improved nutritional status, and decreased hospitalisation risk compared with a five-year pre-treatment period (Bower *et al.*, 2023). Recent evidence from the real world also shows that ETI reduces infection-related hospital visits and the use of antimicrobials (Miller *et al.*, 2022).

Treatment burden is a critical factor in the quality of life of pwCF and simplifying these treatments is one of the top research priorities in the CF community (Cameron *et al.*, 2022). In a recent study, pwCF reported the importance of reducing the treatment burden and it was suggested to capture it as a secondary outcome in clinical trials routinely (Cameron *et al.*, 2022). Nichols *et al.* (2022) conducted a study on the impact of ETI on the use of four chronic inhaled medications, which revealed a decline in their usage after six months. To date, there has been little work published on the real-world evidence of long-term changes in the treatment pattern in cwCF prescribed ETI (Nichols *et al.*, 2022).

3.2 Aims

The objective of this study was to report the impact of ETI after 12 months in cwCF between the ages of 12 and 18 years at the GNCH in a real-life clinical setting. The first aims were to investigate the changes in lung function and body weight in addition to the correlation between the change in lung function and other clinical factors. Furthermore, this study also aimed to investigate the change in the physiotherapy treatment including use of ACTs, mucolytic nebulisers and exercise. This study also evaluated the prevalence of respiratory infections and respiratory culture sample types following ETI treatment.

3.3 Methods

3.3.1 Design and setting

This was a single-centre, retrospective, observational study conducted at the regional paediatric CF service at the GNCH, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne. All cwCF aged between 12 and 18 years and prescribed ETI for at least one year were included. The patients' clinical records were reviewed from September 2019 to January 2023.

3.3.2 Data collection and processing

Clinical data were collected from a two-year period (one year before starting ETI and one year after). The majority of the clinical data were extracted from the electronic patient record at the two census points. The baseline time point was one year before the initiation date of ETI, and the follow-up time was one year after the start date of ETI. Following is the extracted data:

- Age (years) at the time of data collection (December 2022)
- Sex (male/female)
- Ethnicity – categorised as the following, according to NHS data: White, Mixed, Asian, Black, Other Ethnic Groups, Not stated, Not known
- CFTR variants
- Start date of ETI
- Previous use of modulators – (tezacaftor-ivacaftor, lumacaftor-ivacaftor, ivacaftor)
- Weight (kg) and centile (%) using UK–World Health Organisation (WHO) charts

- Height (cm) and centile (%) using UK-WHO charts
- Body mass index (BMI) centile and BMI – z score using UK–WHO charts. BMI z-score is a measure of how many standard deviations a child or adolescent person's BMI is above or below the average BMI for their age and gender (National Institute for Health and Care Excellence, 2013).
- Lung function, percent-predicted forced expiratory volume in 1 second (ppFEV1). The ppFEV1 measure compares the actual volume breathed out during the first second of the test to the average for a person of the same sex, height, and age using the Global Lung Function Initiative (GLI) equation. The GLI has gathered lung function outcomes from researchers and medical professionals worldwide and established spirometry reference equations. Spirometry prediction equations for the age range of 3–95 include appropriate age-dependent lower normal limits. These apply to all racial and ethnic groups worldwide (Quanjer *et al.*, 2012). For this study, all readings of the ppFEV1 were recorded over one year before ETI and one year after starting ETI. The mean for each year was then calculated for every cwCF.
- Use of nebulised mucolytic treatment (dornase alfa or hypertonic saline)
- Airway clearance technique (ACT) – all information recorded in the physiotherapy notes related to ACTs was collected. ACTs are the primary therapy for cwCF to clear airway secretions. The range of different types of ACTs used by cwCF according to the Cystic Fibrosis Trust (2022) were:
    1- Breathing exercises as active cycle of breathing techniques (ACPT) which consists of deep-breathing exercises, relaxed breathing, and huffs.
    2- Positive expiratory pressure (PEP) mask: this device requires breathing against an expiratory resistance.
    3- Oscillating PEP as Aerobika and Acapella: these devices combine positive expiratory pressure and high frequency oscillations.
    4- Mechanical devices such as high-frequency chest wall oscillation (known as the vest): this vest vibrates the chest, causing secretions to loosen.
    5- Others, including non-invasive ventilation (NIV) and NIPPY Clearway™, which is a device for clearing the airway. It has different modes, such as mechanical insufflation and exsufflation. The programmable auto mode, which is activated by

the patient, can be set to deliver multiple insufflations before a single exsufflation. This can be done in cycles (Gaynor and Wood, 2018).

The type of ACT, the frequency per day, and the number of cycles were noted from the electronic record.

- Exercise – all information documented in the physiotherapy notes related to physical activities and exercise was collected.
- Exercise test – Shuttle tests are simple, low-cost field tests that have been used to assess the exercise performance of children. The modified shuttle test (MST) challenges participants to walk back and forth over a 10-metre track at a predetermined speed indicated by an audio track, and this cycle continues for 15 levels of increasing difficulty (Bradley, Howard, Wallace and Elborn, 1999; Singh *et al.*, 1992). The test finishes when the participant fails to reach the cone on two consecutive shuttles, experiences voluntary exhaustion or completes level 15. The total distance, the number of completed levels achieved, and oxygen saturations (SpO_2) are the outcomes reported (Hebestreit *et al.*, 2015). The total distance and number of completed levels were recorded for this study.
- *P. aeruginosa* status – chronic infection as determined by being maintained on long-term, inhaled, antipseudomonal antibiotics (as per GNCH protocol, having isolated *P. aeruginosa* on three occasions in the preceding two years)
- Respiratory microbiology – all recognised CF pathogens isolated, and sample types were recorded over one year before and after starting ETI.

Data were collated using a Microsoft Excel (Microsoft 365 MSO) spreadsheet and were checked for accuracy and completeness before analysis.

3.3.3 Statistical analysis

All analyses were carried out using the Statistical Package for the Social Sciences (SPSS), software version 28 (IBM), and Prism version 9.0 (GraphPad software) was used to prepare graphical representations of data.

The first part of the analysis generated descriptive analyses for all variables. Descriptive data are reported as mean, standard deviation (SD) for normally distributed continuous data, and median and interquartile ranges (IQR) for non-normally distributed continuous data. For

categorical variables, they are described as frequencies and percentages. The second part included, where appropriate, pre–post design tests to assess whether any differences occurred after starting ETI treatment; a p value < 0.05 was defined as statistically significant. Specific tests used were:

- The Shapiro-Wilk test was used to investigate the data's normality.
- A paired t-test was conducted for continuous variables that were normally distributed.
- The Wilcoxon signed-rank test was used to compare continuous, non-normally distributed variables.
- A non-parametric test, the Stuart-Maxwell test was used to compare differences in categorical variables.
- Pearson correlation analysis was conducted to determine the degree of association between two normally distributed variables.
- Spearman correlation analysis was conducted to determine the degree of association between two non-normally distributed variables.
- The Point-Biserial Correlation Coefficient was used to determine the degree of association between continuous and categorical variables.

  All statistical analyses were made following consultation with a statistician.

3.3.4 Ethics

The study was performed as a retrospective audit. Regional ethics committee approval was not required as only medical records were accessed. Patient confidentiality and data protection were ensured using an anonymised identification number for each patient, which was securely stored. The Research and Development Department of Newcastle upon Tyne Hospitals NHS Foundation Trust approved access for the study (see letter of access in Appendix K).

3.4 Results

3.4.1 Study cohort demographics

A total of 61 children and young people between the ages of 12 and 18 years were identified from the regional CF service at GNCH. Out of these, 40 (67%) commenced ETI and were eligible to be included. **Figure 10** displays the inclusion criteria of cwCF in this study.

The characteristics of the study cohort at baseline, prior to the administration of ETI, are presented in **Table 6.** The study cohort was 60% female and 100% white ethnicity. The mean age at the time of data collection was 14.5 years (SD = 1.53), ranging from 12 to 17 years old. Looking at the type of *CFTR* variants in **Figure 11**, homozygous F508del made up 55% of the study cohort, 42.5 % were heterozygous for F508del, and 2.5% were heterozygous for G551D. Out of the 40 children included in the study, more than half (62.5%) were on another CFTR modulator (lumacaftor-ivacaftor (Orkambi) or tezacaftor-ivacaftor (Symkevi)) prior to starting on ETI. Only one child was on a HEMT (ivacaftor) before starting ETI.

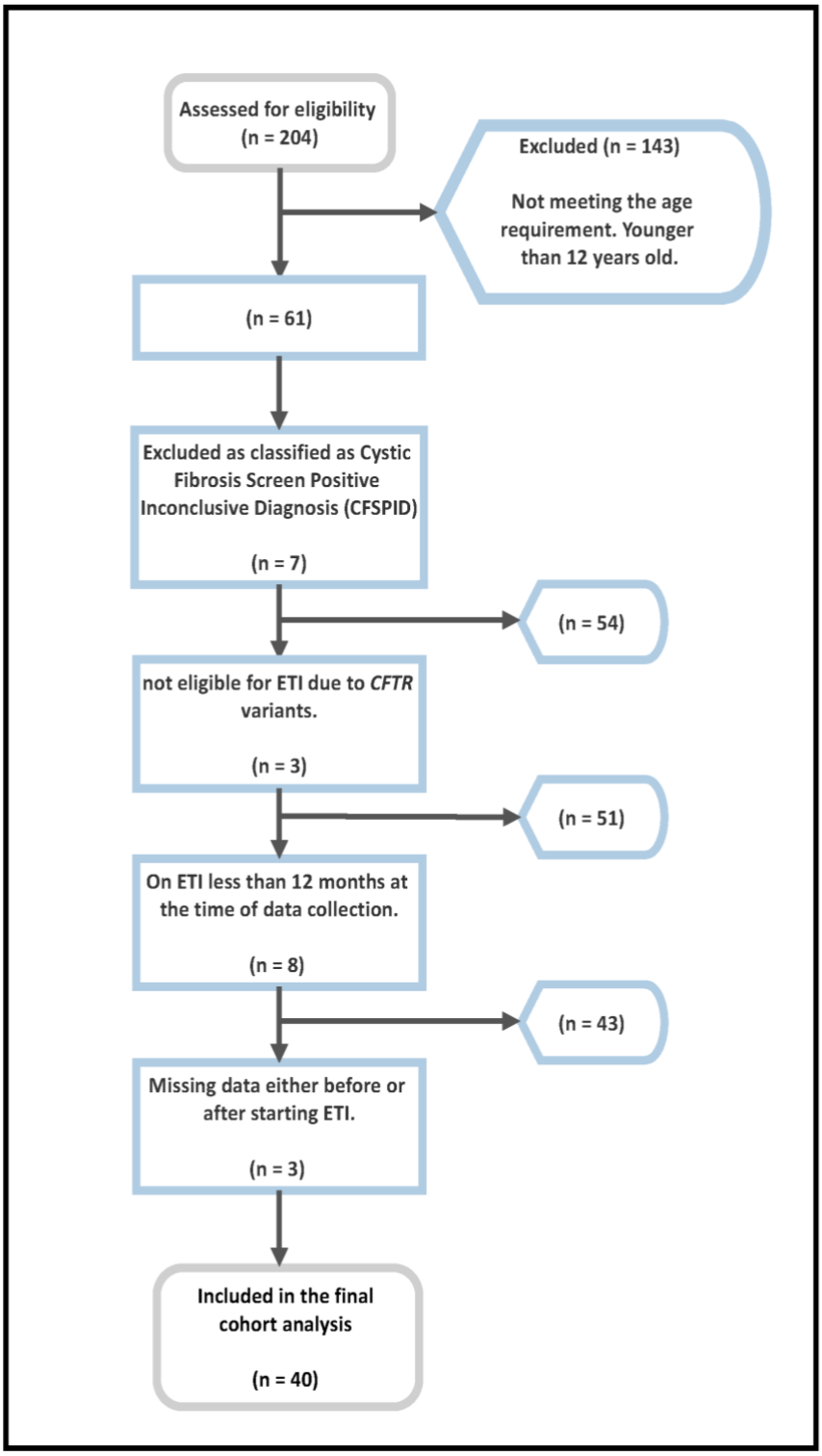


Figure 10. The inclusion criteria of children with cystic fibrosis (CF).

CFTR: cystic fibrosis transmembrane conductance regulator; ETI: elexacaftor-tezacaftor-ivacaftor.

Table 6. Baseline characteristics of children included in the study.

Baseline characteristics	All	Homozygous F508del	Heterozygous F508del
N (%)	40	22 (55)	17 (42.5)
Age (mean ± SD), years	14.5 ± 1.5	14.8 ± 1.6	14.2 ± 1.4
Sex			
• **Male (%)**	16 (40)	7 (43.7)	8 (50)
• **Female (%)**	24 (60)	15 (62.5)	9 (37.5)
Race • **white (%)**	40 (100)	22 (55)	17 (42.5)
Body weight median (IQR), kg	41.8 (36.6 -51.2)	42.5 (36.3 - 47.6)	40.4 (35.4 - 53.51)
Weight centile median (IQR), %	57.2 (19.3 - 84.2)	42.6 (16.3 - 82.0)	68.2 (25.7 - 88.9)
Weight Z-score (mean ± SD)	0.17 ± 1.3	-0.07 ± 1.2	0.36 ± 1.4
BMI median (IQR), kg/m²	19.05 (16.3 – 20.8)	18.02 (16.3 – 20.8)	19.7 (16.4 – 20.8)
BMI centile median (IQR), %	57.8 (22.3 – 89.4)	36.9 (13.9 - 88.4)	71.6 (36.9 - 88.6)
BMI Z-score (mean ± SD)	0.24 ± 1.2	-0.05 ± 1.2	0.38 ± 1.4
Height (mean ± SD), cm	151.1 ± 10.4	149.7 ± 9.0	151.4 ± 10.3
Height centile (mean ± SD), %	52.4 ± 27.1	48.6 ± 27.1	54.3 ± 26.0
ppFEV1 (mean ± SD)	89.6 ± 15.4	88.3 ± 16.2	91.3 ± 15.2

BMI: body mass index; IQR (interquartile): 3rd quartile – 1st quartile; ppFEV1: percent predicted forced expiratory volume in 1 second; SD: standard deviation.

Note: The table presents baseline characteristics for all participants, with detailed results provided for two groups. The heterozygous G551D group, comprising one participant, is not individually broken down.

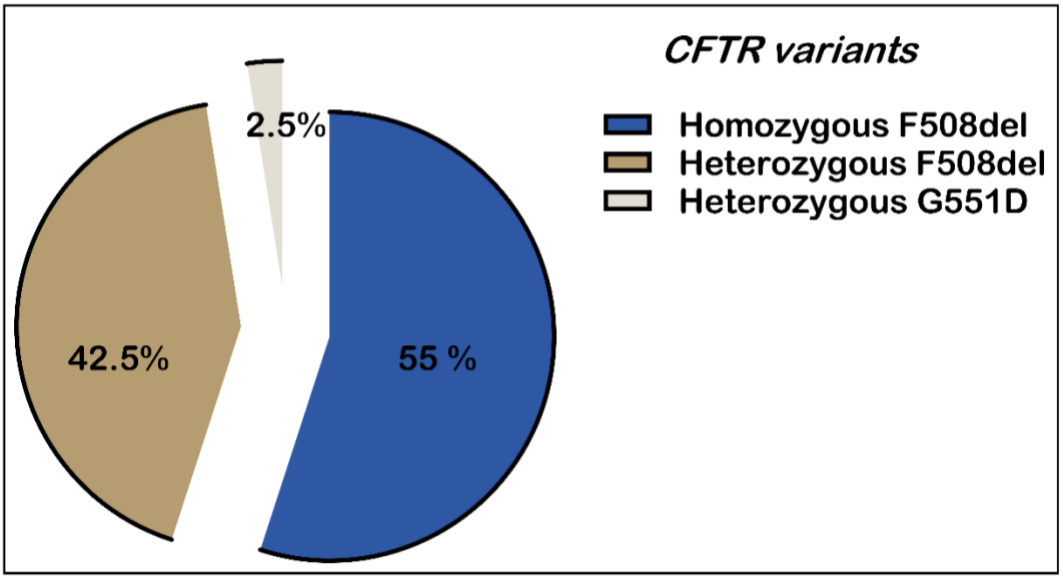


Figure 11. Cystic fibrosis transmembrane conductance regulator (CFTR) variants distribution.

The distribution of CFTR variants among the study cohort showed 55% with homozygous F508del, 42.5% heterozygous F508del, and 2.5% heterozygous G551D. CTFR: cystic fibrosis transmembrane conductance regulator.

3.4.2 Effect of elexacaftor-tezacaftor-ivacaftor (ETI) on weight and body mass index (BMI) percentile

The weight (recorded in kg) and centile percentage for included children are shown in **Table 7.** Descriptive statistics for weight showed a median weight of 41.8 kg (IQR = 36.6 – 51.2) pre-ETI, which increased to 52.3 kg post-ETI. The absolute increase in weight from baseline after 12 months on ETI was 9.8 kg. The median weight centile was 57th pre-ETI, which increased to 65th post-ETI. The absolute increase in weight centile from baseline after 12 months on ETI was 8 centiles. The mean weight z-score was 0.17 pre-ETI, which increased after-ETI to 0.33. The absolute increase in weight z-score from baseline after 12 months on ETI was 0.16.

The BMI median was 19.05 pre-ETI, which improved to 20.8 after -ETI. The absolute increase in BMI after 12 months on ETI was 1.75. The median BMI centile was on the 57th centile pre-ETI, which increased after-ETI to 74th. The absolute increase in BMI centile from baseline after 12 months on ETI was 16 centiles. The mean BMI z-score was 0.24 pre-ETI, which increased after-ETI to 0.56. The absolute increase in BMI z-score from baseline after 12 months on ETI was 0.32. **Figure 12** and **Figure 13** display the weight and BMI parameter pre- and post-ETI.

A Wilcoxon signed-rank test was performed to assess the differences in weight, weight centile, BMI and BMI centile after ETI. The results indicated a statistically significant difference in the median weight before and after ETI: $z = -5.4$, $p < 0.001$, median BMI $z = 3.9$, $p < 0.001$, and BMI centile $z = -2.05$, $p = 0.041$. On the other hand, there was no significant difference concerning weight centile: $z = -0.69$, $p = 0.49$. Paired t-test was used to assess the difference in weight z-score and BMI z-score. The result showed a statistically significant difference in BMI z-score after ETI: $t(35) = -2.77$, $p < 0.009$, while the difference in weight z-score was not statistically significant after ETI: $t(38) = -1.56$, $p = 0.13$

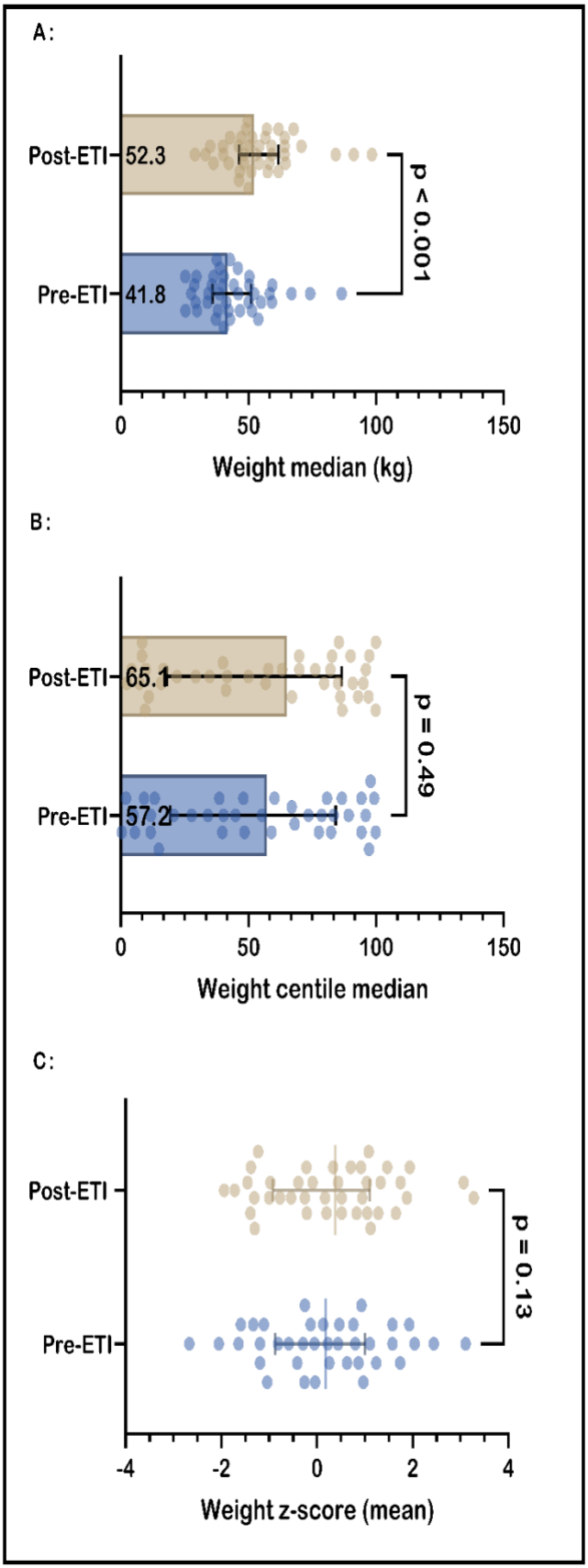
Table 7. Weight difference before and after treatment with elexacaftor-tezacaftor-ivacaftor (ETI).

Parameters	Pre-ETI	Post- ETI	p value
Body weight median (IQR), kg	41.8 (36.6 -51.2)	52.5 (46.4 - 61.8)	< 0.001*
Weight centile median (IQR), %	57.2 (19.3 - 84.2)	65.1 (18.0 - 86.6)	0.49
Weight z-score (mean ± SD)	0.17 ± 1.3	0.33 ± 1.3	0.13
BMI median (IQR), kg/m^2	19.05 (16.3 – 20.8)	20.8 (18.8 – 23.1)	< 0.001*
BMI centile median (IQR), %	57.8 (22.3 – 89.4)	73.8 (29.7 –89.4)	0.041*
BMI z-score (mean ± SD)	0.24 ± 1.2	0.56 ± 1.2	0.009 *

A paired t-test and Wilcoxon signed-rank test was used to test the difference before and after ETI treatment.

BMI: body mass index; ETI: elexacaftor-tezacaftor-ivacaftor; IQR (interquartile): 3rd quartile – 1st quartile; SD: standard deviation.

* p value < 0.05 considered statistically significant.



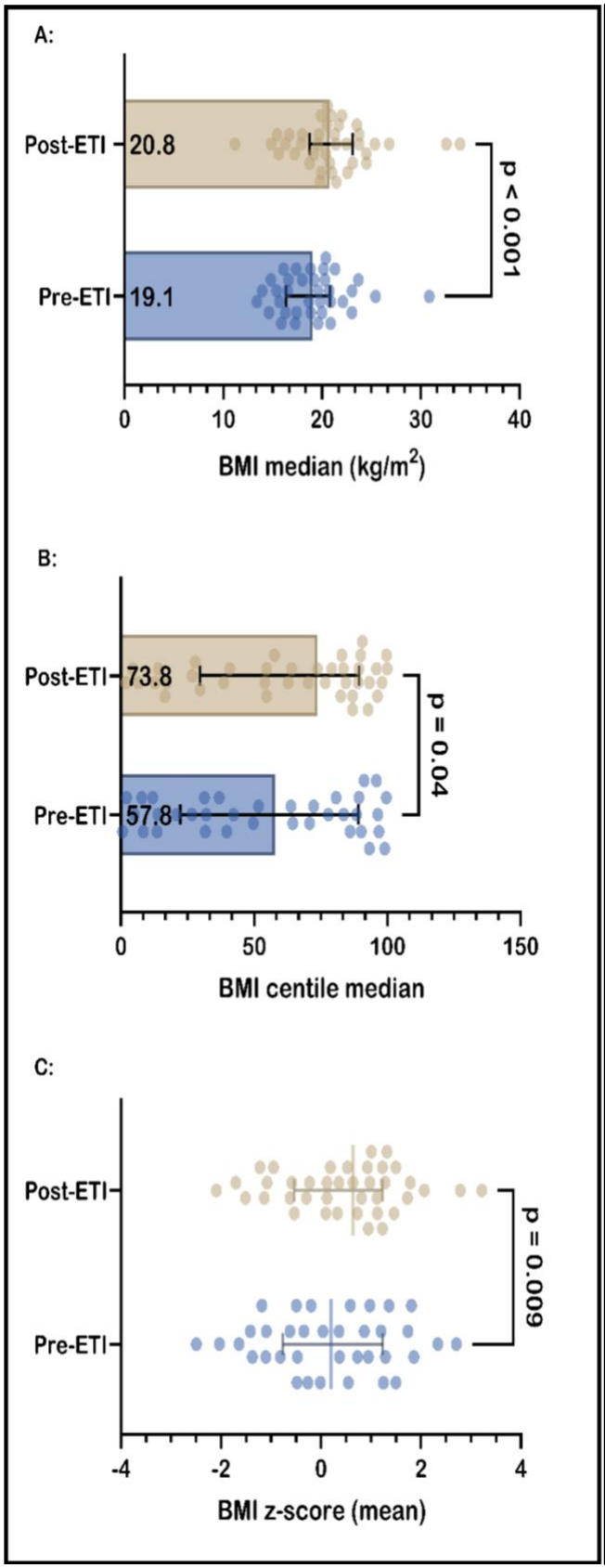
A: Weight median in kg pre-ETI was 41.8 kg and post-ETI increased to 52.3 kg. The error bar represents the interquartile range, and the small dots represent the individual weight readings for all cohort. A Wilcoxon signed-rank test was used to test the difference before and after ETI treatment, which indicates a statistically significant difference: $p < 0.001$.

B: Weight centile median pre-ETI was 57.2 and post-treatment increased to 65.1. The error bar represents the interquartile range, and the small dots represent the individual weight centile data for each child in the cohort. A Wilcoxon signed-rank test was used to test the difference before and after ETI treatment, which shows no statistically significant difference: $p = 0.49$.

C: Weight z-score pre-ETI was 0.17 and post-treatment increased to 0.33. The vertical line represents the mean. The error bar represents the standard deviation, and the small dots represent the individual weight z-score readings for all cohort. Paired t-test was used to assess the difference in weight z-score which showed not statistically significant difference $p = 0.13$.

ETI: elexacaftor-tezacaftor-ivacaftor.

Figure 12. Weight parameters before and after elexacaftor-tezacaftor-ivacaftor (ETI) treatment.



A: BMI median pre-ETI was 19.05 and post-ETI increased to 20.8. The error bar represents the interquartile range, and the small dots represent the individual BMI readings for all cohort. A Wilcoxon signed-rank test was used to test the difference before and after ETI treatment, which shows statistically significant difference: $p < 0.001$.

B: BMI centiles median pre-ETI was 57.8 and post-ETI increased to 73.8. The error bar represents the interquartile range, and the small dots represent the individual BMI centile readings for all cohort. A Wilcoxon signed-rank test was used to test the difference before and after ETI treatment, which shows statistically significant difference: $p = 0.04$.

C: BMI z-score mean pre-ETI was 0.24 (SD ± 1.2) and post-ETI increased to 0.56 (SD ± 1.2). The vertical line represents the mean. The error bar represents the standard deviation, and the small dots represent the individual BMI z-score readings for all cohort. Paired t-test was used to assess the difference in BMI z-score which showed a statistically significant difference $p = 0.009$.

BMI: body mass index, ETI: elexacaftor-tezacaftor-ivacaftor.

Figure 13. Body mass index (BMI) parameters difference after elexacaftor-tezacaftor-ivacaftor (ETI) treatment.

3.4.3 Effect of elexacaftor-tezacaftor-ivacaftor (ETI) on percentage predicted forced expiratory volume in 1 second (ppFEV1)

The ppFEV1 readings were recorded over a period of a year before and a year after starting the ETI. The mean ppFEV1 for each year was then calculated for each cwCF.

The mean ppFEV1 was calculated for all participants and subset groups based on sex, *CFTR* variants, previous use of modulators, and chronic infection with *P. aeruginosa,* as shown in **Table 8** , **Figure 14,** and **Figure 15.**

The mean ± SD ppFEV1 at baseline for all participants was 89.6% ± 15.4. One year after ETI, the mean improved to 99.5% ± 14.4, with an absolute change of + 9.9%. The lung function in terms of ppFEV1 pre-ETI and post-ETI was compared using paired t-tests, and a statistically significant difference was found, $t(38) = -5.37$, $p < 0.001$.

When analysing ppFEV1 based on sex, females showed a higher increase in the mean difference of 11.2 ± 10.5 ($p < 0.001$) compared to males, who improved by 8.4 ± 12.8 ($p < 0.019$). In the *CFTR* variants sub-analysis, the mean difference in ppFEV1 for the homozygous F508del group was 11.6 ± 10.4 ($p < 0.001$) compared to 8.4 ± 12.9 ($p < 0.016$) for heterozygous F508del. Based on the baseline use of a modulator, the mean difference in ppFEV1 for those naïve to modulators was 11.6 ± 13.1 ($p < 0.006$) compared to those who had previously used modulators, with a mean difference of 8.9 ± 10.7 ($p < 0.001$). CwCF chronically infected with *P. aeruginosa* showed a mean difference in ppFEV1 of 14.2 ± 12.8 ($p < 0.001$) compared to those not chronically infected with *P. aeruginosa*, with a mean difference of 6.2 ± 8.9 ($p < 0.005$). However, the mean ppFEV1 statistically significantly improved in all subgroups.

Table 9 presents the breakdown of ppFEV1 before and after the initiation of ETI for all children included in the study. As shown in **Table 9**, 33 children (85%) showed an improvement in their ppFEV1, five children (12.8%) showed deterioration in their ppFEV1, and one child showed no difference in mean ppFEV1 over the 12 months pre-ETI and 12 months post-ETI. The change in ppFEV1 was heterogeneous across children.

Table 8. Percent-predicted forced expiratory volume in 1 second (ppFEV1) difference before and after elexacaftor-tezacaftor-ivacaftor (ETI) treatment.

Outcomes	Subgroup	N	Pre-ETI mean ± SD	Post-ETI mean ± SD	Mean difference ± SD	p value
ppFEV1, %	All	39	89.6 ± 15.4	99.5 ± 14.4	9.9 ± 11.5	< 0.001*
	Female	24	89.0 ± 16.7	100.2 ± 15.3	11.2 ± 10.5	< 0.001*
	Male	16	89.8 ± 13.5	98.4 ± 12.7	8.4 ± 12.8	0.019*
	Homozygous F508del	22	88.3 ±16.2	99.9 ± 14.9	11.6 ± 10.4	< 0.001*
	Heterozygous F508del	17	91.3 ± 15.2	99.7 ±14.3	8.4 ± 12.9	0.016*
	On a modulator previously	26	90.7 ± 15.5	99.6 ± 14.3	8.9 ± 10.7	< 0.001*
	Not on a modulator previously	14	87.8 ± 15.8	99.3 ± 15.1	11.6 ± 13.1	0.006*
	Chronically infected with *P. aeruginosa*	18	86.7 ± 18.0	101.0 ± 16.3	14.2 ± 12.8	< 0.001*
	Not chronically infected with *P. aeruginosa*	21	92.1 ± 12.7	98.3 ± 12.8	6.2 ± 8.9	0.005*

ETI: elexacaftor-tezacaftor-ivacaftor; N: number of children; *P. aeruginosa: Pseudomonas aeruginosa*; ppFEV1: percent-predicted forced expiratory volume in 1 second; SD: standard deviation.

Paired sample t-test was performed.

* p value < 0.05 considered statistically significant.

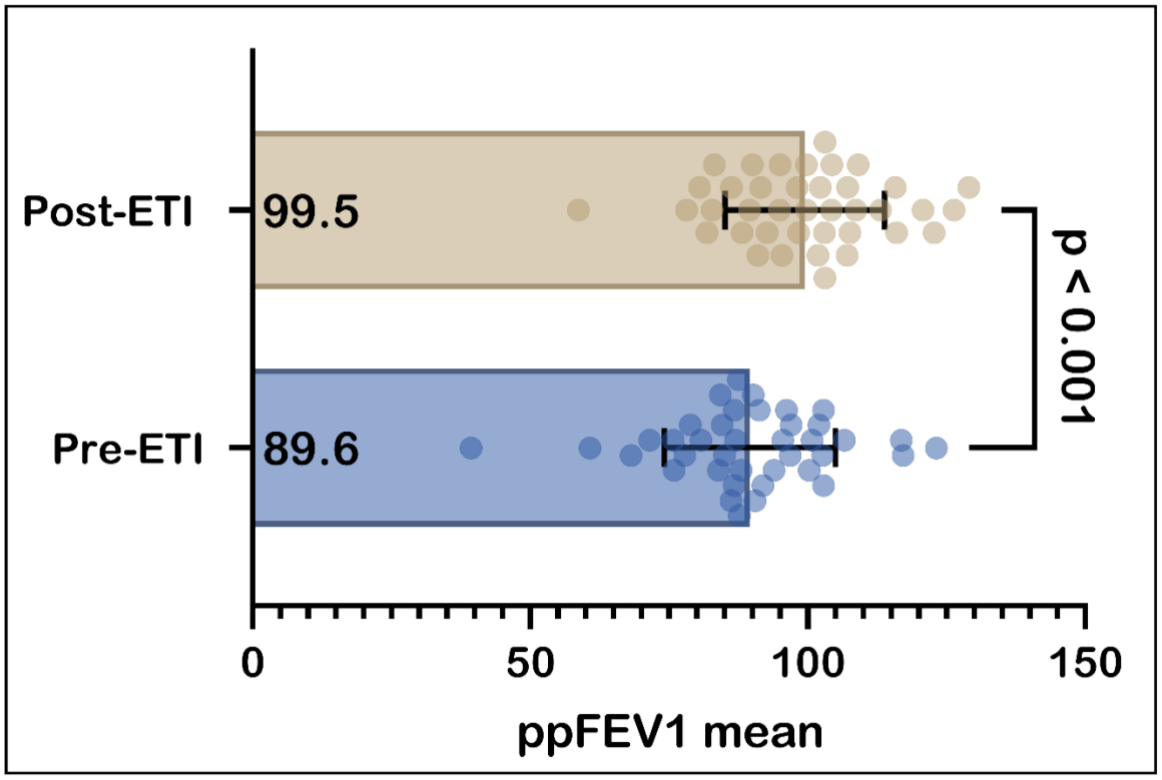


Figure 14. The difference in percent-predicted forced expiratory volume in 1 second (ppFEV1) before and after elexacaftor-tezacaftor-ivacaftor (ETI).

The ppFEV1 mean before treatment was 89.6% ± 15.4 while after ETI it increased to 99.5 ± 14.4. The error bar represents standard deviation, and the dots represent the individual ppFEV1 readings for all cohort. Paired sample t-test showed a statistically significant difference: $p < 0.001$.

ETI: elexacaftor-tezacaftor-ivacaftor; ppFEV1: percent-predicted forced expiratory volume in 1 second.

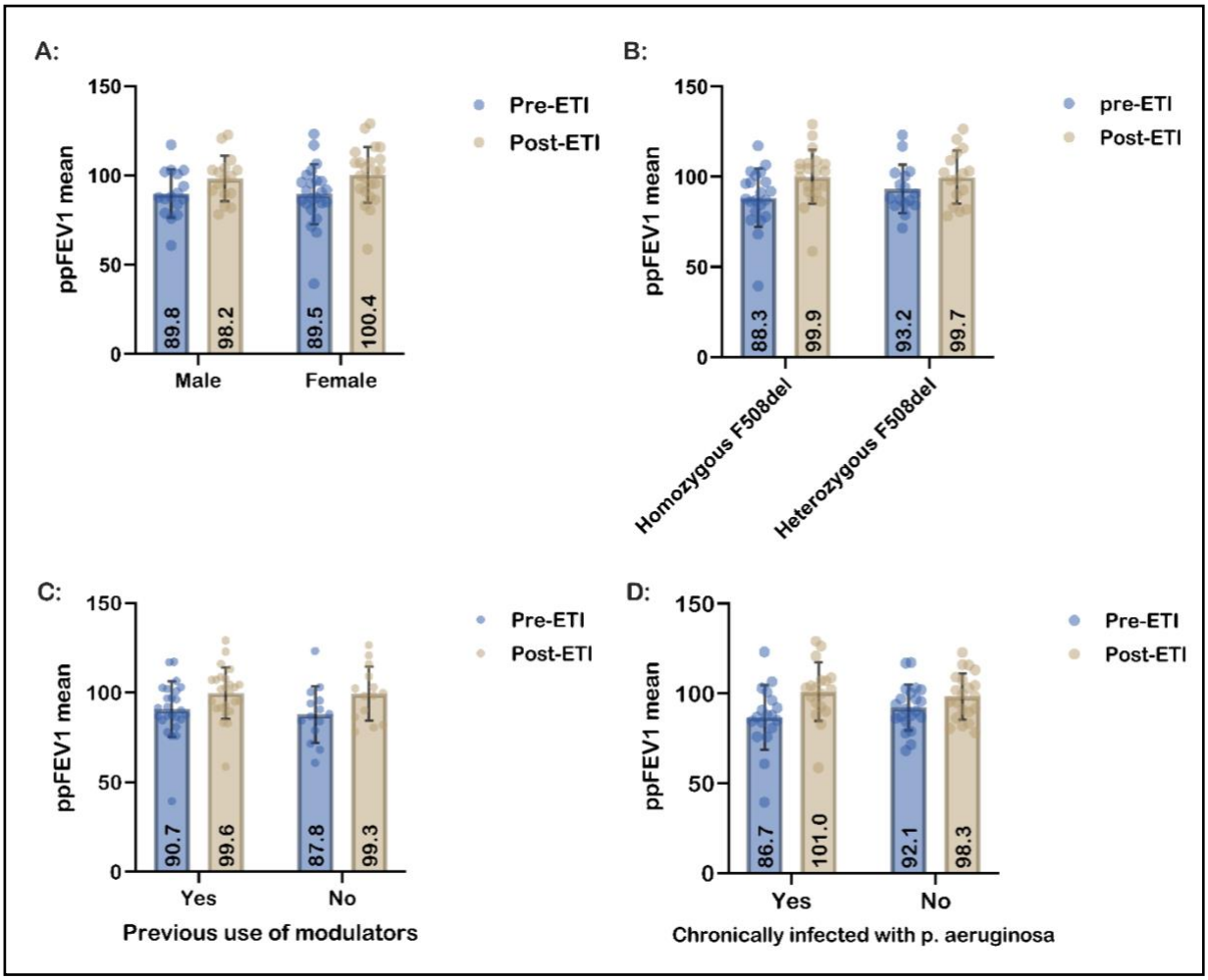


Figure 15. The difference in percent predicted forced expiratory volume in 1 second (ppFEV1) in relation to sex, cystic fibrosis transmembrane conductance regulator (CFTR) variants, the use of modulators, and chronic infection with Pseudomonas aeruginosa (P. aeruginosa).

A: The difference in ppFEV1 in relation to sex. Mean ppFEV1 before ETI was 89% for both male and female. One year after ETI the mean improved to 98.2% for male and 100.4% for female.

B: The difference in ppFEV1 in relation to the *CFTR* variants. The mean ppFEV1 before ETI was higher for heterozygous F508del 91.3% compared to 88.3% for homozygous F508del. While after ETI both groups have the same mean around 100%.

C: The difference in ppFEV1 related to the use of previous modulators (Symkevi, Orkambi, Ivacaftor). Pre-ETI, cwCF who were on modulators have higher ppFEV1 mean 90.7% compared to 87.8% for those not taking any modulators. Post-treatment, both groups were on the same ppFEV1 mean around 99%.

D: The difference on ppFEV1 in relation to chronic infection with *P. aeruginosa*. The mean ppFEV1 before ETI for cwCF who are chronically infected was 86.7%, which increased to 101% after-ETI. The mean ppFEV1 before-ETI for cwCF who are not chronically infected was 92.15%, which increased to 98.3% after-ETI.

Error bars represent standard deviation.

ETI: elexacaftor-tezacaftor-ivacaftor; *P. aeruginosa: Pseudomonas aeruginosa*; ppFEV1: percent predicted forced expiratory volume in 1 second.

Table 9. Percent-predicted forced expiratory volume in 1 second (ppFEV1) readings for entire cohort.

ID	Sex	*CFTR* variants	Modulator previously	12 months pre-ETI			12 months post-ETI			Change in ppFEV1
				Lowest reading of ppFEV1	Highest reading of ppFEV1	Mean ppFEV1	Lowest reading of ppFEV1	Highest reading of ppFEV1	Mean ppFEV1	
P1	F	Heterozygous F508del	tezacaftor-ivacaftor	65.9	92.7	85.04	90	95	92.7	+ 7.66
P2	F	Homozygous F508del	tezacaftor-ivacaftor	86.6	95.4	91.95	92.7	96.8	94.95	+ 3.00
P3	F	Homozygous F508del	None	59.7	79.4	68.2	80.2	94.1	86.3	+ 18.10
P4	M	Heterozygous F508del	None	56	66.1	60.75	98	102.2	99.8	+ 39.05
P5	F	Heterozygous F508del	None	85	94.9	90.5	92	107.6	102.3	+ 11.80
P6	F	Homozygous F508del	tezacaftor-ivacaftor	74	85.7	80.75	101.2	105.4	103.01	+ 22.26
P7	F	Heterozygous F508del	tezacaftor-ivacaftor	81.9	90.7	87.5	78.6	89	83.2	- 4.30
P8	M	Heterozygous G551D	ivacaftor	81	95.8	90.2	84.8	94.6	89.5	- 0.70
P9	M	Homozygous F508del	tezacaftor-ivacaftor	75.3	94	87.7	93	113	103.1	+ 15.40
P10	M	Homozygous F508del	tezacaftor-ivacaftor	83	90.1	86.8	90.6	92.6	91.5	+ 4.70
P11	F	Homozygous F508del	tezacaftor-ivacaftor	91	108.4	96.85	89.8	103	99.8	+ 2.95
P12	M	Homozygous F508del	tezacaftor-ivacaftor	89.7	112.4	102.9	104	112.8	108.7	+ 5.80
P13	F	Heterozygous F508del	tezacaftor-ivacaftor	111.7	124.4	116.9	110.1	116.4	113.1	- 3.80

ID	Sex	*CFTR* variants	Modulator previously	12 months pre-ETI			12 months post-ETI			Change in ppFEV1
				Lowest reading of ppFEV1	Highest reading of ppFEV1	Mean ppFEV1	Lowest reading of ppFEV1	Highest reading of ppFEV1	Mean ppFEV1	
P14	M	Homozygous F508del	tezacaftor-ivacaftor	115.1	121	117.2	120.4	125.2	122.8	+ 5.60
P15	F	Homozygous F508del	tezacaftor-ivacaftor	84.8	87	86.2	85.4	96.6	91.7	+ 4.80
P16	M	Homozygous F508del	Lumacaftor-ivacaftor	Missing			Missing			
P17	M	Heterozygous F508del	tezacaftor-ivacaftor	100.6	103.4	102	100	103.7	102	- 0.15
P18	M	Heterozygous F508del	None	73.1	101.1	88.03	119	124.4	120.8	+ 32.77
P19	F	Heterozygous F508del	None	95.8	103.5	100.3	111.9	118.4	115.8	+ 15.50
P20	M	Homozygous F508del	Lumacaftor-ivacaftor	63.8	85.8	75.98	79	86.2	82.8	+ 6.82
P21	F	Homozygous F508del	Lumacaftor-ivacaftor	60.8	103.2	84.6	120	138.7	129	+ 44.40
P22	M	Heterozygous F508del	None	76	81	78.9	70.7	84.1	78.2	- 0.70
P23	F	Homozygous F508del	Lumacaftor-ivacaftor	87.9	95	91.3	94	96.3	95.4	+ 4.10
P24	F	Heterozygous F508del	None	82.1	107.3	95.5	106.4	110.2	109.1	+ 13.60
P25	F	Homozygous F508del	Lumacaftor-ivacaftor	68	106	87	100	112	107.6	+ 20.60
P26	F	Homozygous F508del	tezacaftor-ivacaftor	86.4	104.6	96.2	105	109.9	107.2	+ 11.00

ID	Sex	*CFTR* variants	Modulator previously	12 months pre-ETI			12 months post-ETI			Change in ppFEV1
				Lowest reading of ppFEV1	Highest reading of ppFEV1	Mean ppFEV1	Lowest reading of ppFEV1	Highest reading of ppFEV1	Mean ppFEV1	
P27	F	Homozygous F508del	Lumacaftor-ivacaftor	73.3	78.9	75.8	82.3	95.6	88.2	+ 12.40
P28	F	Heterozygous F508del	None	77.5	89.5	84.3	84.2	110	98.4	+ 14.10
P29	M	Heterozygous F508del	None	81	85.2	83.95	86	94	90	+ 6.05
P30	M	Heterozygous F508del	None	101.1	104.7	102.9	94	106.2	103.1	+ 0.20
P31	F	Homozygous F508del	tezacaftor-ivacaftor	28.7	49.3	39.4	55.1	63.7	58.7	+ 19.30
P32 *	F	Homozygous F508del	tezacaftor-ivacaftor	97	97	97	116	116	116	+ 19.00
P33	M	Heterozygous F508del	None	89.5	96	93.95	73	91.2	81.9	- 12.05
P34	F	Heterozygous F508del	None	118.4	128.9	123.2	121.8	130.6	126.4	+ 3.20
P35	M	Homozygous F508del	Lumacaftor-ivacaftor	95.5	105.4	100.8	100	106.7	104.3	+ 3.50
P36	F	Homozygous F508del	Lumacaftor-ivacaftor	100.5	105	102.7	103	105.2	104.4	+ 1.70
P37	F	Homozygous F508del	tezacaftor-ivacaftor	104	112.1	106.6	95	111.3	107.1	+ 0.50
P38	M	Heterozygous F508del	None	44.2	81.3	71.5	76	83.5	80.5	+ 11.30
P39	F	Heterozygous F508del	None	80	94.8	86.8	95	103.5	98.1	+ 9.00

ID	Sex	*CFTR* variants	Modulator previously	12 months pre-ETI			12 months post-ETI			Change in ppFEV1
				Lowest reading of ppFEV1	Highest reading of ppFEV1	Mean ppFEV1	Lowest reading of ppFEV1	Highest reading of ppFEV1	Mean ppFEV1	
P40	F	Homozygous F508del	Orkambi	73	83.5	77.9	93	98	95	+ 17.10

* Only one reading found in the patient's record 12 month before ETI and one reading 12 months after ETI.

ETI: elexacaftor-tezacaftor-ivacaftor; ppFEV1: percent-predicted forced expiratory volume in 1 second

Next, the relationship between the change in the ppFEV1 and other variables was explored. A Point-biserial correlation coefficient was used to assess the strength of the relationship between the difference in ppFEV1 and sex, *CFTR* variants, use of previous modulators, and chronic infection with *P. aeruginosa*. Results showed insufficient evidence to conclude that there is a significant relationship between the difference in ppFEV1 after ETI with sex, type of mutation, and the use of previous modulators**.** However, a low but statistically significant correlation was found with chronic infection with *P. aeruginosa*, r_{pb}= - 0.35, p = 0.026, as shown in **Table 10.**

Table 10. Point-biserial correlation coefficient between the difference in percent-predicted forced expiratory volume in 1 second (ppFEV1) and sex, cystic fibrosis transmembrane conductance regulator (CFTR) variants, the use of modulators previously, and chronic infection with Pseudomonas aeruginosa (P. aeruginosa).

The difference in ppFEV1		**The difference in ppFEV1**	**Sex**	**CFTR variants**	**On modulators previously**	**Chronic infection with *P. aeruginosa***
	Point-biserial Correlation	1	0.108	-0.138	0.111	- 0.355
	Sig. (2-tailed)		0.513	0.409	0.501	0.026 *
	N	39	39	38	39	39

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

This table shows the correlation between the difference of ppFEV1 after ETI and sex (1 = Male, 2 = Female), *CFTR* variants (1 = Homozygous F508del, 2 = Heterozygous F508del), the use of modulators previously (1 = Yes, 2 = No), and cwCF chronically infected with *P. aeruginosa* (1 = Yes, 2 = No). There was a low but significant correlation only between the difference in ppFEV1 and chronic infection with *P. aeruginosa*. CwCF who were chronically infected with *P. aeruginosa* showed a higher difference in ppFEV1.

Scale of correlation: r = 1__ perfect linear correlation, 1 > r ≥ 0.8 __strong linear correlation, 0.8 > r ≥ 0.4 __ moderate linear correlation, 0.4 > r > 0 weak linear correlation, r = 0 no correlation.

CFTR: cystic fibrosis transmembrane conductance regulator; *P. aeruginosa: Pseudomonas aeruginosa*; ppFEV1: predicted percent-predicted forced expiratory volume in 1 second.

A Spearman's correlation was used to assess the relationship between the difference in ppFEV1, baseline BMI centile, and baseline weight centile. A Pearson correlation analysis was computed to assess the strength of the linear relationship between the difference in ppFEV1 and baseline ppFEV1. As shown in **Table 11, Table 12** and **Figure 16,** there were medium but statistically significant negative correlations between the change in the ppFEV1 after ETI and baseline ppFEV1: r (38) = - 0.46, p = 0.003, baseline BMI centile, r_s (33) = - 0.63, p < 0.001, baseline weight centile, r_s (35) = - 0.59, p = < 0.001.

This finding aligns with the expectations considering the positive correlation between the baseline ppFEV1 and baseline weight centile: r_s(38) = 0.49, p = 0.002, as shown in **Figure 17.**

In conclusion, the results suggest a higher difference in ppFEV1 after ETI treatment is associated with lower baseline BMI centile, weight centile and ppFEV1. In addition, chronic infection with *P. aeruginosa* pre-ETI associated with a higher difference in ppFEV1 after ETI treatment.

Table 11. Spearmen's correlation between the difference in percent-predicted forced expiratory volume in 1 second (ppFEV1) and baseline weight centile and baseline body mass index (BMI) centile.

		ppFEV1 difference	**Pre-ETI weight centile**	**Pre-ETI BMI centile**
ppFEV1 difference	Correlation coefficient	1	- 0.557 **	- 0.631 **
	Sig. (2-tailed)		< 0.001	< 0.001
	N	39	37	35

** Correlation is significant at the 0.01 level (2-tailed).

This table shows the correlation between the difference of ppFEV1 after ETI and the baseline weight centile, BMI centile. There is a medium but significant negative correlation between the difference of ppFEV1 and all variables. Scale of correlation: r = 1__ perfect linear correlation, 1 > r ≥ 0.8 __strong linear correlation, 0.8 > r ≥ 0.4 __ moderate linear correlation, 0.4 > r > 0 weak linear correlation, r = 0 no correlation.

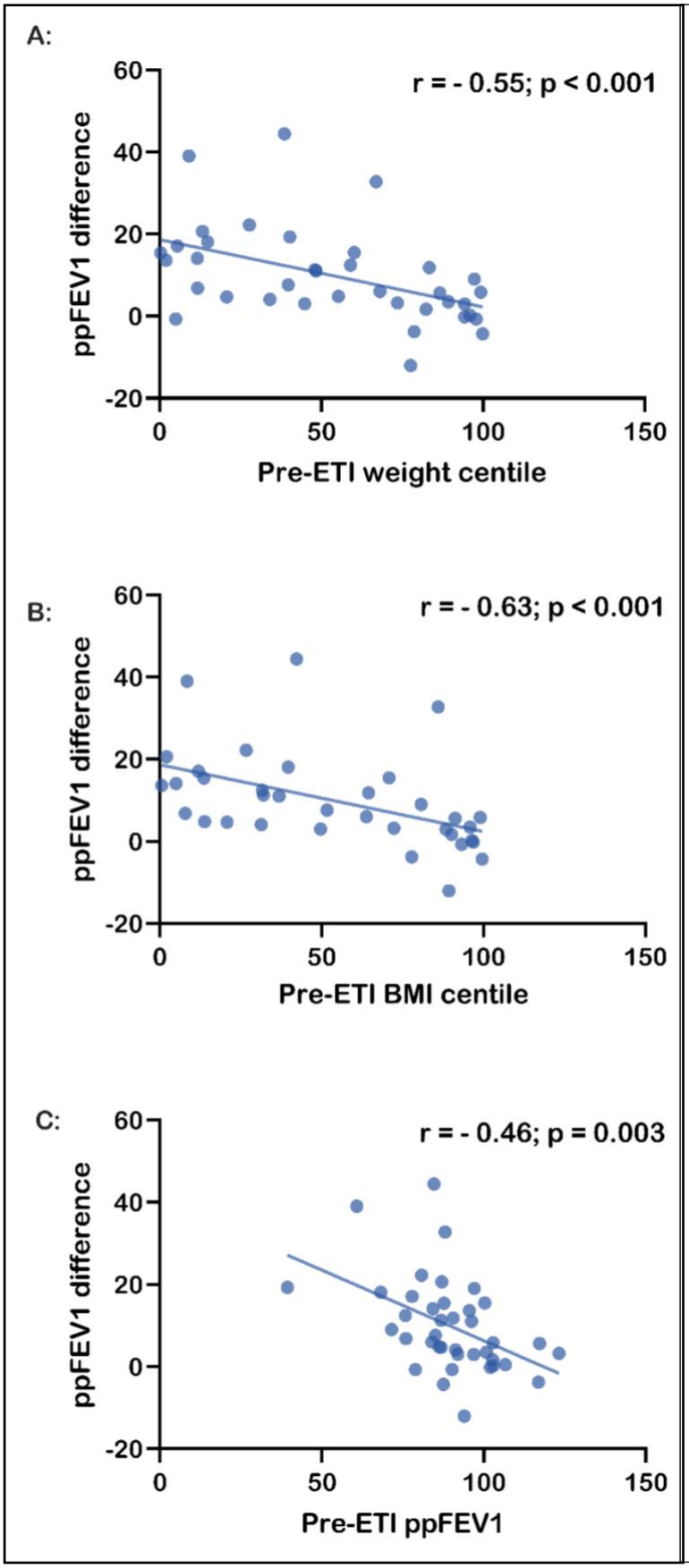
BMI: body mass index; ETI: elexacaftor-tezacaftor-ivacaftor; ppFEV1: percent-predicted forced expiratory volume in 1 second

Table 12. Pearson correlation between the difference in percent-predicted forced expiratory volume in 1 second (ppFEV1) and baseline percent-predicted forced expiratory volume in 1 second (ppFEV1).

		ppFEV1 difference	Pre-ETI ppFEV1
ppFEV1 difference	Pearson correlation	1	- 0.462 **
	Sig. (2-tailed)		0.003
	N	39	39

** Correlation is significant at the 0.01 level (2-tailed).

This table shows the correlation between the difference of ppFEV1 after ETI and the baseline ppFEV1. There is a medium but significant negative correlation between the difference of ppFEV1 and baseline ppFEV1. Scale of correlation: r = 1__ perfect linear correlation, 1 > r ≥ 0.8 __strong linear correlation, 0.8 > r ≥ 0.4 __ moderate linear correlation, 0.4 > r > 0 weak linear correlation, r = 0 no correlation.
ETI: elexacaftor-tezacaftor-ivacaftor; ppFEV1: percent-predicted forced expiratory volume in 1 second.



A: Spearman correlation between the difference of ppFEV1 and the baseline of weight centile. A medium, negative, linear association is displayed in this scatterplot.

B: Spearman correlation between the difference of ppFEV1 and the baseline of BMI centile. A medium, negative, linear association is displayed in this scatterplot.

C: Pearson correlation between the difference of ppFEV1 and the baseline of ppFEV1. A low, negative, linear association is displayed in this scatterplot.

Scale of correlation: r = 1__ perfect linear correlation, 1 > r ≥ 0.8 __strong linear correlation, 0.8 > r ≥ 0.4 __ moderate linear correlation, 0.4 > r > 0 weak linear correlation, r = 0 no correlation.

BMI: body mass index; ETI: elexacaftor-tezacaftor-ivacaftor, ppFEV1: percent predicted forced expiratory volume in 1 second.

Figure 16. Correlation coefficient between the change in percent-predicted forced expiratory volume in 1 second (ppFEV1) and baseline weight centile, baseline body mass index (BMI) centile and baseline percent-predicted forced expiratory volume in 1 second (ppFEV1)

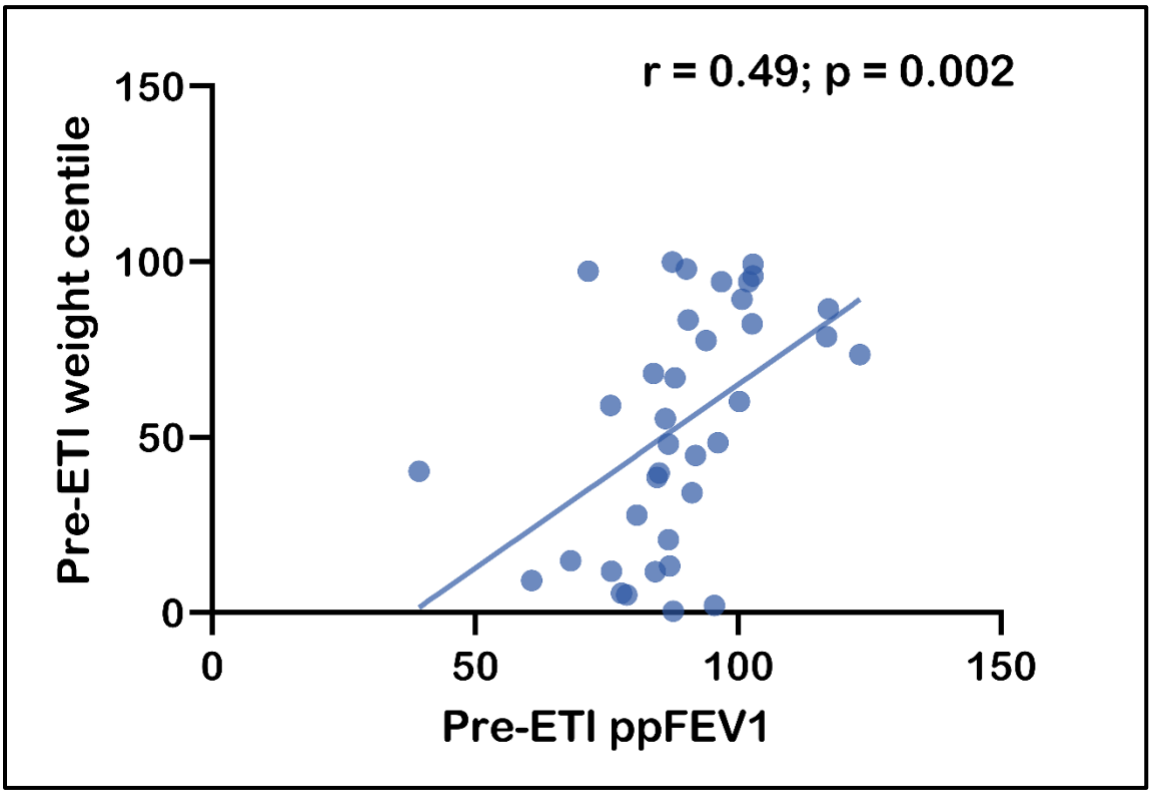


Figure 17. Spearman correlation between baseline percent-predicted forced expiratory volume in 1 second (ppFEV1) and baseline weight centile

A medium, positive, linear statistically significant association is displayed in this scatterplot.

Scale of correlation: r = 1__ perfect linear correlation, 1 > r ≥ 0.8 __strong linear correlation, 0.8 > r ≥ 0.4 __ moderate linear correlation, 0.4 > r > 0 weak linear correlation, r = 0 no correlation.

ETI: elexacaftor-tezacaftor-ivacaftor, ppFEV1: percent predicted forced expiratory volume in 1 second.

3.4.4 Physiotherapy treatments

One year before starting ETI, the overall physiotherapy regime for children included in the study was as follows:

- Thirty-nine children (97.5%) had ACTs in their treatment regime, and one child was not able to do any physiotherapy treatment for medical reasons.
- Seventeen children (42.5%) were on two mucoactive nebulisers, and 30 children (75%) were on at least one nebuliser.
- Thirty-seven children (92.5%) were exercising as part of their physiotherapy regime.

3.4.4.1 Airway clearance techniques (ACTs)

This study compared the patients reported ACTs done before and after starting ETI in three aspects:

A. The presence of ACTs in their physiotherapy regime.
B. The frequency of ACTs per day.
C. The number of ACTs cycles per treatment.

As shown in **Figure 18**, the most frequently used type of ACTs before ETI was PEP (37.5%), followed by Aerobika (32.5%), Acapella (20%), and other types (7.5%). While after ETI, the most used ACT was Aerobika (47.5%), followed by PEP (30%), Acapella (10%), and other types (5%).

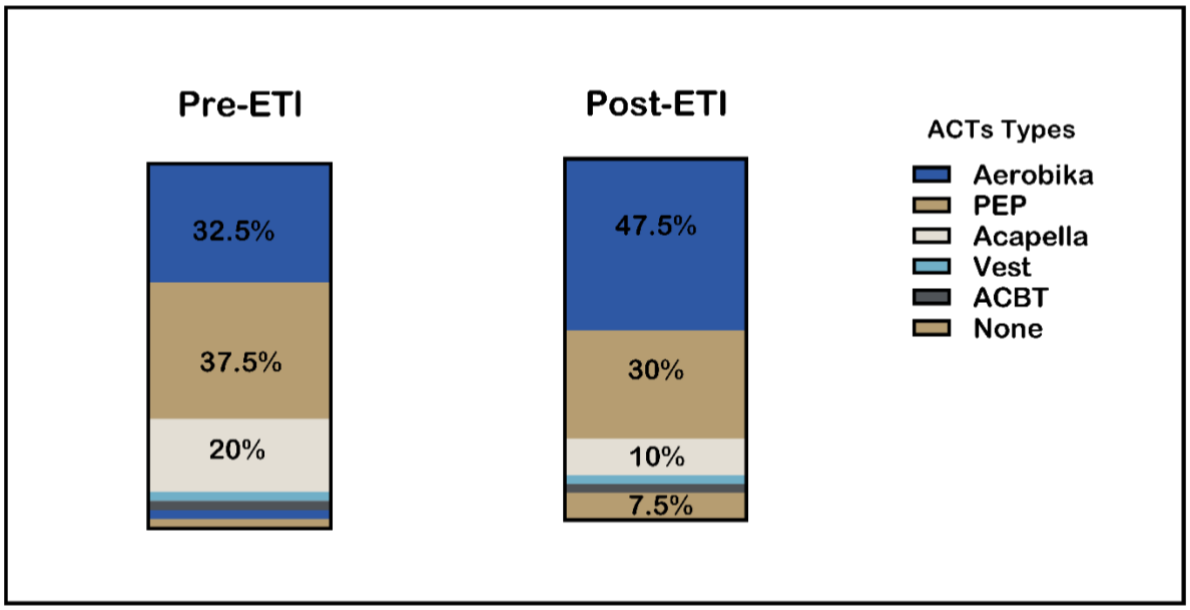


Figure 18. Airway clearance techniques (ACTs) type used before and after elexacaftor-tezacaftor-ivacaftor (ETI).

Before ETI, PEP was the most frequently used ACT (37.5%), followed by Aerobika 32.5%, 20% used Acapella, and 2.5% for the other types. After ETI, 47.5% of cwCF used Aerobika, 30% used PEP, 10% used Acapella, 7.5% used nothing, and 2.5% used vest and ACBT.

ACBT: Active cycles breathing techniques; ACTs: Airway clearance techniques; ETI: elexacaftor-tezacaftor-ivacaftor.

As displayed in **Figure 19**, the majority of cwCF (85%) were on daily ACTs treatment before ETI, 12.5% of children used ACTs when they had respiratory symptoms, and 2.5% of children were not using ACTs as part of their regime. After ETI, the number of cwCF on daily ACTs dropped to 67.5%, the number of children using it only when symptomatic increased to 25%, and the number of children who stopped using ACTs increased to 7.5%.

Using a Stuart-Maxwell test, the change in the proportion of using ACTs following ETI was statistically significant (p = 0.028).

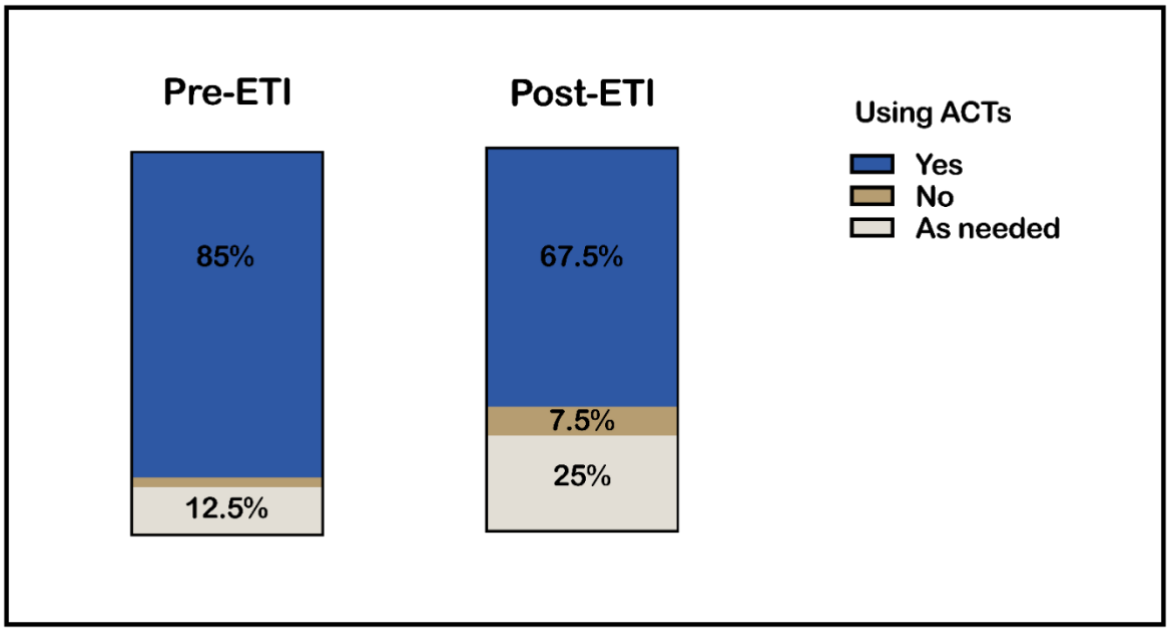


Figure 19. The difference in using airway clearance techniques (ACTs) before and after elexacaftor-tezacaftor-ivacaftor (ETI).

Before ETI, 85% of children were on daily ACTs treatment, 12.5% of children used ACTs when they had respiratory symptoms, and 2.5% of children were not using ACTs as part of their regime. After ETI, 67.5% of children were on daily ACTs treatment, 25% of children used ACTs when they had respiratory symptoms, and 7.5% of children were not using ACTs as part of their regime. A Stuart-Maxwell test was performed to test the difference after ETI, and it was statistically significant: p = 0.028.

ACTs: Airway clearance techniques; ETI: elexacaftor-tezacaftor-ivacaftor

A further factor examined was the frequency of ACTs per day. It can be seen from the data in **Figure 20** that most children (65%) were using ACTs twice a day, 22.5% of children were using ACTs once a day, and 12.5% were using it when they had symptoms. After ETI, the number of cwCF using ACTs twice daily dropped substantially to 25%, the number of children using ACTs once a day increased to 35%, and those using ACTs when having symptoms dramatically increased to 40%.

The frequency of using ACTs per day before ETI changed significantly after one year of ETI ($p < 0.001$) using a Stuart-Maxwell test.

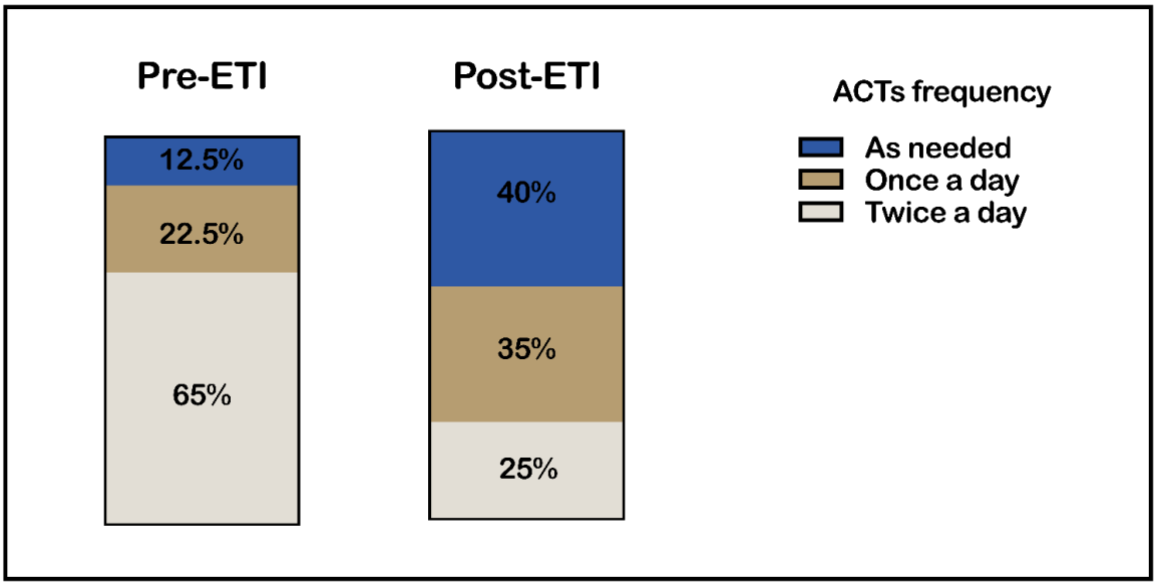


Figure 20. The difference in the frequency of airway clearance techniques (ACTs) after elexacaftor-tezacaftor-ivacaftor (ETI).

The frequency of ACTs per day before starting ETI: 65% of cwCF were doing ACTs two times per day, 22.5% were doing ACTs once per day, 12.5% were doing it as they need. After starting ETI: 25% of cwCF were doing ACTs two times per day, 35% were doing ACTs once per day, 40% were doing it as they needed. A Stuart-Maxwell test was performed to test the difference after ETI, and it was statistically significant: $p < 0.001$.
ACTs: Airway clearance techniques; ETI: elexacaftor-tezacaftor-ivacaftor.

Further analysis of the number of cycles of ACTs was performed in this study. **Figure 21** shows the median of cycles before ETI was 10 (IQR = 7 - 10), which dropped to 5.5 cycles after ETI (IQR 0 - 10). The most frequent number of cycles was ten cycles (45%) which changed after ETI to as much as needed when having symptoms for 30% of children.

These data were subjected to the Wilcoxon signed-rank test for paired samples, with results showing a statistically significant change in the number of cycles: z = -2.3, p = 0.02.

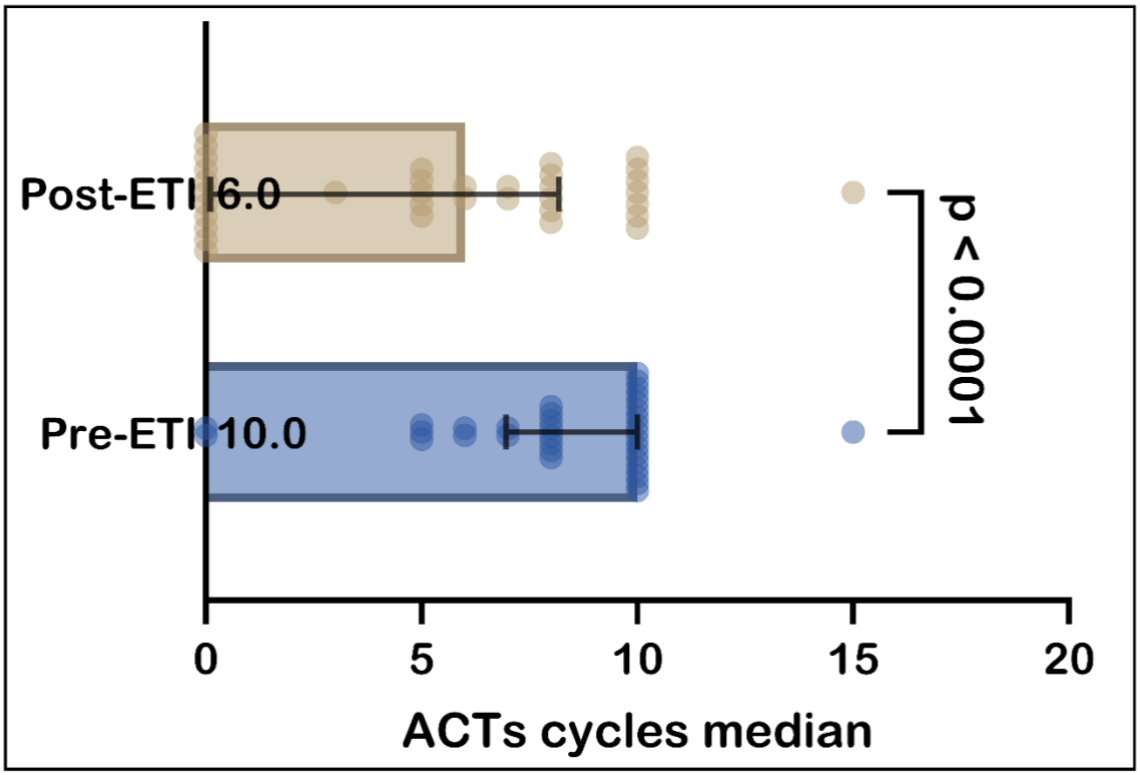


Figure 21. The difference in the number of cycles of airway clearance techniques (ACTs) after elexacaftor-tezacaftor-ivacaftor (ETI).

The median cycles of ACTs before ETI were 10 cycles, whereas after ETI it reduced to six cycles. The error bar represents the interquartile range, and the small dots represent the individual readings for all cohort. A Wilcoxon signed-rank test was used to test the difference before and after ETI treatment which shows a statistically significant difference: $p < 0.0001$.
ACTs: Airway clearance techniques; ETI: elexacaftor-tezacaftor-ivacaftor.

3.4.4.2 Nebulised Mucolytics

This study looked at both mucoactive therapy hypertonic saline and dornase alfa.

As shown in **Figure 22**, the frequency of cwCF on dornase alfa pre-ETI was 72.5 %, which reduced to 42.5% after ETI. The number of children using the dornase alfa as needed increased from zero before ETI to 7.5%. A Stuart-Maxwell test was used to assess the change in the proportion using dornase alfa after ETI. There was a statistically significant difference in using dornase alfa (p = 0.002).

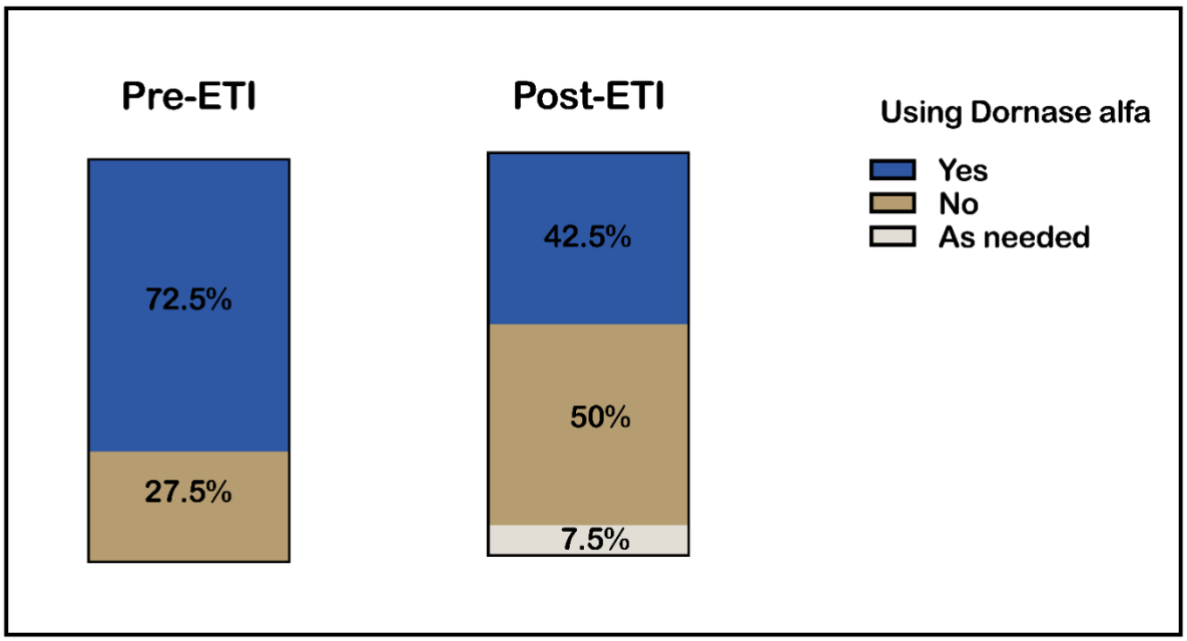


Figure 22. The difference in the use of dornase alfa after elexacaftor-tezacaftor-ivacaftor (ETI).

The frequency of using dornase alfa before starting ETI: 72.5% of cwCF were using dornase alfa as part of their treatment regime, while 27.5% were not taking it. After starting ETI: 42.5% of cwCF were using dornase alfa as part of their treatment regime, 50% were not taking it, and 7.5% were taking it when they had a respiratory symptom. A Stuart-Maxwell test was used to test the difference before and after ETI treatment, which shows a statistically significant difference: p = 0.002.

ETI: elexacaftor-tezacaftor-ivacaftor.

A smaller number of children were on hypertonic saline compared to dornase alfa before ETI**.** **Figure 23** displays that the frequency of using hypertonic saline before ETI was 42.5%, which decreased to 17.5% after ETI. A Stuart-Maxwell test was used to assess the change in the proportion using hypertonic saline after ETI. The result indicates a statistically significant difference (p = 0.002).

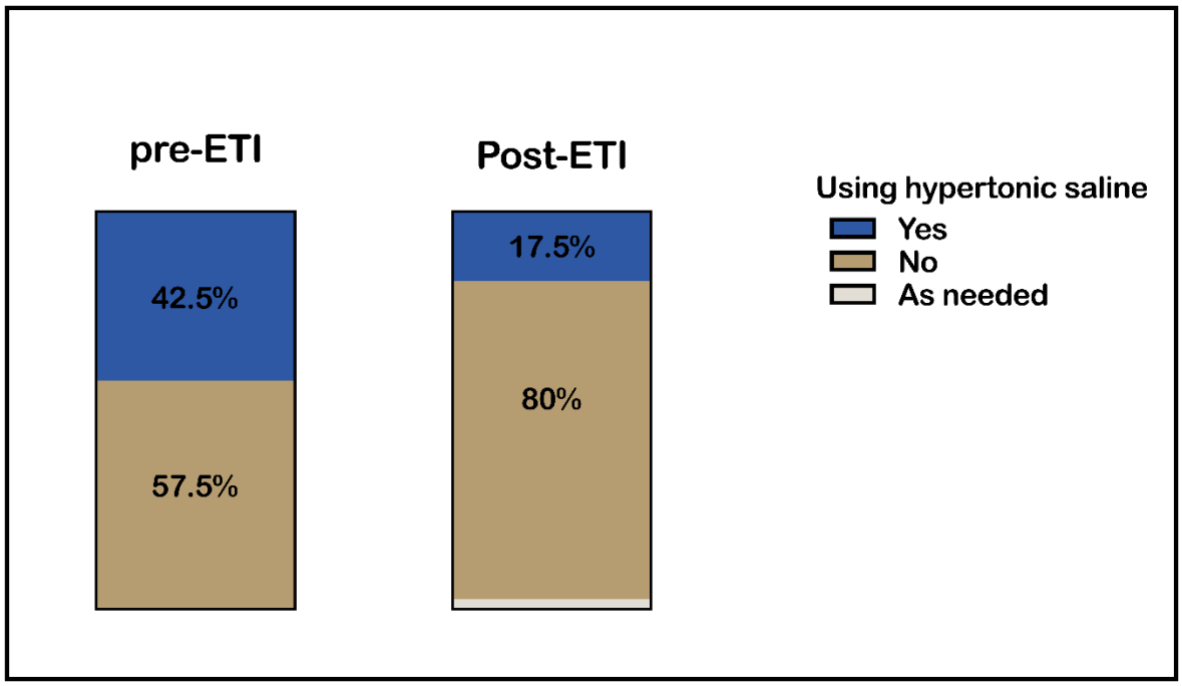


Figure 23. The difference in the use of hypertonic saline after elexacaftor-tezacaftor-ivacaftor (ETI).

The frequency of using hypertonic saline before starting ETI: 42.5% of cwCF were using hypertonic saline as part of their treatment regime, while 57.5% were not taking it. After starting ETI: 17.5% of cwCF were using hypertonic saline as part of their treatment regime, 80% were not taking it, and 2.5% were taking it when they had a respiratory symptom. A Stuart-Maxwell test was used to test the difference before and after ETI treatment, which shows a statistically significant difference: p = 0.002.
ETI: elexacaftor-tezacaftor-ivacaftor.

3.4.4.3 Exercise

This study recorded the frequency of exercise before and after ETI, as reported by cwCF. The exercise frequency was categorised as follows:

- No exercise.
- 1–2 times/week.
- 3–4 times/week.
- 5 or more/week.

One year before starting ETI, the majority of cwCF were distributed equally between exercising 1 to 2 times per week and 5 or more times per week, with 35% each. The frequency of exercise after ETI increased to 40% for those exercising five times or more weekly. The number of cwCF who were not exercising decreased from 12.5% to 7.5%. **Figure 24** shows the difference in the exercise frequency before and after ETI.

Changes in the exercise frequency were compared using the Stuart-Maxwell test. No significant differences were found between the two groups ($p = 0.138$).

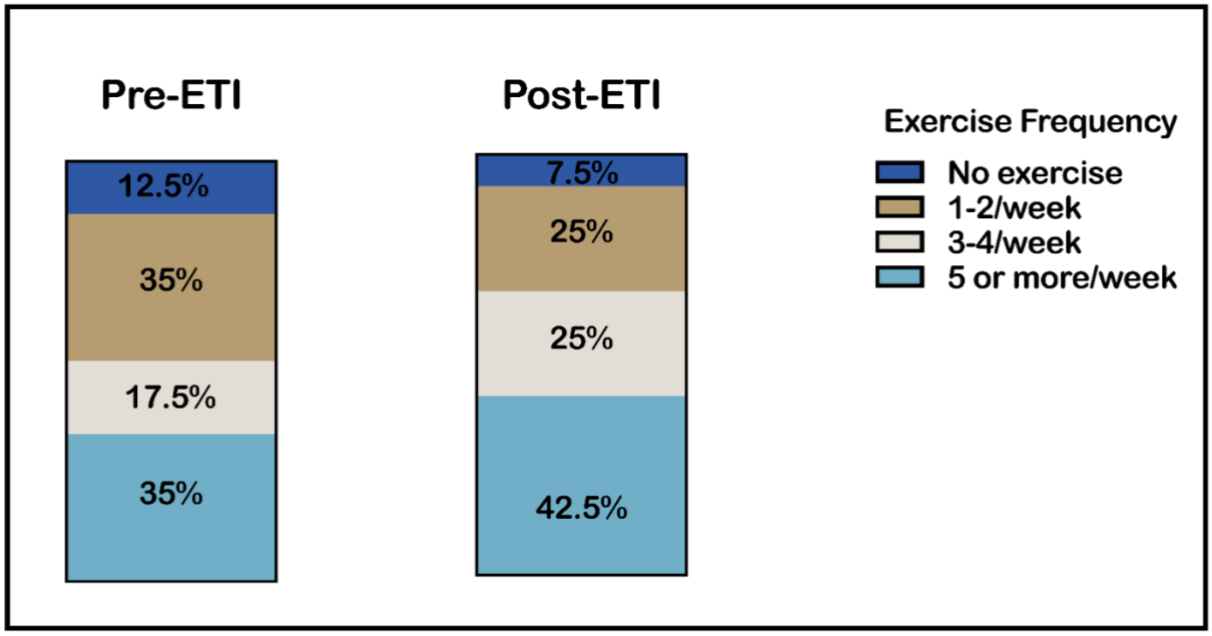


Figure 24. The difference in the exercise frequency after elexacaftor-tezacaftor-ivacaftor (ETI).

The frequency of exercise before ETI was 35% for cwCF who exercised 1 to 2 times per week and 5 or more times per week, followed by 17.5% for exercising 3 to 4 times per week, and 12.5% for no exercise.

After ETI, 42.5% of cwCF exercised 5 or more times per week, followed by exercising 1 to 2 times and 3 to 4 times per week equally with 25% each, and 7.5% of cwCF did not exercise.

A Stuart-Maxwell test was used to test the difference before and after ETI treatment which shows no statistically significant difference: $p = 0.138$

ETI: elexacaftor-tezacaftor-ivacaftor.

3.4.4.4 Exercise testing

This study also looked at the MST and recorded the following:

- The number of completed levels.
- The total distance achieved.

Out of the 40 included cwCF, 19 children performed the MST both before and after starting ETI. As shown in **Figure 25,** the median score for a completed level before ETI was 12 (IQR = 10 - 12), which increased to 13 levels (IQR = 11 - 14) after ETI. A Wilcoxon signed-rank test was used to test the difference after ETI. The results indicate a statistically significant change in the number of completed levels: z = - 2.6, p = 0.009.

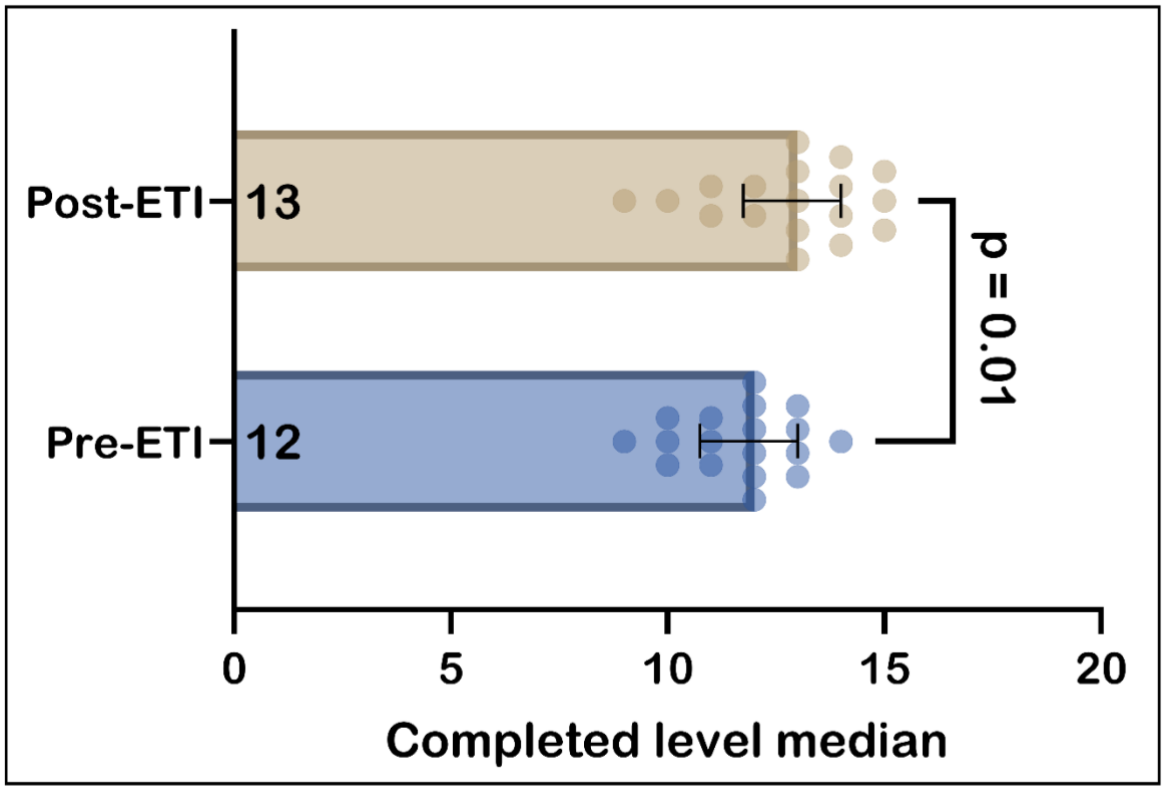


Figure 25. The median difference of completed level of shuttle test after elexacaftor-tezacaftor-ivacaftor (ETI).

The mean of completed level of shuttle test was 12 levels before-ETI, which improved to 13 levels after ETI. The error bar represents the interquartile range, and the small dots represent the individual completed level readings for all cohorts. A Wilcoxon signed-rank test was used to test the difference before and after ETI treatment, which shows a statistically significant difference: p = 0.01.
ETI: elexacaftor-tezacaftor-ivacaftor.

Figure 26 shows the mean total distance achieved in the MST before ETI was 1,013.68 metres (95% CI = 929.2 – 1098.2), which improved to 1,204.74 metres (95% CI = 1083.3 – 1326.2) after ETI. A paired t-test was conducted to compare the total distance between the two groups. There was a statistically significant difference in the total distance after ETI: t (18) = - 3.31, p = 0.004.

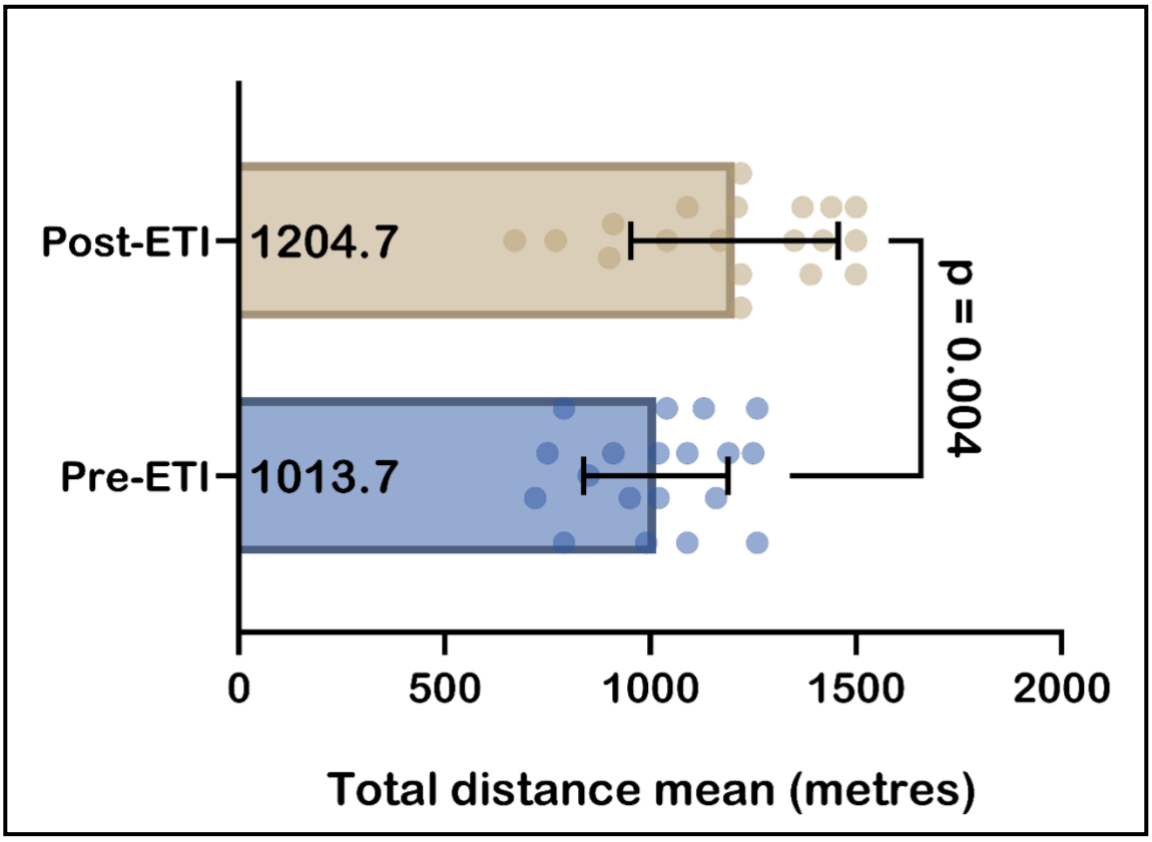


Figure 26. The mean difference of total distance achieved on shuttle test after elexacaftor-tezacaftor-ivacaftor (ETI).

The mean of total distance achieved in the shuttle test was 1,014 metres before ETI, and after-ETI increased to 1,205 metres. The error bar represents the standard deviation, and the small dots represent the individual distance readings for all cohorts. A paired sample t-test was used to test the difference before and after ETI treatment, which shows a statistically significant difference: p = 0.004.
ETI: elexacaftor-tezacaftor-ivacaftor.

3.4.5 Lung infections and respiratory culture sample types

This study was designed to document the number of samples collected annually as well as the number of positive microbiology results reported throughout a period of one year both before and after treatment. The data were collected from 39 cwCF, with one patient having missing data. The data collected includes a mixture of dates, covering both periods before, during, and after the COVID-19 pandemic.

The total number of samples performed over the 12 months before ETI for the included cwCF was 398, distributed as follows:

- 217 cough swabs.
- 172 sputum samples.
- One nasopharyngeal swab.
- One bronchoalveolar lavage.

The total number of samples decreased to 176 times in the year following ETI as follows:

- 140 cough swabs.
- 34 sputum samples.
- Two bronchoalveolar lavages .

Interestingly, the cough swab became more prevalent after ETI, representing around 80% of all the samples instead of 55% before ETI. **Table 13** and **Figure 27** present an overview of the sample type.

One year following ETI, all documented positive results and number of the respiratory microbiology samples had decreased. **Table 14** shows the frequency of the infections one year before and after ETI. **Table 15** provides an overview of the reduction in the respiratory microbiology samples for the cohorts before and after ETI.

Table 13. The difference in sample types before and after elexacaftor-tezacaftor-ivacaftor (ETI).

Sample types	Pre-ETI	Post-ETI
Total number of samples	382	179
Cough; % (n)	56.6 (215)	82.7 (148)
Sputum; % (n)	41.8 (159)	16.2 (29)
Bronchoalveolar lavage; % (n)	1.3 (5)	1.1 (2)
Nasopharyngeal; % (n)	0.3 (1)	0 (0)

ETI: elexacaftor-tezacaftor-ivacaftor.

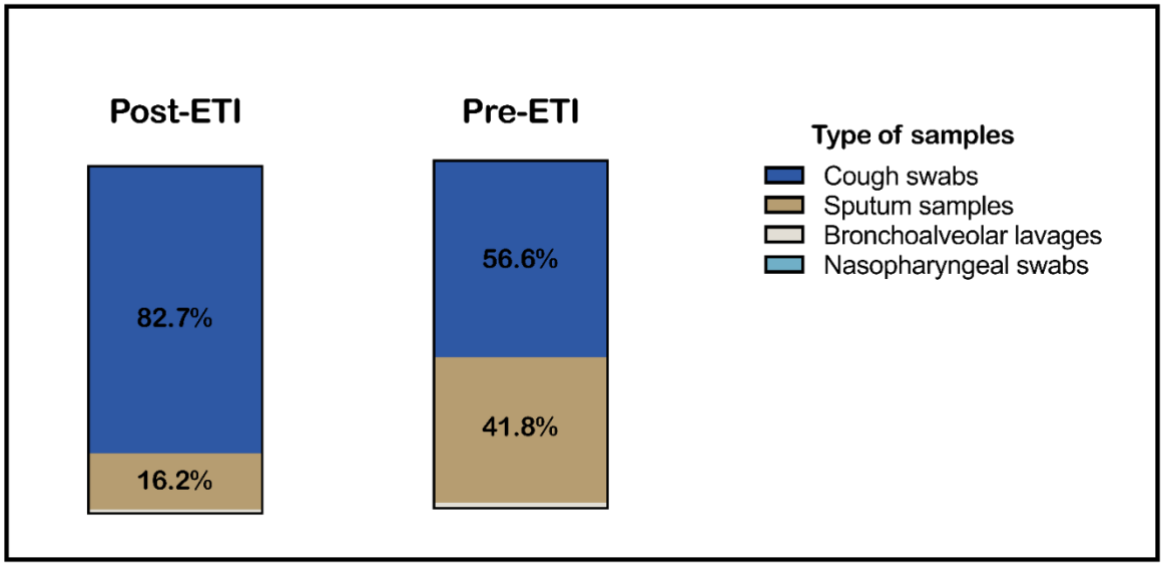


Figure 27. The difference in sample types before and after elexacaftor-tezacaftor-ivacaftor (ETI).

Before starting ETI, 56.6% of samples were cough swabs, 41.8% were sputum samples, 1.3% were bronchoalveolar lavages, and 3% were nasopharyngeal swabs. After starting ETI, 82.7% of samples were cough swabs, 16.2% were sputum samples, and 1.1% were bronchoalveolar lavages.

ETI: elexacaftor-tezacaftor-ivacaftor.

Table 14. Respiratory microbiology results in the 12 months before and after starting ETI.

	Proportion of samples positive				**Proportion of children isolating an organism at least once**			
	Pre-ETI; % (n)	**Post-ETI; % (n)**	**The trend in Relative change in proportion**	**Change in absolute positive samples**	**Pre-ETI; % (n)**	**Post-ETI; % (n)**	**The trend in Relative change in proportion**	**Change in absolute positive samples**
P. aeruginosa	13.4 (51)	8.9 (16)	↓	- 35	35 (14)	17.5 (7)	↓	- 7
S. aureus	2.6 (10)	4.5 (8)	↑	- 2	20 (8)	15 (6)	↓	- 2
H. influenzae	3.4 (13)	2.8 (5)	↓	- 8	17.5 (7)	7.5 (3)	↓	- 4
NTM	0 (0)	0 (0)	=	0	0 (0)	2.5 (1)	↑	+1
Aspergillus	9.4 (36)	1.7 (3)	↓	- 33	30 (12)	2.5 (1)	↓	- 11
MRSA	0 (0)	0 (0)	=	0	0 (0)	0 (0)	=	0
B. cepacian	0 (0)	0 (0)	=	0	0 (0)	0 (0)	=	0
Achromobacter	12.6 (48)	5 (9)	↓	- 39	7.5 (3)	10 (4)	↑	+ 1
Acinetobacter	1.6 (6)	1.1 (2)	↓	- 4	12.5 (5)	5 (2)	↓	- 3
S. maltophilia	4.5 (17)	0.6 (1)	↓	- 16	5 (2)	2.5 (1)	↓	- 1

B. cepacian: Burkholderia cepacian; ETI: elexacaftor-tezacaftor-ivacaftor; *H. influenzae*: *Haemophilus influenzae;* N: number; NTM: nontuberculous mycobacterium; MRSA: Methicillin-resistant Staphylococcus aureus; *P. aeruginosa*: *Pseudomonas aeruginosa*; *S. aureus: Staphylococcus aureus; S. maltophilia: Stenotrophomonas maltophilia*.

Table 15. Comparison of respiratory microbiology samples before and after starting elexacaftor-tezacaftor-ivacaftor (ETI).

Identification	Pre-ETI total number of samples /years.	Post-ETI total number of samples/years.	Percentage change
P1	10	4	- 60%
P2	6	4	- 33.3%
P3	21	18	- 14.3%
P4	19	6	- 68.4%
P5	10	6	- 40%
P6	9	4	- 55.5%
P7	6	3	- 50%
P8	2	1	- 50%
P9	9	4	- 55.5%
P10	6	4	- 33.3%
P11	11	2	- 81.8%
P12	11	6	- 45.5%
P13	6	4	- 33.3%
P14	7	3	- 57.1%
P15	6	4	- 33.3%
P16	7	4	- 42.8%
P17	4	2	- 50%
P18	5	3	- 40%
P19	5	4	- 20%
P20	24	7	- 70.8%
P21	16	3	- 81.25%
P22	7	5	- 28.5%
P23	6	4	- 33.3%
P24	14	3	- 78.5%
P25	5	1	- 80%
P26	12	4	- 66.6%
P27	11	4	- 63.3%
P28	10	2	- 80%
P29	5	3	- 40%
P30	7	3	- 57.1%
P31	27	14	- 48.1%
P32	7	4	- 42.8%
P33	11	4	- 63.6%
P34	14	7	- 50%
P35	5	2	- 60%
P36	11	3	- 72.7%
P37	9	7	- 22%
P38	12	6	- 50%
P39	9	5	- 44.4%

ETI: elexacaftor-tezacaftor-ivacaftor

3.4.6 Children not eligible for elexacaftor-tezacaftor-ivacaftor as a contemporaneous comparator group

A small number of cwCF were not eligible for ETI in the GNCH service between the ages of 12 – 18 during the same census period. Clinical data were collected in early 2020, 12 months prior to the approval of ETI, and in early 2022, approximately one year after the approval.

3.4.6.1 Baseline characteristics

The characteristics of this group at baseline are presented in **Table 16.** Only three children were ineligible for ETI due to *CFTR* variants, with a median age of 17 years (IQR= 14.5 – 17) at the time of data collection, and all were females with the following genotypes: c.1519_1521deATC + c.1021_1022dup TC, heterozygous for c.1558G>T, and G542X homozygous.

Table 16. Baseline characteristics of non-eligible children.

Baseline characteristics	
N	3
Age median (IQR), years	17 (14.5 – 17)
Sex • **Female (%)**	3 (100)
Race • **White (%)**	3 (100)
Genotypes (%) • **deltal507 + 1154insTC**	1 (33.3)
• **heterozygous c.1558G>T**	1 (33.3)
• **homozygous G542x**	1 (33.3)
Height median (IQR), cm	165.83 (151.3 – 166.6)
Height centile median (IQR), %	72.5 (56.6 – 80.1)

N: number; IQR (interquartile): 3rd quartile – 1st quartile.

As shown in **Table 17,** the mean weight remained the same over the two years at 44.9 kg. The mean weight centile dropped from the 40th centile to the 20th. Also, the mean BMI centile dropped from the 40th centile to the 16th. Another drop was noted in the mean ppFEV1 from 76% to 66%.

Table 17. The difference of reading before and after the approval of elexacaftor-tezacaftor-ivacaftor (ETI) of non-eligible children.

Parameters	Children Non eligible before ETI.	Children Non eligible after ETI.
Body weight median (IQR), kg	44.9 (41.2 – 52.1)	44.9 (42.5 – 48.8)
Weight centile median (IQR), %	50.3 (43.2 – 51.8)	28.8 (20.1 – 30.1)
BMI percentile median (IQR), %	40.9 (35.6 – 44.0)	14.6 (12 – 19.6)
ppFEV1 median (IQR), %	73.9 (64.0 – 86.7)	53.6 (52.5 – 73.3)

ETI: elexacaftor-tezacaftor-ivacaftor; IQR (interquartile): 3rd quartile – 1st quartile; ppFEV1: percent predicted forced expiratory volume in 1 second.

3.4.6.2 Physiotherapy treatments

3.4.6.2.1 Airway clearance techniques (ACTs)

Two cwCF were on ACTs twice per day, which stayed the same over time, while one was on ACT twice per day, dropping to once a day.

3.4.6.2.2 Nebulised Mucolytics

The mucolytic nebulised treatment with hypertonic saline and dornase alfa did not change for these three children. Two children were on dornase alfa and hypertonic saline for the recorded period, and one was not on nebulised treatment.

In general, these cwCF who were not eligible for ETI showed a decline in their weight centile, BMI centile, and ppFEV1 compared to the eligible group, who showed improved weight and lung function.

On the other hand, their physiotherapy regime and nebulised mucolytics treatment did not change over time, compared to those who were on ETI, which shows a change in the physiotherapy treatment following ETI.

3.5 Discussion

This chapter reports the results of a single-centre, retrospective study among cwCF to examine the effect of ETI on body weight, lung function, physiotherapy treatment including, mucolytics nebulised treatment, ACTs, and exercise, and lung infections.

3.5.1. Body weight and lung function

In clinical trials, ETI treatment has been shown to increase weight and lung function significantly (Heijerman *et al.*, 2019; Middleton *et al.*, 2019). However, real-world data is needed to demonstrate that benefits occur with the strict conditions of a randomised trial and to understand the longer-term effects.

An initial objective of the project was to identify the impact of ETI on anthropometric parameters and ppFEV1 after 12 months of treatment. This study showed a statistically significant improvement in weight, BMI centile and BMI z-score after 12 months of ETI. However, the improvement in weight centile was not statistically significant after 12 months of ETI. This study also showed a significant improvement in the ppFEV1 after 12 months of ETI in all subgroups.

On the other hand, children in the small comparator cohort who were not eligible for ETI underwent a decrease in weight parameters and ppFEV1 over the same time. These findings broadly agree with other real-world studies, showing improved body weight parameters and ppFEV1 after initiating ETI.

An ongoing prospective observational study aimed to investigate the effect of ETI in a diverse group of pwCF in the US (Nichols *et al.*, 2022). The study included 487 participants aged 12 years and older with at least one copy of F508del. The assessment was taken before and at one, three, and six months after ETI treatment, with additional 18- and 30-month visits planned. The study assessed different factors of lung function, BMI, sweat Cl^- concentration,

and self-reported respiratory symptoms. They found that after six months, the mean ppFEV1 improved by 9.7%, and mean BMI increased by 1.2 kg/m^2 for adult populations and 0.3 z-score in adolescents (Nichols *et al.*, 2022). In a prospective study conducted by Mainz *et al.* (2022) involving 107 CF patients aged 12 years and older across multiple centres in the UK and Germany, the researchers observed significant changes in mean BMI z-scores and weight among the participants receiving ETI treatment after 22 weeks. The mean BMI z-scores in children increased from - 0.71 to - 0.29 ($p = 0.02$) at week 24, and the mean weight increased from 47 kg to 51.4 kg ($p < 0.0001$). In adults, there was an 8% increase in mean BMI ($p < 0.0001$) compared to baseline and an 8% increase in mean weight ($p < 0.0001$) (Mainz *et al.*, 2022). A real-life retrospective study reports the outcomes of the first six months of ETI in 46 cwCF above the age of 6 in Germany. The study findings indicate a significant improvement in lung function in 24 cwCF aged 12 – 17 after three months, with a mean increase of 13 percentage points compared to the baseline, which was sustained at a six-month visit. The mean difference in BMI z-score showed an improvement of 0.41, while the mean weight z-score showed an improvement of 0.34 at the three-month follow-up compared to the baseline, and these improvements were also sustained at the six-month visit (Olivier *et al.*, 2023). Lee *et al.* (2023) studied the impact of ETI over two years on the annual decline of lung function in 468 pwCF aged 12 years and older with at least one copy of F508del compared to a similar group of untreated controls from the US cystic fibrosis Foundation Patient Registry (CFFPR). The study revealed that following two years of ETI, the mean change in ppFEV1 increased annually by 0.39 percentage points. In contrast, the matched control group experienced an annual decline of 1.92 percentage points in ppFEV1 (Lee *et al.*, 2023).

ETI has also been shown to enhance lung function, body weight, and BMI in several studies involving adult populations (Granados *et al.*, 2023; Petersen, Begnel, Wallendorf and Litvin, 2022). Real-world data have also been published on advanced CF lung disease, as this population was excluded from randomised clinical trials. These studies have demonstrated the efficacy of ETI in improving various clinical outcomes (Burgel *et al.*, 2021; Carnovale *et al.*, 2022b; Djavid *et al.*, 2021).

The current study revealed variability in the improvement of ppFEV1 after 12 months of ETI. There is limited published literature on the relationship between the change in ppFEV1 after ETI and other clinical variables. I found in this study that the difference in the mean ppFEV1

was negatively associated with baseline ppFEV1, weight centile and BMI centile. Also, cwCF chronically infected with *P. aeruginosa* infection correlated with greater change in ppFEV1. On the other hand, no correlation was found with sex, different *CFTR* variants or previous use of a modulator. These results reflect those of Nichols *et al.* (2022), who also found no association between the change in ppFEV1 and sex or *CFTR* variants in pwCF aged 12 or older. An observational study reported ppFEV1, BMI, and microbiological data collected from 48 pwCF aged 12 and older over one year, with measurements taken at initiation and three-month intervals. The results showed significant improvements in ppFEV1 and BMI during the first six months of ETI, with no further changes observed thereafter. Additionally, there was a significant positive correlation between the change in ppFEV1 and baseline BMI at three months ($r = 57.2$, $p < 0.01$) (Sheikh *et al.*, 2023). This positive correlation is contrary to the finding of my study, which indicated a negative correlation between the change in ppFEV1 and baseline BMI centile. A possible explanation for this difference could be attributed to the variables measured. In the study by Sheikh *et al.* (2023), BMI was analysed, while in my study, I focused on BMI centile. Another possible explanation could be the variation in demographics, including the age of the participants, which included children and adults with a mean age of 28.8 years. More research is needed to understand the association between the change in ppFEV1 and other factors, including weight, baseline ppFEV1, sex, *CFTR* variants, previous use of modulators, and chronic infection with *P. aeruginosa.*

On the other hand, a few studies have explored the factors affecting the response in lung function after ETI. In Germany, a study aimed to examine the age and lung function severity as determinants of response to ETI in 42 children aged 6 – 11 years and 41 adolescents aged 12 – 17. The data were categorised based on age group and subsequently classified into age-specific ppFEV1 severity. The age strata were divided into three groups based on their baseline ppFEV1. They found that after three and 12 months on ETI, individuals with more severe lung function at baseline experienced a more significant improvement in ppFEV1. They concluded that age and baseline ppFEV1 are predictive factors for the change in lung function after 12 months of ETI (Schütz *et al.*, 2023). A recent single-centre retrospective study was conducted in the adult CF population in the US to investigate the effect of ETI treatment on outcomes based on sex. They included 251 pwCF who began ETI for at least six months between 2014 and 2022. Data were collected 5.5 years before and 2.9 years after ETI. The findings showed that after adjusting for age, race, previous use of CFTR modulator, and baseline ppFEV1, there

was no significant difference in the change in ppFEV1 based on sex after six months of ETI (p = 0.85) (Wang *et al.*, 2023).

Preliminary results of the GOAL study reported no difference in the change in the ppFEV1 between males and females using ivacaftor (Secunda *et al.*, 2019). Before the CFTR modulator era, several researchers studied the factors influencing lung function (Kerem *et al.*, 2014; Konstan *et al.*, 2007; Schaedel *et al.*, 2002). Previous research by Kerem *et al.* (2014) used data from the European CF Society (ECFS) registry for pwCF aged 6 years and above. They established that chronic *P. aeruginosa* infection and BMI are risk factors that affect lung function in paediatric and adult populations. Another study included cwCF aged 6 to 17 years from the ESCF registry and investigated the risk factors for the rate of decline in ppFEV1 over 3 to 6 years. Female sex, *P. aeruginosa* infection, and low weight for age were identified as risk factors for ppFEV1 decline (Schaedel *et al.*, 2002).

Several studies showed the effect of *CFTR* variants on lung function before the era of HEMT (Corey, Edwards, Levison and Knowles, 1997; Hatziagorou *et al.*, 2023). A longitudinal study in the US for pwCF born between 1960 to 1974 from a CF database was designed to estimate lung function decline in relation to various factors. The study's findings suggested that homozygous F508del mutations are associated with a steeper decline in the rate of pulmonary function (Corey, Edwards, Levison and Knowles, 1997). Another study by Hatziagorou *et al.* (2023) examined the risk factors for FEV1 decline before the CFTR modulators using data from the ECFS registry in pwCF aged 6 to 50 between 2008 to 2016. They found a significant decline in patients with both class I and II mutations or those with homozygous F508del mutation compared to other mutation groups. Further work is required to gain a better understanding of the possible factors that influence the response in ppFEV1 after ETI.

3.5.2. Physiotherapy treatments

3.5.2.1 Airway clearance techniques

In light of the remarkable improvements in the overall health status of pwCF-prescribed ETI, this is expected to influence their daily ACTs and physical activity regimes. This study set out to assess the impact of ETI on ACTs in three aspects, including the ongoing presence of ACTs in their physiotherapy regime, the frequency of ACTs per day, and the number of ACT cycles per treatment. A statistically significant reduction in the number of cwCF doing ACTs, ACTs

frequency and the number of cycles was noted. In reviewing the literature, one study was found that investigated the impact of ETI on ACTs. The outcomes of our research align with the findings reported in a prospective, single-centre evaluation of services for adults with CF (Faulkner *et al.*, 2022). The study documented self-reported adherence to ACTs and nebulised therapies and objective nebuliser adherence, through the CF Health Hub platform at baseline, three, six and 12 months after ETI in 112 pwCF. At baseline, self-reported adherence to daily ACTs was 64%, and at 12 months dropped to 37%. Adherence to nebulised therapies was reported to be 72% at baseline and declined to 49% at 12 months. Data on objective nebuliser adherence were available for 56 patients, with 57% adherence at baseline which decreased to 36% at 12 months (Faulkner *et al.*, 2022).

In the ivacaftor era, a retrospective questionnaire was developed to evaluate changes in ACTs and adherence to nebulised therapies in pwCF, as reported by the patients (Hickey *et al.*, 2015). After starting ivacaftor, a significant reduction in the number of ACT sessions per week was observed. These sessions were also shorter, as 61% of patients spent less than ten minutes during these sessions. Participants reported a significant reduction in the time spent on physiotherapy treatments, including ACTs and inhaled therapies, with 64% spending less than 30 minutes daily after ivacaftor (Hickey *et al.*, 2015).

3.5.2.2 Nebulised mucolytics

In addition, the current study found that the proportion of people using mucolytic nebulisers decreased after ETI, consistent with the previous prospective observational study by Nichols *et al.* (2022). According to their findings, the self-reported use of dornase alfa decreased by 6%, hypertonic saline by 9.8%, azithromycin by 9.1%, and inhaled antibiotics by 34% after six months of ETI in 487 pwCF aged 12 or older. Despite the lack of evidence on the safety of discontinuing mucolytic treatment, we noticed in our cohort of cwCF a decrease in the usage of nebulised treatments (dornase alfa and hypertonic saline). A retrospective study on 15 adults with CF showed a decline in dornase alfa and hypertonic saline use but no significant decrease in inhaled antibiotics one year after ETI (Song *et al.*, 2022). In contrast to previous findings, Olivier *et al.* (2023) found no significant change in the use of dornase alfa, hypertonic saline, and nebulised antibiotics in cwCF above 6 years after six months of ETI.

A possible explanation for the reduction in the usage of mucolytic treatment might be the improvement in respiratory symptoms and a decrease in cough and mucus production after ETI. These changes in the physiotherapy treatments in most cases involved in this retrospective study were gradually decreased after a discussion with the CF team based on the patient's condition.

A recent clinical trial across the US for cwCF between the ages of 12 – 18 aimed to evaluate the effects of discontinuing nebulised hypertonic saline or dornase alfa on ppFEV1 in patients receiving ETI for at least 90 days before screening (Mayer-Hamblett *et al.*, 2022). The children were randomly assigned to continue and discontinue therapy for six weeks. They defined a non-inferiority margin of - 3% for the difference between groups in the six-week change in ppFEV1. Mayer-Hamblett *et al.* (2022) concluded that discontinuing hypertonic saline and dornase alfa was non-inferior to continuing treatment in terms of the absolute six-week change in ppFEV1. This suggested that routine use of inhaled therapies, including dornase alfa and hypertonic saline, might not be required to maintain pulmonary function in individuals likely to experience substantial drug-induced restoration of CFTR function and relatively good pulmonary health as a result of ETI (Mayer-Hamblett *et al.*, 2022).

3.5.2.3 Exercise

The potential role of exercise to replace ACTs has increased in the era of ETI. A UK-based e-Delphi survey of pwCF, caregivers, and HCPs aimed to determine the appropriate type, duration, and exercise intensity to replace ACT. They agreed that exercise could be used as a substitute for ACTs during stable CF and suggested that the intervention is effective in a trial setting. The consensus among experts is that in stable CF, aerobic exercise needs to last longer than 20 minutes with an intensity which triggers deep breathing to achieve the optimal benefits (Saynor *et al.*, 2023). Following this e-Delphi survey conclusion, an ongoing multi-centre randomised pilot trial aims to test the feasibility and safety of replacing ACTs with 20 minutes of aerobic exercise, including breathing, huffs, and coughs, to remove secretions. Participants in this trial are from two centres in the UK, are aged 10 years and above, have been on ETI for at least three months, and are clinically stable (Urquhart *et al.*, 2022).

One interesting finding of our study is the self-reported increase in exercise frequency in cwCF after 12 months of ETI, but these changes were not statistically significant. However, the exercise reported ranged from low to high intensity, such as walking, running, swimming, cycling, and boxing. A possible explanation for this improvement in exercise may be the fact that cwCF have more energy to do physical activity after ETI as well as education and encouragement from the CF team (Almulhem *et al.*, 2022). These encouraging findings support the call to replace ACTs with exercise (Saynor *et al.*, 2023). However, this result has not previously been described in the ETI period. In ivacaftor's period, a retrospective questionnaire assessed the patient-reported changes in exercise performance (Hickey *et al.*, 2015). The researchers found that exercise increased after ivacaftor administration, with 66% of participants reporting involvement in exercise less than three times weekly before and 36% after (Hickey *et al.*, 2015).

It is crucial to note the challenge of determining precise adherence levels for physiotherapy treatment. Lack of objective measurements and dependence on subjective assessments like self-report, which have been showed to overestimate adherence in other treatment modalities like nebulised therapy, are contributing factors (Daniels *et al.*, 2011).

3.5.2.4 Exercise testing

The gold standard for assessing aerobic exercise capacity is an incremental exercise test that measures peak oxygen consumption (VO2 peak) on either the treadmill or cycle ergometer (Hebestreit *et al.*, 2015). Measuring VO2 peak and assessing exercise ventilation and circulation characteristics is vital to determine the causes of low exercise capacity. However, gas exchange measurement equipment is expensive, challenging to implement with children, and requires expert interpretation (Hebestreit *et al.*, 2015). In addition to laboratory exercise testing, field tests, like the six-minute walk test (6MWT), shuttle walk, and step tests, are used to assess exercise capacity in CF. These field tests are portable and do not require costly equipment but provide limited information regarding exercise capacity, reasons for exercise limitation, and potential exercise-associated adverse reactions in patients with CF (Hebestreit *et al.*, 2015).

The MST is a field exercise capacity test that reflects everyday functional capacity (submaximal). A systematic review study which aimed to analyse the validity and reliability of available tools to assess exercise tolerance in children and adolescents with CF concluded that the cycle ergometer and the MST have the best properties to test exercise capacity in cwCF (Blanco-Orive *et al.*, 2022). Another study compared the 6MWT and an incremental shuttle walk test (ISWT), reporting that the ISWT is preferable to measure exercise tolerance in terms of cardiorespiratory response and is a better reflection of exercise tolerance in CF than the 6MWT (Saglam *et al.*, 2016). However, the 6MWT is still the most used field test in clinical practice and research, as reported by Blanco-Orive *et al.* (2022).

In adults with chronic lung disease, a change of 47.5 metres is reported to be the minimal importance difference in the ISWT (Singh *et al.*, 2014). A recent study in Spain proposed a minimum detectable change of 97.08 metres to assess the exercise response of cwCF, and 60 metres was considered the minimum importance difference in the ISWT (Del Corral, Gómez Sánchez and López-de-Uralde-Villanueva, 2020). In my retrospective study, the results from the MST improved significantly after treatment with ETI, with a 191-metres increase in the mean distance walked. It is important to acknowledge the potential influence of age as a confounding factor in the observed improvement in exercise capacity. As children naturally age, their ability to enhance exercise capacity may be a contributing factor alongside the effects of ETI . In addition, these results could correlate to the significant improvement in lung function after ETI.

To date, no published study has examined the impact of CFTR modulators on the MST in cwCF. However, a pilot single-centre study by Gur *et al.* (2023) reported an improvement in exercise performance using the 6MWT by 51.8 metres three months after ETI was initiated in adults with CF compared to the value collected two years earlier. Another retrospective study investigated the difference after 12 weeks of ETI in adults with CF and found significant improvement in the 6MWT with a mean difference of 45.2 metres (Wollsching-Strobel *et al.*, 2022).

3.5.3. Lung infections and respiratory culture sample type

This study compared the culture frequency of specific organisms on respiratory microbiology. We found a reduction in *P. aeruginosa, S. Aureus, H. influenzae, Aspergillus, Achromobacter,*

Acinetobacter, and S. maltophilia after 12 months on ETI. In addition, the most common sample type changed from sputum before ETI to cough swabs after ETI. These results were derived from data collected before, during, and after COVID-19. This mixed timeframe requires careful consideration when interpreting the results, as this reduction in the total number of respiratory culture samples could be influenced by COVID-19 and can be attributed to factors such as restrictions on in-person visits. In addition, it is unclear if decreased airway secretions, along with reduced sputum, played a role in increasing the number of cough swabs instead of sputum samples. However, it is essential to understand that detecting positive culture is more likely with sputum samples.

These results are in keeping with some published studies on the impact of ETI treatment on respiratory microbiology. Beck *et al.* (2023) examined the effects of ETI on the isolation of *P. aeruginosa*, MRSA, and Methicillin-sensitive Staphylococcus aureus (MSSA) retrospectively and discovered a decrease in positive cultures after 12 months of therapy in 124 pwCF aged 12 and older. Also, they reported decreased sputum samples from 70% to 34% and increased throat swabs from 30% to 66% after ETI. Similar findings were reported in a prospective study by Sheikh *et al.* (2023). They found a reduction in reported *P. aeruginosa* and MRSA after 12 months on ETI, with a decline in sputum samples from 73% to 23% versus throat samples from 27% to 77% after ETI. In a retrospective, multi-centre study conducted in Israel, 15 pwCF older than 6 who had at least one positive NTM airway culture within the previous two years and were treated with ETI for at least one year were included. They reported the annual NTM and bacterial isolation before and after ETI. Following ETI, NTM isolation was eliminated in 66% of pwCF, which correlated with improved pulmonary function (Wiesel *et al.*, 2023).

A case-control study in Italy for 26 pwCF presented the impact of ETI on a wider range of pathogens, including *S. aureus*, *P. aeruginosa*, *Aspergillus*, *Acromobacter*, and *S. maltophilia.* The pwCF were divided into two groups with similar clinical features, whereas the control group were not eligible for any CFTR modulators at the time of the study. After a year of treatment, 45.3% of the collected samples from the treated group were no longer colonised by microorganisms compared with the time before ETI (Migliorisi *et al.*, 2022).

It is unclear if decreased airway secretions, along with reduced sputum, played a role in increasing the number of cough swabs instead of sputum samples. However, it is essential to understand that detecting positive culture is more likely with sputum samples.

3.5.4. Limitations and strengths

The study has a number of limitations that need to be acknowledged. Firstly, it is a single-centre retrospective and includes a relatively small number of participants who received ETI. Moreover, the study had a smaller number in the comparator group, which limited the ability to conclude the difference. Another limitation was the limited length of follow-up, which may have prevented a comprehensive evaluation of long-term outcomes. The use of physiotherapy treatments, including ACTs, nebulised therapies, and exercise, was assumed based on self-report and active prescriptions found via chart review, which could be overestimated (Daniels *et al.*, 2011). Lastly, this study covers the period of the COVID-19 pandemic, which may have contributed to a substantial improvement in FEV1 due to reduced exposure to respiratory viruses and a decrease in pulmonary exacerbations (Doumit *et al.*). Also, during COVID-19, cwCF were seen less frequently and phone/video consultations were introduced. This approach results in a decreased number of samples taken for microbiology. Overall, the study provides valuable real-world insight, and these limitations should be considered when interpreting and applying the results to clinical practice.

3.6 Conclusions

This retrospective study revealed that after 12 months of ETI, there was an improvement in lung function and weight parameters consistent with the literature. Also, cwCF showed a change in the pattern of physiotherapy treatment, including a reduction in the use of ACTs and nebulised mucolytics and improved exercise frequency. Further work is required to assess the longer-term impact of ETI on clinical outcomes. This would involve conducting follow-up studies beyond the current time frame to evaluate the sustained effects and safety of ETI. A further study is suggested focusing on the changes in the physiotherapy treatment pattern, including ACTs, nebulised therapy, and exercise following ETI. This would offer insightful information about the efficiency and best therapeutic approaches in conjunction with ETI to enhance patient care

Chapter 4. Definitions of Pulmonary Exacerbation in People with Cystic Fibrosis: Scoping Review Study.

4.1 Introduction

Lung disease remains the major cause of morbidity and mortality in people with CF (Elborn, 2016). CF lung disease is characterised by intermittent episodes of increased respiratory symptoms known as PEx. Depending on severity and the organism detected in respiratory cultures, PEx are typically managed with antibiotics (often IV), intensified chest physiotherapy, enhanced nutritional support, and in some cases hospitalisation (Anstead *et al.*, 2014). They are normally associated with increased infection and inflammation in the airway. PEx become more frequent as pwCF become older and lung disease progresses (Goss and Burns, 2007).

Multiple studies have demonstrated the clinical importance of PEx in pwCF. PEx usually cause an acute drop in lung function and several studies have also examined the effect of PEx on lung function in the medium term. In around a quarter of patients there is a failure to recover to baseline lung function after a PEx (Sanders *et al.*, 2010a; Sanders *et al.*, 2010b). Furthermore, the greater the drop in FEV_1 from baseline, the more prone patients are to fail to regain their baseline lung function after the treatment of a PEx (Sanders *et al.*, 2010a; Sanders *et al.*, 2010b).

The frequency of PEx has also been strongly associated with the rate of lung function decline over the next three years in both adults and children (Sanders *et al.*, 2011). A single-centre analysis led by VanDevanter, Morris and Konstan (2016) also showed that the number of PEx treated with IV antibiotics in the previous year is significantly associated with future risk of PEx. They found that individuals with 1, 2, 3, or ≥4 PEx in the previous year treated with IV antibiotics were, respectively, 1.8, 2.9, 4.8, and 8.7 times more likely to experience a PEx in the future (VanDevanter, Morris and Konstan, 2016). Ultimately, pwCF who experience frequent PEx have reduced survival (Liou *et al.*, 2001).

PEx also impact on quality of life in both psychosocial and physical aspects (Britto *et al.*, 2002). A systematic review looking for the factors associated with HRQOL found that FEV_1 and PEx had the strongest impact on HRQOL in adolescents and adults with CF (Habib *et al.*, 2015). Consistent with the findings in adults, a study in 5-year-old children found that their parent-rated HRQOL was inversely associated with PEx rates (Cheney *et al.*, 2020). Economically, PEx are associated with a financial burden in terms of healthcare costs, time away from employment, and knock-on effects from longer term morbidity (Rubin *et al.*, 2017). In addition, pwCF described PEx as disruptions of

normality and a source of emotional distress. PEx symptoms also associated with energy consumption and restrictions of physical activity and daily-life routine (Schmid-Mohler *et al.*, 2019).

Due to the clinical importance of PEx, they are frequently used as an outcome measure in clinical trials or studies in CF (McLeod *et al.*, 2020). A large number of pivotal trials of new treatments have included PEx as a primary or secondary outcome: for example, dornase alfa (Fuchs *et al.*, 1994); tobramycin (Ramsey *et al.*, 1999); hypertonic saline (Elkins *et al.*, 2006); azithromycin (Saiman *et al.*, 2003); and HEMT including ivacaftor and ETI (Flume *et al.*, 2018; Middleton *et al.*, 2019). Despite this, there is no agreed uniform definition of PEx and, furthermore, no age-specific criteria (McLeod *et al.*, 2020).

This heterogeneity in definitions makes it challenging to evaluate, meta-analyse, and compare findings between studies and limits conclusions that can be drawn to impact clinical practice. Development of a standardised, validated, and age-specific definition(s) is essential for the precise diagnosis of PEx.

4.2 Aims

The aim of this study was to perform a scoping review to systematically map the different definitions used to identify exacerbations as an outcome in primary research studies. In addition, this review aimed to identify which signs and symptoms are most commonly included in definitions. This allowed common themes to be identified and will feed into the development of consensus-based, age-specific definitions for PEx in pwCF by the ECFS Pulmonary Exacerbation Working Group.

4.3 Methods

4.3.1 Overview

The review was originally planned as a systematic review of the PEx definitions reported in the CF literature. The protocol for systematic review of this topic was approved and registered prospectively on the PROSPERO international prospective register of systematic reviews (reference CRD42020161128) (Appendix L). However, after further consideration and preliminary review of the

literature, a scoping review approach was identified as the most appropriate for addressing the research questions. Scoping reviews are most appropriate for the following indications as described by Munn *et al.* (2018a):

1- To determine what kinds of evidence are available in a particular field
2- To clarify important definitions and concepts in the literature
3- to investigate the methods used in research on a certain subject or area
4- To determine essential attributes or components associated with an idea
5- In advance of a comprehensive review
6- To determine and evaluate any gaps in knowledge

In addition, scoping reviews can be conducted to examine the extent, nature, range, and variety of the evidence on a topic and summarise findings from literature that is heterogeneous in methods (Arksey and O'Malley, 2005; Tricco *et al.*, 2018).

The protocol of the systematic review registered in PROSPERO was adapted to fit a scoping review (Appendix M). This was reported using the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) (Tricco *et al.*, 2018).

4.3.2 Research questions

The research question was developed using the PICo tool where P stand for population, I for interest, and Co for context (Munn *et al.*, 2018b). As a result, the research question was formulated as: What definitions are reported for PEx in people of different age groups with CF in primary research studies? An additional question is what the most common reported signs and symptoms are reported in the PEx's definitions.

4.3.3 Criteria for considering studies for this review

To get a comprehensive understanding of the definitions used in primary research studies, all clinical trials (randomised clinical trial (RCT) and non-RCT) and prospective observational studies that reported PEx as an outcome were included. In addition, included articles had to be available in English and clearly specified the PEx definition used in pwCF in any age group. Articles were considered if the abstracts were available in English and were published or in press. Authors were contacted by email if studies were not accessible.

This review excluded secondary resources such as reviews and retrospective studies, case reports, *in vitro* and *in vivo* experiments and animal studies.

4.3.4 Search strategy

Embase, MEDLINE, Cochrane Library, Scopus, and CINAHL databases were searched between January 1990 and December 2022.

A comprehensive search strategy was developed in consultation with a librarian specialising in health databases. Medical subject heading (MeSH) and keywords were used with 'AND' and 'OR' to narrow or broaden the search depending on the search strategy for each database. Details of search strategies based on each database are shown in **Table 18**. The following search terms were employed: cystic fibrosis AND pulmonary exacerbation limited to English language and 1990-2022. This choice of search terms was to minimise the risk of missing relevant studies that may use PEx definition in different subject headings and to ensure that results were highly relevant to the research questions. Several pilot searches were run in each database to ensure that key articles were picked up.

Table 18. Search strategies

Databases	**Search strategies**
Medline (OVID) (1946 onward) Embase (OVID) (1988 onward)	1- Cystic Fibrosis/ 2- (Cf).tw. 3- (Cystic adj5 fibrosis).tw. 4- 1 OR 2 OR 3 5- (pulmonary adj5 exacerbation*).tw. 6- Exacerbation*.tw. 7- (pulmonary adj1 exacerbation*).af. 8- 5 OR 6 OR 7 9- Limit 8 to (human and english language and yr="1990 - 2022")
CINAHL	1- MH cystic fibrosis OR AB cystic fibrosis OR TI cystic fibrosis 2- MH pulmonary exacerbation OR AB pulmonary N5 exacerbation* OR TI pulmonary N5 exacerbation* OR TX pulmonary N5 exacerbation* OR TX exacerbation 3- 1 AND 2 4- Limiters - Published Date: 19900101-20221231 5- Expanders - Apply equivalent subjects 6- Narrow by Language: - english 7- Search modes - Boolean/Phrase
Cochrane (central)	1- MeSH descriptor: [Cystic Fibrosis] this term only 2- (cystic NEXT fibrosis):ti,ab,kw 3- (pulmonary NEXT exacerbation*):ti,ab,kw 4- (exacerbation*):ti,ab,kw 5- #1 OR #2 6- #3 OR #4 7- #5 AND #6 with Publication Year from 1990 to 2022, in Trials
Scopus	(TITLE-ABS-KEY ("cystic fibrosis") AND TITLE-ABS-KEY (pulmonary PRE/15 exacerbation) OR TITLE-ABS-KEY (exacerbation)) AND PUBYEAR > 1989 AND PUBYEAR < 2023 AND (LIMIT-TO (LANGUAGE , "English")) AND (LIMIT-TO (DOCTYPE , "ar") OR LIMIT-TO (DOCTYPE , "cp")

All the references were then imported into Endnote 20 reference management software. Duplication was checked using different field settings as suggested by Bramer *et al.* (2016), since

each database formats the information slightly differently, which makes recognising duplicates difficult. Duplication was checked by setting the 'find duplicates' preferences to the following:

1- Author, Year, Title, Journal

2- Author, Year, Title, Pages

3- Title, Journal, Pages

4- Year, Title, Pages

5- Title, Pages

6- Author, Year, Journal, Pages

7- Author, Year, Title

8- Author, Year, Journal

9- Author, Year

10- Year, Title

11- Title

After removing the duplicates all results were exported to the Rayyan website (Ouzzani, Hammady, Fedorowicz and Elmagarmid, 2016) to screen the title and abstract.

4.3.5 Study selection and data charting

The titles and/or abstracts of studies retrieved using the search strategy were screened by myself. Decisions about the inclusion or exclusion of studies were decided in a series of meetings with the supervisory team. I, subsequently, retrieved and assessed the eligible studies in full by. The supervisor screened 10% of the included articles to ensure accuracy and agreement.

I designed an electronic data charting form and tailored for the specific methodology used in the review (Appendix N). The form was piloted on three articles and subsequently optimised after discussion with my supervisory team. The following data were charted from the included articles: title, citation, study design and type of publication, population characteristics (age of participants), definition of PEx reported as a free text field, and the reported signs/symptoms.

The purpose of the review was purely to explore definitions of PEx reported in the literature, not to extract data from papers, and, therefore, the quality and risk of bias in individual studies did not require assessment.

4.3.6 Data synthesis

A thematic qualitative synthesis was used for this study (Dixon-Woods *et al.*, 2005) to facilitate systematic identification of prominent themes and summarise definitions under these themes in a structured way. Thematic synthesis has three stages: the coding of text line by line; the development of descriptive themes; and the generation of analytical themes. The charted data, according to my research question, were pooled, and then coded – each line of text according to its content. I then started looking for similarities and differences between codes to begin grouping them (Thomas and Harden, 2008). Two main themes were developed from the coded data, based on clinical presentation and treatment. For each theme, I reported the frequencies of extracted definitions. In addition, the frequency of signs and symptoms used were recorded.

4.4 Results

4.4.1 Characteristics of articles identified by search strategy.

In total, 14,039 citations were identified by the search strategy across all databases. **Figure 28** shows the PRISMA flow diagram for the study. Once duplicates were removed, 7,647 titles and abstracts were screened. From these, 377 articles met the inclusion criteria for the scoping review and were included and analysed in the qualitative synthesis (the complete list of included articles is provided in Appendix O).

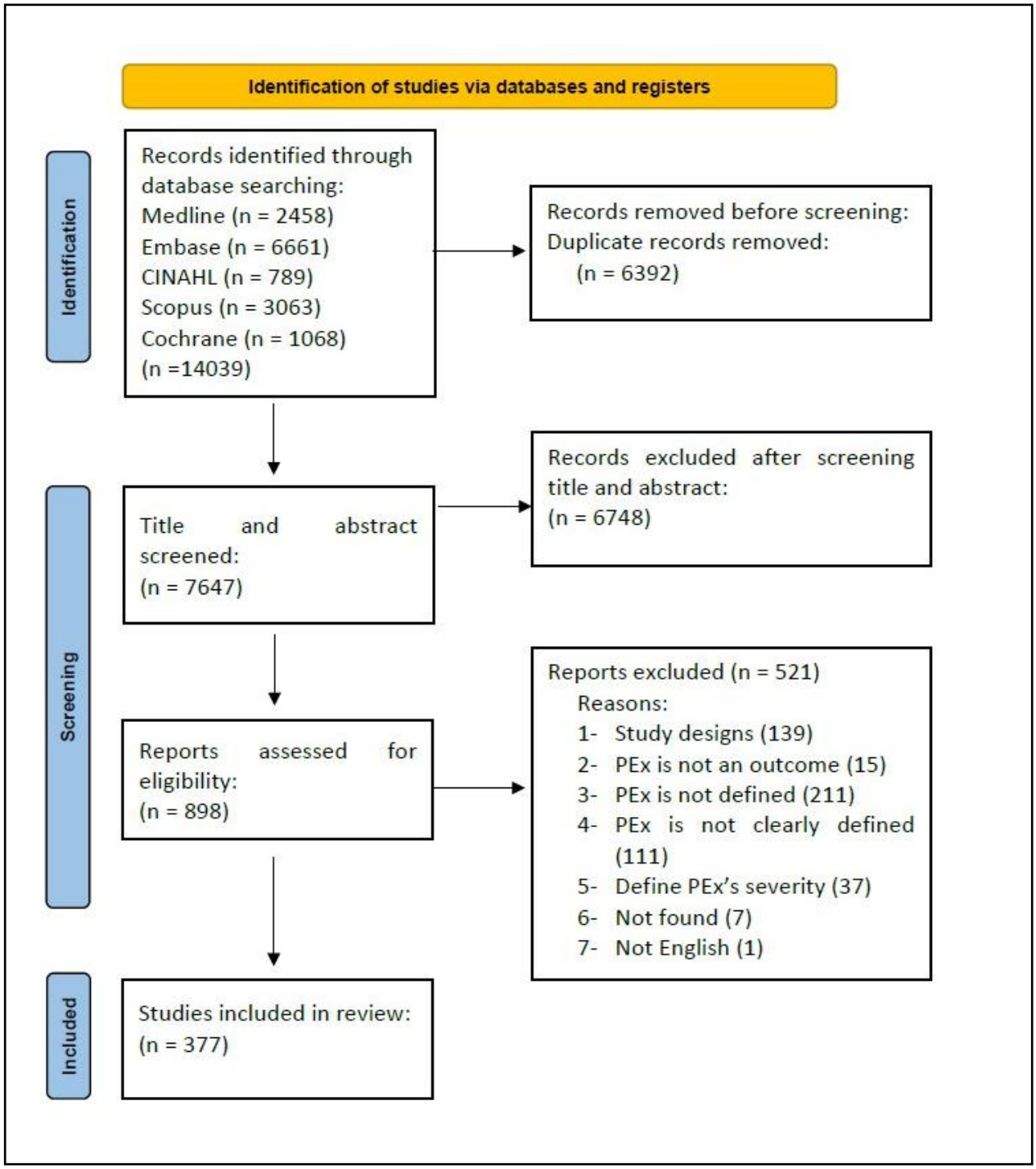


Figure 28. PRISMA flow diagram.

Source (Page *et al.*, 2021).

In terms of the different types of study included, these consisted of 272 observational studies and 105 experimental studies. The majority of studies were full articles, while 16 studies were available in abstract form only. **Figure 29** shows the breakdown of different study types.

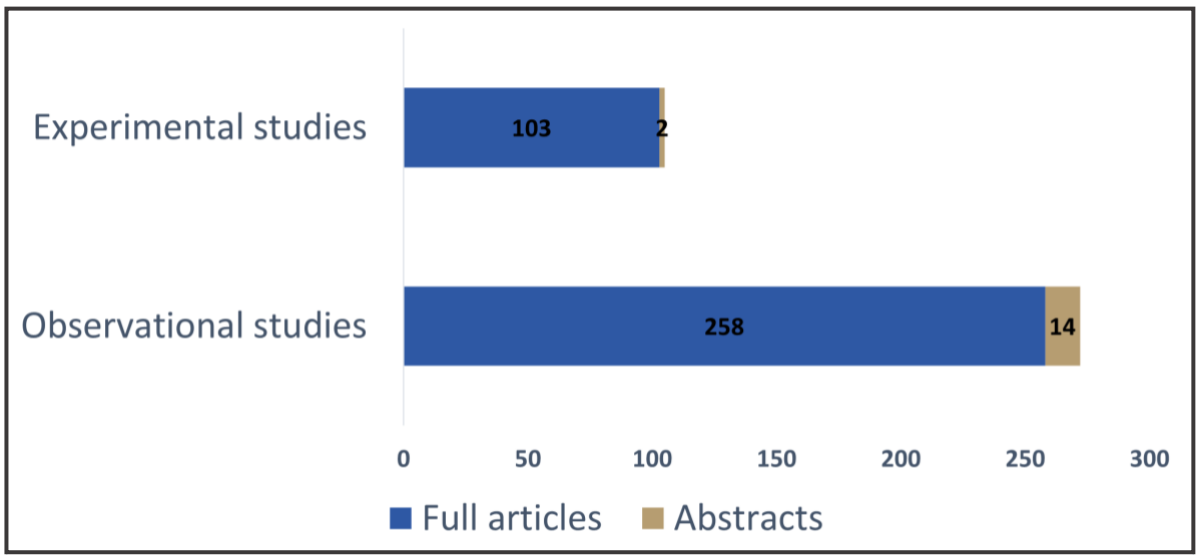


Figure 29. Breakdown of types of study included.

4.4.2 Themes of definitions reported for PEx

Two key themes were developed for the definitions reported in the included articles. After manually coding the definitions, the definition of PEx were categorised into two themes: One based objectively on specific criteria, and the second based on subjective decisions as shown in **Figure 30.**

1. Subjective – based solely on clinician's judgement and decision.
    a) Without any specific criteria.
    b) With initiation of acute treatment and/or hospitalisation.

2. Objective – predefined criteria indicating presentation of threshold set of clinical signs and symptoms, sub-divided into three categories.
    a) Objective definition – involving a specific combination of systematic and/or respiratory signs and symptoms.
    b) Objective score – different clinical features each with a specific weighting or score within a definition.
    c) Predefined combination of systematic or respiratory signs and symptoms and initiation of acute treatment.

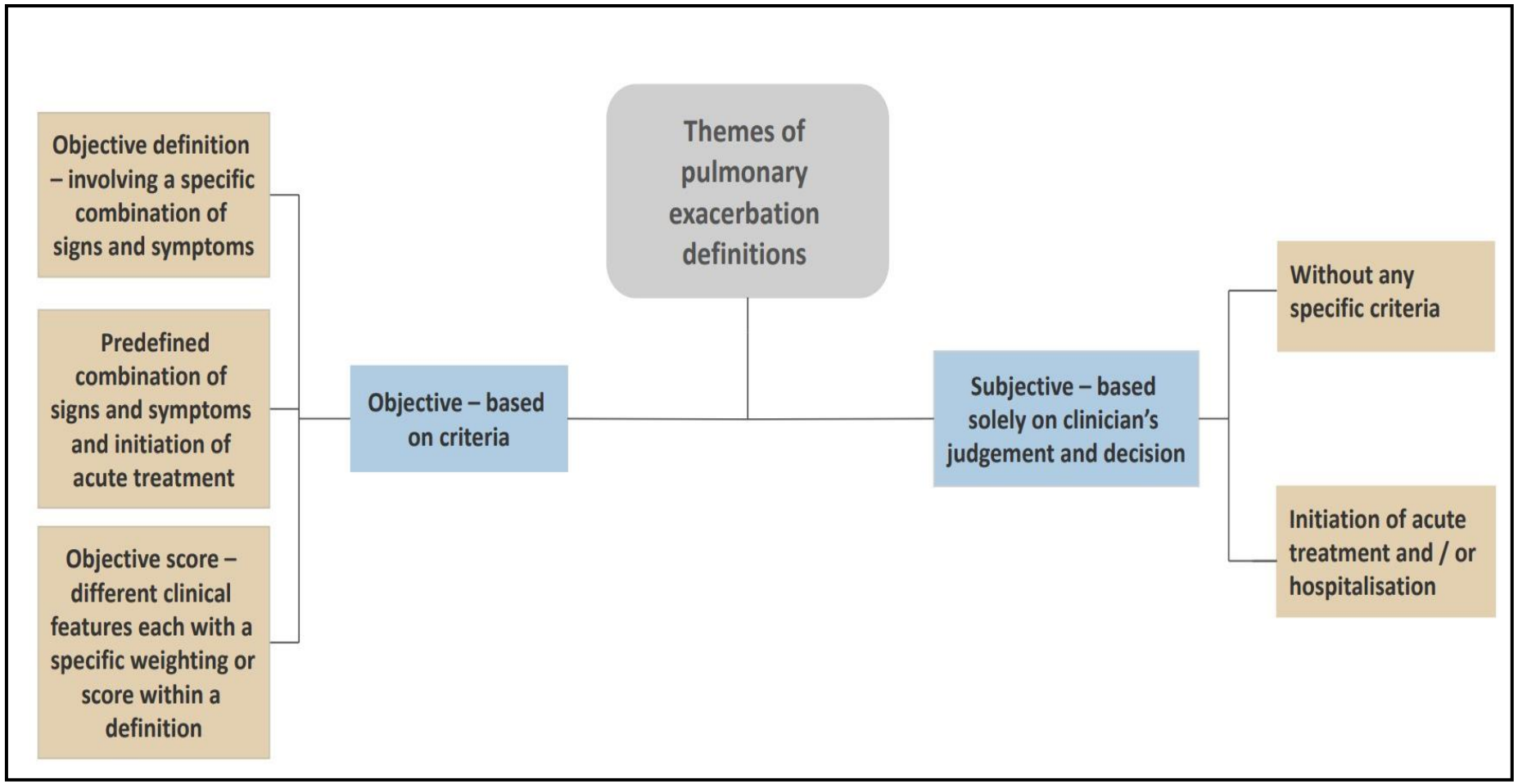


Figure 30. Pulmonary exacerbation's (PEx) definition themes.

As shown in **Figure 31**, out of 377 identified articles, there were 94 (25%) articles that used a subjective definition, and 283 (75%) articles were classified as using an objective definition. The breakdown was as follows:

1. Subjective
    a) Without any specific criteria – 22 studies.
    b) With initiation of acute treatment and/or hospitalisation – 72 studies.
2. Objective
    a) Objective definition – 144 studies.
    b) Objective score – 9 studies.
    c) Predefined combination of signs and symptoms and initiation of acute treatment – 135 studies.

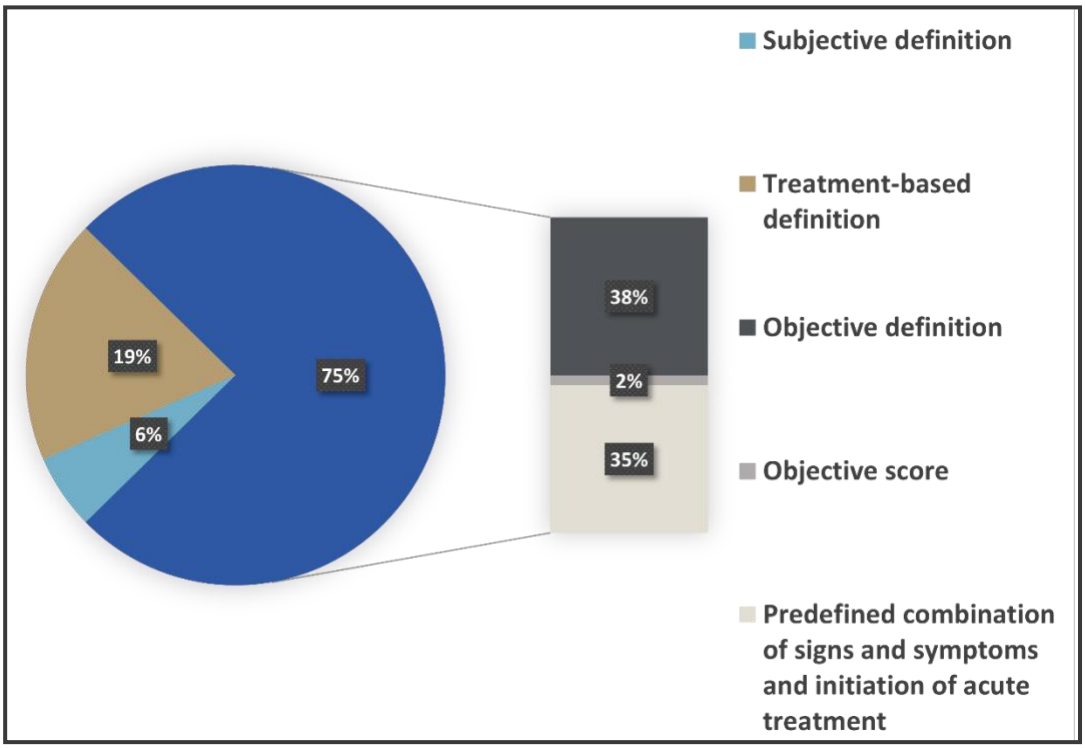


Figure 31. Frequency of pulmonary exacerbation (PEx) definitions used in studies.

Another factor used in defining PEx is the duration of signs and symptoms, or the duration of the course of treatment, which was reported in 23 included articles. Some specified the duration of signs and symptoms to be at least three days (9 studies), five days (4 studies), or seven days (5 studies).

In addition, some studies delineated a minimum course of treatment as seven days to meet the criteria of PEx (3 studies), whereas others required the administration of an IV course for 21 days (2 studies).

4.4.3 Commonly used definitions

Out of the 377 articles, 148 studies used previously defined definitions. In this review, I recorded those which developed their definition and those which subsequently used these previously defined definitions. There were six commonly used definitions that were detected from the analysis of the articles, as shown in **Table 19**.

Table 19. Commonly reported definitions for pulmonary exacerbation (PEx).

Definition	Number of articles (%)
Fuchs modifications	73 (49%)
Fuchs definition (1994)	38 (26%)
CFF (1994)	22 (15%)
EPIC study (2009)	12 (8%)
Akron pulmonary exacerbation score (2009)	4 (3%)
Rosenfeld score definition (2001)	4 (3%)

These were in order of frequency: the Fuchs modifications definition taken from a trial of inhaled dornase alfa and original 'Fuchs' definition (Fuchs *et al.*, 1994) were used 111 times; the CFF definition (Cystic Fibrosis Foundation, 1994) was used 22 times; the EPIC study (Treggiari *et al.*, 2009) relating to a study of early acquisition of *P. aeruginosa* in children was used 12 times; the 'Akron' pulmonary exacerbation score (Kraynack and McBride, 2009) and the 'Rosenfeld' definition (Rosenfeld *et al.*, 2001) were used four times. Overall, 64% of the experimental studies included in the scoping review applied one of these definitions.

4.4.3.1 Fuchs definition (1994)

Fuchs *et al.* (1994) based their definition for a PEx on signs and symptoms and the need for IV antibiotics in pwCF aged >5 years. The definition involves the presence of four out of 12 possible signs or symptoms along with IV antibiotic treatment. These signs and symptoms are (Fuchs *et al.*, 1994):

1. change in sputum.
2. New or increased haemoptysis.
3. Increased cough.
4. Increased dyspnoea.
5. Malesia, fatigue, or lethargy.
6. Temperature above 38 C.
7. Anorexia or weight loss.
8. Sinus pain or tenderness.
9. Change in sinus discharge.
10. Change in physical examination of the chest.
11. Decreased in pulmonary function by %10 or more from previous recorded value.
12. Radiographic changes indicative of pulmonary infection.

This original Fuchs definition was reported in 38 of the included publications. In addition, 73 articles reported a modification of the original Fuchs definition either by altering the criteria around IV treatment or using variations in the signs and symptoms requirement. One of the most commonly reported modifications of the original Fuchs criteria is the one proposed by the EuroCareCF Working Group in 2011 (Bilton *et al.*, 2011). They defined a PEx as the need for an additional antibiotic because of a change in at least two out of the following six signs or symptoms: change in sputum; increased cough; increased dyspnoea; increased malaise, fatigue or lethargy; anorexia or weight loss; and decrease in pulmonary function by 10% or new chest radiographic changes (Bilton *et al.*, 2011). Another modification, known as 'expanded Fuchs criteria/definition' differs from the original in terms of treatment, involving any oral, inhaled, and/or IV antibiotics prescribed in response to the presence of four out of the 12 Fuchs criteria (Flume *et al.*, 2018). The 'modified Fuchs criteria' involves only the presence of four out of 12 signs and symptoms without a specified requirement for treatment. Several other modifications of the original Fuchs criteria have also been reported in studies.

Hind *et al*. (2019) defined an exacerbation as treatment with IV antibiotics and meeting any single symptom/sign of the Fuchs criteria. Other modifications include the removal of one of the criteria involving sinus discharge or sinus pain and tenderness (Tate *et al.*, 2002) or adding decreased exercise tolerance to the criteria (Accurso *et al.*, 2011).

In summary, the Fuchs criteria in one form or another has been commonly reported as an objective-based definition that characterises a PEx based on predefined signs and symptoms either combined with treatment or not.

4.4.3.2 US CF Foundation (CFF) definition

In 2005, the CFF Microbiology and Infectious Disease Consensus defined a pulmonary exacerbation as three out of the 11 following signs or symptoms being present (Cystic Fibrosis Foundation, 1994):

1. Increased cough.
2. Increased sputum production and/or a change in appearance of expectorated sputum.
3. Fever (>38 C for at least four hours in a 24-hour period) on more than one occasion in the previous week.
4. Weight loss > 1 kg or 5% of body weight associated with anorexia and decreased dietary intake or growth failure in an infant or child.
5. School or work absenteeism (due to illness) in the previous week
6. Increased respiratory rate and/or work of breathing.
7. New findings on chest examination (e.g., rales, wheezing, crackles).
8. Decreased exercise tolerance.
9. Decrease in Forced Expiratory Volume at one second (FEV1) of > 10% from previous baseline study within past three months.
10. Decrease in haemoglobin saturation (as measured by oximetry) from baseline value within past three months of > 10%.
11. New finding (s) on chest radiograph.

There was no specification of the age of patient in the original definition. Some studies have used this definition in paediatric patients aged 2–12 years (Jafari *et al.*, 2013), although it requires a measurement of FEV_1 which is usually done for patients aged 6 years and above only. This objective-based definition is largely formed on predefined signs and symptoms.

4.4.3.3 The Early Pseudomonas Infection Control (EPIC) definition

The EPIC definition published by Treggiari *et al.* in 2009 is based on signs and symptoms and specifically applies to cwCF aged 1 to 12 years (Treggiari *et al.*, 2009). It divides signs and symptoms into four major and six minor criteria. A presentation involving one major and/or two of the minor criteria signs or symptoms for a specified duration fulfil the definition for a PEx. Major criteria are:

1. Decrease in FEV1 of ≥10% from best baseline within past 6 months, unresponsive to albuterol (in participants able to reproducibly perform spirometry)
2. Oxygen saturation b90% on room air or ≥5% decline from previous baseline
3. New lobar infiltrate(s) or atelectasis(e)s on chest radiograph
4. Hemoptysis (more than streaks on more than one occasion in past week).

Additionally, two minor criteria are required in the absence of major criteria of ≥5 days duration or significant symptom severity. These minor criteria are:

1. Increased work of breathing or respiratory rate
2. New or increased adventitial sounds on lung exam.
3. Weight loss ≥5% of body weight or decrease across 1 major percentile in weight percentile for age in past 6 months.
4. Increased cough
5. Decreased exercise tolerance or level of activity.
6. Increased chest congestion or change in sputum.

Some studies have also used the EPIC definition in adults and children over 12 years old (Mayer-Hamblett *et al.*, 2018; Sagel *et al.*, 2018). Another adjustment to the EPIC definition that has been made in some studies is to shorten the duration of symptoms for the minor criteria from 5 to 3 days (Lechtzin *et al.*, 2013; Maggie Patricia *et al.*, 2013).

4.4.3.4 Akron Pulmonary Exacerbation Score (PES) definition

An alternative method to objectively define a PES is to use a scoring system where each sign or symptom has a specific weighting with a total score greater than a predefined value being diagnostic of a PEx. The Akron PES score (Kraynack and McBride, 2009) was designed for pwCF aged 6 years and over. This score contains 14 elements that are divided into systemic, pulmonary signs and symptoms, and objective measurements. A score of five or above is required to meet the criteria for a pulmonary exacerbation. Further details of the PES elements are shown in Table 20. Although the original PES definition was developed for a population aged 6 years and older, it has been used in studies for participants down to the age of 6 months, for example by Hoen *et al.* (2015).

Table 20. Akron Pulmonary Exacerbation Score (PES) definition criteria .

Systemic signs/symptoms	
Fever > 38 °C in the prior 2 weeks	Yes=1, No=0
Malaise or fatigue in the prior 2 weeks	Yes=1, No=0
Increased or new school absences in the prior 2 weeks	Yes=2, No=0
Anorexia or poor appetite in the prior 2 weeks	Yes=1, No=0
Weight loss (≥ 5%) of poor weight gain compared to last clinic visit (or in the last 3 months)	Yes=2, No=0
Pulmonary signs/symptoms	
Increased cough (frequency, intensity, duration) for ≥ 1 week	None=1, Mild=1, Significant=2
Major change in sputum or change in chest congestion for ≥ 1 week	None=1, Mild=1, Significant=2
Increased dyspnoea on exertion or shortness of breath	Yes=2, No=0
Change in chest exam or increased work of breathing or respiratory rate	Yes= 2, No=0
Objective measurement	
Decrease in FEV_1 (compared to highest value of the prior 6 months)	<10%=0, ≥10%=3, ≥15%=5
New chest radiograph abnormality	None=1, Increased air trapping or mucus plugging=1, New atelectasis or infiltrate=2, Pneumothorax=5
Haemoptysis	None=0, Streaked=3, Increased or new onset=5
Decreased oxygen saturation from baseline (compared to highest value of the prior 6 months)	<4% change=0, ≥4% decrease=2, ≥10% decrease=5

Source: (Kraynack and McBride, 2009)

4.4.3.5 Rosenfeld definition

The Rosenfeld definition (Rosenfeld *et al.*, 2001) is another example of a score-based method. They developed two models. In model one, the score is based on six clinical findings, each weighted by a particular coefficient (shown in brackets) as follows to reach a final 'PEx score': decreased exercise tolerance (1.8); increased cough (1.5); increased cough/sputum congestion (1.5); school or work absenteeism (1.6); increased adventitial sound on lung examination (1.2); and decreased appetite (1.1).

A PEx is defined as when the score is greater than 2.6. The Rosenfeld model two score is based on the following: decreased exercise (1.7); increased cough (1.6); increased sputum/chest congestion (1.4); school or work absenteeism (1.7); increased adventitial sound on lung examination (1.2); decreased appetite (0.9); and change in FEV_1 (0.05).

A final score greater than 2.5 defines a PEx. This score is designed for use in a population aged 6 years and above, and we identified four studies where it has been reported.

4.4.4 *Definitions used in different age groups.*

Out of a total of 377 articles, only one of the included abstracts in press did not report the age of participants clearly. The age of these populations divided into three groups: adult (aged ≥18 years), paediatric (aged <18 years), and mixed for studies applying definitions to both adult and paediatric age groups. 131 articles included adult population, 110 articles included paediatric population, and 135 articles included mixed group of adult and paediatric.

The result showed the objective definition, defining PEx based on signs/symptoms, is the most common definition reported in the adult and paediatric population. While in studies with a mixed age group the predefined combination of signs and symptoms and initiation of acute treatment definition is the most reported. The types of definitions used in different age groups are shown in **Figure 32**.

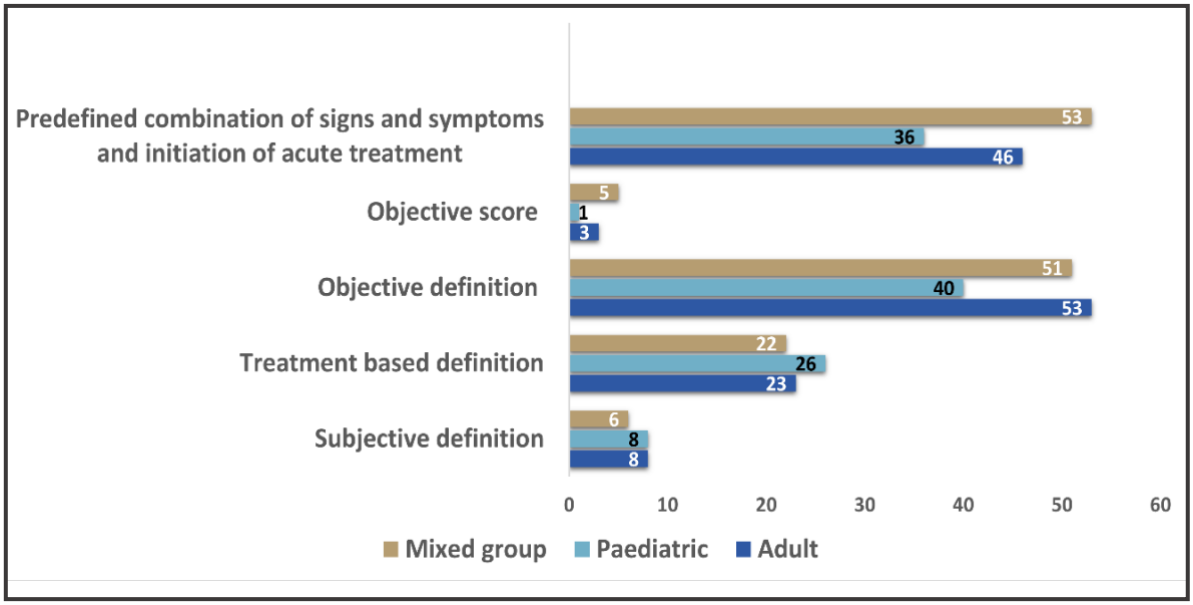


Figure 32. Types of definitions of pulmonary exacerbation (PEx) reported in paediatric and adult studies.

4.4.5 The most commonly reported signs and symptoms in PEx definitions

The second aim for this review was to identify the number of times each symptom was used in defining PEx. Out of the 377 included articles, 288 articles defined PEx using signs and symptoms. As shown in **Figure 33**, the signs and symptoms most commonly used among these studies were: sputum (used in 270 articles), cough (260 times), lung function (245 times), weight/appetite (230 times), dyspnoea (198 times), chest x-ray (177 times), chest sound (174 times), high temperature (166 times), malesia, fatigue or lethargy (147 times), haemoptysis (123 times), sinus pain/discharge (93 times), exercise tolerance (70 times), respiratory rate (56 times), oxygen saturation (52 times), absenteeism (37 times), laboratory findings (14 times), chest pain (8 times), tachycardia and blood pressure (1 time), and sore throat (1 time).

75% of the studied used increase the amount of sputum, increase cough, decline in lung function, and weight loss and decrease appetite in defining PEx.

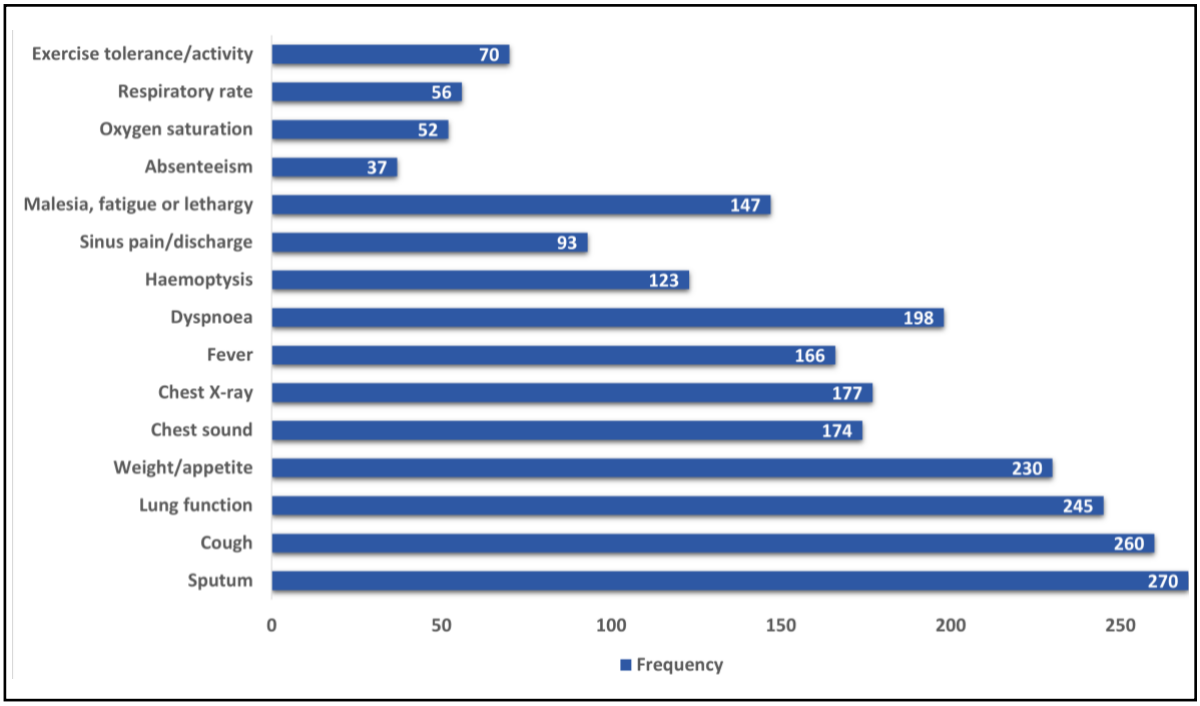


Figure 33. The frequency of most common signs and symptoms used in the reported PEx definitions.

4.5 Discussion

The results of this scoping review show a large amount of heterogeneity in the definitions used for PEx in the CF literature with a diverse range of definitions used. A minority of publications or studies proposed their own novel definition of a PEx, with the remainder instead using definitions or elements derived from previous studies. This heterogeneity and lack of an accepted and validated standardised definition make it challenging to design clinical trials with PEx as a clinical outcome measure and limit meta-analysis of data from previous studies. It may be argued that the lack of standardised definitions reduces the effectiveness and applicability of clinical research in CF.

Using a predefined combination of signs and symptoms is the most frequently used method to define PEx. This approach has some objectivity and depends on clinical presentation and parameters rather than clinical interventions. However, there may still be inconsistencies in the symptoms and their duration used to define PEx in the literature. Akron PEx score (Kraynack and McBride, 2009) specified the duration of pulmonary symptoms as 7 days or more to define a PEx, the EPIC study (Treggiari *et al.*, 2009) required five days or more, while another trial (Rosenfeld *et al.*, 2012) required three days or more. Another conflict in the literature is the minimum requirement of symptoms to fulfil a definition. This ranges from at least one symptom (Asner *et al.*, 2012) to four and more symptoms (Britto *et al.*, 2002).

Another factor that should be considered is the difference in clinical presentations between adults and children when determining which clinical characteristics best predict a PEx. Some studies contribute to the PEx definition by highlighting the difference in the reported signs and symptoms between ages (Abbott *et al.*, 2009; Abbott *et al.*, 2012). Several studies used the cluster of signs and symptoms definition. However, all of these definitions are not validated yet.

The need for a change in treatment, most commonly prescribing antibiotics, is frequently part of definitions used for PEx (Hind *et al.*, 2019; Paff *et al.*, 2013). Few would argue that this is a crucial intervention relevant to both patients and multidisciplinary clinical teams. However, there is variation in the threshold for recognising and treating PEx at multiple levels in reality.

Kraynack, Gothard, Falletta and McBride (2011) found that clinicians varied in their diagnosis and treatment of PEx. This variation was present between centres, within the same centre, and at the individual physician level. The indications for oral, inhaled, or IV antibiotics also vary between centres and individual clinicians.

For these reasons, the use of treatment-based definitions was not recommended by the EuroCareCF Group (Bilton *et al.*, 2011) and CFF (Ramsey and Boat, 1994), arguing that treatment as a definition of PEx in CF should not stand alone because of rapid changes in treatment modalities. Furthermore, the need for antimicrobials could result from concurrent pulmonary infection rather than a PEx per se. Some studies required hospitalisation and/or treatment based to define exacerbation (Brody *et al.*, 2005; Carnovale *et al.*, 2022a). One article defined the exacerbation by the need for hospitalisation without any specific treatment requirements (Foong *et al.*, 2018). Due to the commonality of recording antibiotics treatment in the medical records and the fact that a clinician's decision to administer antibiotic treatment indicates a change in respiratory status that justifies intervention, several PEx definitions use the requirement for antibiotics treatment. This approach to defining PEx confirms that the PEx meets the minimum severity threshold that needs intervention. However, the aim of my work was to identify a PEx but not categorise PEx severity. Furthermore, as the rate of IV antibiotic administration at home has increased, this definition will not capture such cases (Cystic Fibrosis Trust, 2020b). Despite this, a definition based on treatment or hospitalisation is widely used in 19 % of the included studies.

The original Fuchs definition (Fuchs *et al.*, 1994) builds upon predefined criteria with the need for IV treatment. Although this definition has been used broadly in research, it is yet to be formally validated. The EuroCareCF group (Bilton *et al.*, 2011) proposed a modified version of Fuchs, which requires additional antibiotics as indicated by specific signs/symptoms, which they believe provides the best definition. This definition included any type of antibiotics used to capture all PEx that met minimum severity.

On reviewing the literature, multiple versions were identified that were adapted from the original Fuchs definition (Fuchs *et al.*, 1994). There is inconsistency in the use/meaning of the term ‘modified Fuchs’. Some studies use this name for the EuroCareCF Working definition (Bilton *et al.*, 2011), while others use it to define a PEx as Fuchs criteria without the need for

IV antibiotic treatment (Choyce *et al.*, 2017). Another modified Fuchs definition excludes one of the original 12 signs/symptoms (Britto *et al.*, 2002). Due to this variation in the terminology, some articles were excluded from this review if they did not specify clearly which Fuchs definition they used (original, modified or expanded) (Grosse-Onnebrink *et al.*, 2017; Lam *et al.*, 2015).

Two scoring systems to define PEx were found in the included literature. These scores were based on clinical assessment and independent of treatment decisions (Kraynack and McBride, 2009; Rosenfeld *et al.*, 2001). Akron PES (Kraynack and McBride, 2009) is comprehensive and covers both systemic and pulmonary signs/symptoms and objective measurement of FEV_1. Most of these measurements are obtained during routine CF clinic visits. A randomised controlled trial by Rosenfeld *et al.* (2001) developed two scoring model definitions for patients older than 6 years. These definitions involve clinical investigation results rather than just signs and symptoms. The difference between the two scores is that FEV_1 is included in the second model. Some studies used this definition without clearly stating which model they used (Hakim *et al.*, 2007). The advantage of these scoring methods is that they do not rely on therapeutic decisions as recommended by The CFF Consensus Conference on Outcome Measures for Clinical Trials (Ramsey and Boat, 1994) and the EuroCareCF Group (Bilton *et al.*, 2011) because of rapid developments in treatment modalities.

The least-well-specified method to define a PEx in the literature is a subjective decision made by the attending clinician's judgment rather than predefined criteria. This type of definition is open to variability and bias depending on physicians' preferences and backgrounds. Patients' preferences and backgrounds can also influence this decision. Such a definition makes the PEx ineffective as a clinical tool for facilitating decision-making and evaluating the outcomes in clinical trials.

Rather than definitions based on clinical presentation and or treatment, patient-reported indicators of PEx has been suggested to help recognise PEx at an earlier stage and facilitate prompt intervention (Abbott *et al.*, 2009; Abbott *et al.*, 2012). Abbott and colleagues (2009) interviewed adults with CF who experienced exacerbations. They asked them to report the symptoms experienced during pulmonary exacerbations and how they consequently recognised when they had recovered (Abbott *et al.*, 2009). For many patients, the onset of an

exacerbation was recognised by fatigue and alterations in sleep, cough, sputum, appetite, mood, and daily activities. When describing the improvement, they reported enhancement mainly in the activity level, ability to sleep, cough, and less sputum production. Abbott and partners extended their work to include children, using the same method (Abbott *et al.*, 2012). They found that, in general, the most frequently reported symptoms for the onset of exacerbations were tiredness and increased cough and 'cold' symptoms, while in moderate or severe disease, activity-induced breathlessness, sleep disturbances, and mood fluctuations were most common. Those with severe disease also reported increases in sputum production and lack of appetite (Abbott *et al.*, 2012). The child-reported indicators of pulmonary exacerbation tended to map onto those reported by adults, with some exceptions. This approach would be helpful for developing a tool to monitor the progression of the disease, requisite intervention, and progression of treatment across the CF lifespan (Lim and Fitzgerald, 2015).

Notably, although there were various definitions used in the literature, ranging from physician's opinion to predefined signs/symptoms, none of these definitions is validated. This disagreement poses problems in evaluating the exacerbation as outcomes in clinical trials.

It is important to note that all of these definitions developed before the era of CFTR modulators, which has impacted PEx rates (Middleton *et al.*, 2019). While in the pre-CFTR modulator era criteria for PEx relied heavily on signs and symptoms like cough, sputum, weight loss, and fatigue, CFTR modulators have changed the presentation of PEx. Reduced sputum production, weight gain, improved energy, and potentially less severe symptoms present a challenge to traditional definitions. This evolving landscape necessitates reevaluation of the criteria used to accurately capture PEx in the post-CFTR modulator era..

Although the introduction of HEMT caused a reduction in the rates of PEx, there will remain pwCF who experience PEx and some with CF-related lung damage for whom PEx management is complicated and challenging.

4.5.1 Strengths and limitations

This review's strengths come from the novelty of mapping the entire range of PEx definitions available in the literature across a large number of publications. A comprehensive search strategy of five large and reliable databases (Embase, MEDLINE, Cochrane Library, Scopus, and

CINAHL) was used, meaning that it is likely that all relevant articles were identified. In addition, the review covers a long period from 1990 to 2022. However, the review was limited to studies in English only, potentially missing some relevant non-English papers. The main limitation of this review is the lack of a rigorous quality assessment process, which could result in including studies of poor quality.

4.6 Conclusions

This study reaffirms that there is no agreed definition of PEx in pwCF used in the medical literature. Rather several definitions are commonly used, and considerable variation exists amongst them, with a lack of validation. The most commonly used definition in the literature was based on observed signs and symptoms which offers a potentially more objective method compared to clinical interventions. However, it is important to note that there may still be variations in the symptoms and the duration used to define PEx in existing literature, leading to potential inconsistencies.

This inconsistency in defining a PEx is almost certainly detrimental to CF clinical research by making the comparison of studies challenging and limiting meta-analysis. It is also essential to recognise the differences in the profile of PEx between ages of patients. There is no single definition that will fit all age groups, and criteria must be age-specific to be truly clinically relevant. Adult and paediatric populations vary in their ability to perform spirometry reliably, typical presenting symptoms (Abbott *et al.*, 2009; Abbott *et al.*, 2012), and the preferred route of treatment (Waters and Ratjen, 2015). An ideal definition, as proposed by Dakin *et al.* (Dakin, Henry, Field and Morton, 2001) would involve an objective chemical, physiologic, or histologic marker. However, no such marker has been identified of PEx in the CF population.

My findings confirm the need for internationally agreed and age-specific definitions of PEx in CF that include specific signs and symptoms and the need for treatment according to the best available evidence to optimise health outcomes. We suggest that a combined consensus definition for PEx could be reached by integration of evidence from the literature together with the opinions of multidisciplinary experts, practising healthcare professionals, and patients themselves. Such definitions will advance clinical research in CF in general and

facilitate impactful research in to PEx. Such definitions should also reflect the impact of HEMT on the clinical characteristics of PEx (Shteinberg and Taylor-Cousar, 2020).

Chapter 5. General Discussion.

5.1 Overview

This final discussion will summarise the key results described in this thesis together with suggested potential areas for future research and clinical implications and conclude with some reflections on the work.

5.2 General Discussion

The development of ETI treatment has changed the face of CF practice. This thesis's key aim was to understand the changes in ACTs, nebulised mucolytics, and exercise after children started on ETI treatment. This aim is addressed in Chapter Two, where semi-structured interviews were conducted with cwCF, families, and HCPs to understand the impact of ETI on their experience regarding ACTs and nebulised mucolytics. This study has provided a deep understanding of the change in the experience of cwCF and their families after starting ETI. Three themes were developed to capture participants' experiences. In the first theme, participants emphasised the change in their quality of life due to improved physical and mental symptoms and reduced treatment burden. In the second theme, they explained their opinion about simplifying ACTs and nebulised mucolytics. The final theme revealed the changes in CF practice as a result of ETI.

CwCF and their families have experienced improvements in symptoms after ETI, prompting some to question the necessity of daily ACTs and nebulised mucolytics despite the lack of high-quality evidence that supports this practice. The call to simplify ACTs and nebulised mucolytics and replace them with exercise came across in my interviews. This shift in attitudes toward ACTs, nebulised mucolytics treatment, and emerging weight gain have created a new challenge for HCPs as they manage cwCF while still providing the necessary treatments to ensure long-term health and well-being.

Furthermore, to achieve this thesis's aim, the third chapter quantifies the longitudinal change in physical therapy treatment in cwCF at the GNCH following one year on ETI to further comprehend the real-world effect of ETI on physiotherapy and other clinical outcomes. The study shows a statistically significant increase in body weight, BMI centile, BMI z-score, and

ppFEV1 associated with ETI treatment. The study also revealed a statistically significant decline in ACTs and nebulised mucolytics use. In addition, exercise capacity showed a statistically significant improvement. However, self-reported exercise frequency improvement was not statistically significant.

These findings support those from my qualitative study. The improvement in ppFEV1 indicates that the lungs become healthier over time with ETI, potentially reducing the need for ACTs and nebulised mucolytics (Mayer-Hamblett *et al.*, 2022). The increased self-reported exercise frequency and capacity support the possibility of replacing ACTs with regular exercise for cwCF on ETI (Urquhart *et al.*, 2022). Further, the observed increase in body weight is consistent with the issue of weight gain reported among participants in the qualitative study. This highlights the need for education, regular monitoring, and modification of nutrition status and lifestyle (Mantzios, Egan and Patchell, 2016).

The last objective of this thesis concerned the lack of a consensus definition of PEx. In randomised trials of ETI the PEx rate decreased significantly (Heijerman *et al.*, 2019; Middleton *et al.*, 2019). However, PEx remains a common event in pwCF and there is still an evidence gap to guide best practices in treating exacerbations. The scoping review findings highlighted the heterogeneity in definitions used in the literature and helped in understanding the components used to define them. This is considered the first step to establish universally agreed definitions for different age groups.

5.3 Future Research and Clinical Implications

From this thesis's findings, interesting areas to explore in future research include:

- Most participants in the qualitative study expressed concerns about maintaining ETI's positive effects and preventing future side effects. Analysing continuous real-world data to confirm long-term safety and efficacy is fundamental. This would involve conducting follow-up studies beyond the current time frame to evaluate the sustained effects and safety of ETI.

- HEMT has led to remarkable improvements, making simplifying ACTs and nebulised therapy inevitable. Setting up a framework to simplify therapy will have future implications for how the CF team may modify the treatment.
- Several studies have examined the possibility of replacing ACT with exercise before HEMT (Dwyer *et al.*, 2019; Heinz *et al.*, 2022; Rowbotham *et al.*, 2020). Many participants believed that exercise could be used in place of ACTs, which is consistent with earlier research (Ward, Stiller and Holland, 2019). Examining the efficacy of individualised exercise regimes to replace ACT after the introduction of ETI is essential to determine benefit (Urquhart *et al.*, 2022).
- Adherence with treatment is an ongoing issue that CF teams face, although the factors that influence it after HEMT could be different. Future studies are needed to address the emerging barriers to adherence in ETI groups.
- Further research is suggested focusing on the changes in the physiotherapy treatment pattern, including ACTs, nebulised therapy, and exercise following ETI. This would offer insightful information about the efficiency and best therapeutic approaches in conjunction with ETI to enhance patient care and develop more personalised approaches.
- Weight management is a new area that has broadened in the era of ETI and needs more studies and research. For some pwCF, weight gain substantially influences body image and self-esteem, and they may need further assistance to achieve lifestyle adjustments. Physiotherapists, dieticians, and psychologists need to work together in designing programmes to assist pwCF in improving their relationship with food and adopting healthier lifestyles (Mantzios, Egan and Patchell, 2016).
- Around 10% of CF patients are ineligible for CFTR modulators. These people will not have the same opportunities and may experience mental distress and need support from the CF team.
- Following the scoping review of the definitions used for PEx, future work should include developing consensual age-specific definition(s) for PEx by combining evidence from the scoping review's findings with the opinions of multidisciplinary experts, practising HCPs, and patients. A series of Delphi surveys through ECFS to measure the diversity of opinions on what defines PEx towards consensus will help to achieve this objective. This approach would ensure that the definition of PEx considers the perspectives of all relevant stakeholders and incorporates both evidence-based and real-life experiences. This

collaborative effort would clarify what constitutes a PEx and promote a shared understanding among healthcare providers, leading to improved diagnosis, treatment, and overall management of this condition.

5.4 Reflection

This PhD journey has been a challenging but rewarding experience. My research journey was multifaceted, involving multi-method designs, all while confronting the challenges of the COVID-19 pandemic.

As a respiratory therapist from Saudi Arabia, my first encounter with CF was through textbooks and lectures. However, direct interviews with the cwCF, their families, and HCPs enriched my knowledge with a deep perspective of CF. I also learned the following:

- How to conduct qualitative research and the skills of interviewing people from different backgrounds and professional levels, including children, families, and HCPs.
- How to work with medical records and find the information and deal with heterogenous and incomplete data.
- Searching thousands of papers for a scoping review enhanced my analytics and organisational abilities to connect the information.
- The ethics application procedure and preparation of all the documents needed such as protocol, PIS, and consent forms.
- Writing scientific papers and poster presentations.

COVID-19 presented unanticipated challenges to my research, starting with changing the original objectives and conducting the interviews remotely. Adjusting methodologies while preserving the integrity of the research was an exercise in adaptability.

These various opportunities I have encountered have significantly enhanced my overall experience and contributed towards the continued pursuit of a research career.

5.5 Final Statement

The findings of this thesis contribute to this growing area of CF. The main contribution of this thesis is that it is one of the first investigations to focus specifically on the changes in ACTs and nebulised mucolytics by exploring the experience of cwCF and their families and analysing the longitudinal changes after ETI. It also confirms previous findings and contributes additional evidence of the longitudinal effect of ETI on other clinical outcomes, including lung function and weight. Lastly, it establishes the first step for the development of a consensus definition of PEx.

References:

Abbott, J., Holt, A., Hart, A., Morton, A. M., MacDougall, L., Pogson, M., Milne, G., Rodgers, H. C. and Conway, S. P. (2009) 'What defines a pulmonary exacerbation? The perceptions of adults with cystic fibrosis', *Journal of Cystic Fibrosis*, 8(5), pp. 356–359. DOI: https://doi.org/10.1016/j.jcf.2009.07.003.

Abbott, J., Holt, A., Morton, A. M., Hart, A., Milne, G., Wolfe, S. P. and Conway, S. P. (2012) 'Patient indicators of a pulmonary exacerbation: Preliminary reports from school aged children map onto those of adults', *Journal of Cystic Fibrosis*, 11(3), pp. 180–186. DOI: 10.1016/j.jcf.2011.11.005.

Accurso, F. J., Moss, R. B., Wilmott, R. W., Anbar, R. D., Schaberg, A. E., Durham, T. A. and Ramsey, B. W. (2011) 'Denufosol tetrasodium in patients with cystic fibrosis and normal to mildly impaired lung function', *American Journal of Respiratory and Critical Care Medicine*, 183(5), pp. 627–634*, NLM*. DOI: 10.1164/rccm.201008-1267OC.

Agent, P. and Parrott, H. (2015) 'Inhaled therapy in cystic fibrosis: agents, devices and regimens', *Breathe (Sheff)*, 11(2), pp. 110–8*, NLM*. DOI: 10.1183/20734735.021014.

Almulhem, M., Harnett, N., Graham, S., Haq, I., Visram, S., Ward, C. and 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', *British Medical Journal Open Respiratory Research*, 9(1), pp. e001420. DOI: 10.1136/bmjresp-2022-001420.

Anstead, M., Saiman, L., Mayer-Hamblett, N., Lands, L. C., Kloster, M., Goss, C. H., Rose, L., Burns, J. L., Marshall, B. and Ratjen, F. (2014) 'Pulmonary exacerbations in CF patients with early lung disease', *Journal of Cystic Fibrosis*, 13(1), pp. 74–79*, NLM*. DOI: 10.1016/j.jcf.2013.07.006.

Arksey, H. and O'Malley, L. (2005) 'Scoping studies: towards a methodological framework', *International Journal of Social Research Methodology*, 8(1), pp. 19-32, Available at: Routledge. DOI: 10.1080/1364557032000119616 (Accessed 15 June 2023).

Asner, S., Waters, V., Solomon, M., Yau, Y., Richardson, S. E., Grasemann, H., Gharabaghi, F. and Tran, D. (2012) 'Role of respiratory viruses in pulmonary exacerbations in children with cystic fibrosis', *Journal of Cystic Fibrosis*, 11(5), pp. 433–439. DOI: https://doi.org/10.1016/j.jcf.2012.04.006.

Aspinall, S. A., Mackintosh, K. A., Hill, D. M., Cope, B. and 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)*, NLM*. DOI: 10.3390/ijerph19106114.

Badlan, K. (2006) 'Young people living with cystic fibrosis: an insight into their subjective experience', *Health & Social Care in the Community*, 14(3), pp. 264–270. DOI: https://doi.org/10.1111/j.1365-2524.2006.00619.x.

Barry, P. J., Mall, M. A., Álvarez, A., Colombo, C., de Winter-de Groot, K. M., Fajac, I., McBennett, K. A., McKone, E. F., Ramsey, B. W., Sutharsan, S., Taylor-Cousar, J. L., Tullis, E., Ahluwalia, N., Jun, L. S., Moskowitz, S. M., Prieto-Centurion, V., Tian, S., Waltz, D., Xuan, F., Zhang, Y., Rowe, S. M. and Polineni, D. (2021) 'Triple therapy for cystic fibrosis phe508del–gating and –residual function genotypes', *New England Journal of Medicine*, 385(9), pp. 815–825, Available at: Massachusetts Medical Society. DOI: 10.1056/NEJMoa2100665.

Beck, M. R., Hornick, D. B., Pena, T. A., Singh, S. B. and Wright, B. A. (2023) 'Impact of elexacaftor/tezacaftor/ivacaftor on bacterial cultures from people with cystic fibrosis', *Pediatric Pulmonology*, 58(5), pp. 1569–1573*, NLM*. DOI: 10.1002/ppul.26362.

Bilton, D., Canny, G., Conway, S., Dumcius, S., Hjelte, L., Proesmans, M., Tümmler, B., Vavrova, V. and De Boeck, K. (2011) 'Pulmonary exacerbation: Towards a definition for use in clinical trials. Report from the EuroCareCF Working Group on outcome parameters in clinical trials', *Journal of Cystic Fibrosis*, 10, pp. S79–S81. DOI: doi: 10.1016/S1569-1993(11)60012-X.

Blanco-Orive, P., Del Corral, T., Martín-Casas, P., Ceniza-Bordallo, G. and López-de-Uralde-Villanueva, I. (2022) 'Quality of life and exercise tolerance tools in children/adolescents with cystic fibrosis: Systematic review', *Medicina Clínica* 158(11), pp. 519–530*, NLM*. DOI: 10.1016/j.medcli.2021.06.025.

Bobadilla, J. L., Macek, M. J., Fine, J. P. and Farrell, P. M. (2002) 'Cystic fibrosis: A worldwide analysis of CFTR mutations—correlation with incidence data and application to screening', *Human Mutation*, 19(6), pp. 575–606. DOI: https://doi.org/10.1002/humu.10041.

Bower, J., Shih, J. L., Seliger, V., Campbell, D., Berhane, I., Wu, R. and Elbert, A. (2021) 'Real-world effects of tezacaftor/ivacaftor (TEZ/IVA) in people with cystic fibrosis (pwCF): interim results of a long-term safety study using US CF Foundation Patient Registry (CFFPR) data', *European Respiratory Journal*, 58(supplement 65), pp. PA2099. DOI: 10.1183/13993003.congress-2021.PA2099.

Bower, J. K., Volkova, N., Ahluwalia, N., Sahota, G., Xuan, F., Chin, A., Weinstock, T. G., Ostrenga, J. and Elbert, A. (2023) 'Real-world safety and effectiveness of elexacaftor/tezacaftor/ivacaftor in people with cystic fibrosis: Interim results of a long-term registry-based study', *Journal of Cystic Fibrosis*, 22(4), pp. 730–737. DOI: https://doi.org/10.1016/j.jcf.2023.03.002.

Boyle, M. P., Bell, S. C., Konstan, M. W., McColley, S. A., Rowe, S. M., Rietschel, E., Huang, X., Waltz, D., Patel, N. R. and Rodman, D. (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', *The Lancet Respiratory Medicine*, 2(7), pp. 527–538, Available at: Elsevier. DOI: 10.1016/S2213-2600(14)70132-8.

Bradley, J., Howard, J., Wallace, E. and Elborn, S. (1999) 'Validity of a modified shuttle test in adult cystic fibrosis', *Thorax*, 54(5), pp. 437–439*, NLM*. DOI: 10.1136/thx.54.5.437.

Bramer, W. M., Giustini, D., de Jonge, G. B., Holland, L. and Bekhuis, T. (2016) 'De-duplication of database search results for systematic reviews in EndNote', *Journal of the Medical Library Association*, 104(3), pp. 240–243*, NLM*. DOI: 10.3163/1536-5050.104.3.014.

Braun, V. and Clarke, V. (2006) 'Using thematic analysis in psychology', *Qualitative Research in Psychology*, 3(2), pp. 77—101. DOI: 10.1191/1478088706qp063oa.

Braun, V. and Clarke, V. (2013) *Successful Qualitative Research : A Practical Guide for Beginners.* London : SAGE.

Braun, V. and Clarke, V. (2021) 'To saturate or not to saturate? Questioning data saturation as a useful concept for thematic analysis and sample-size rationales', *Qualitative Research in Sport, Exercise and Health*, 13(2), pp. 201–216, Available at: Routledge. DOI: 10.1080/2159676X.2019.1704846.

Braun, V. and Clarke, V. (2022) *Thematic Analysis: A Practical Guide.* London: SAGE.

Britto, M. T., Kotagal, U. R., Hornung, R. W., Atherton, H. D., Tsevat, J. and Wilmott, R. W. (2002) 'Impact of recent pulmonary exacerbations on quality of life in patients with cystic fibrosis', *Chest*, 121(1), pp. 64–72. DOI: https://doi.org/10.1378/chest.121.1.64.

Brody, A. S., Sucharew, H., Campbell, J. D., Millard, S. P., Molina, P. L., Klein, J. S. and Quan, J. (2005) 'Computed tomography correlates with pulmonary exacerbations in children with cystic fibrosis', *American Journal of Respiratory and Critical Care Medicine*, 172(9), pp. 1128–1132*, NLM*. DOI: 10.1164/rccm.200407-989OC.

Bryman, A. (2016) *Social Research Methods.* Oxford: Oxford University Press.

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., Da Silva, J. and 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), pp. 64–73, Available at: American Thoracic Society - AJRCCM. DOI: 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., Silva, J. D., Paillasseur, J.-L. and Hubert, D. (2020) 'Real-life safety and effectiveness of lumacaftor–ivacaftor in patients with cystic fibrosis', *American Journal of Respiratory and Critical Care Medicine*, 201(2), pp. 188–197. DOI: 10.1164/rccm.201906-1227OC.

Button, B., Cai, L. H., Ehre, C., Kesimer, M., Hill, D. B., Sheehan, J. K., Boucher, R. C. and Rubinstein, M. (2012) 'A periciliary brush promotes the lung health by separating the mucus layer from airway epithelia', *Science*, 337(6097), pp. 937–941*, NLM*. DOI: 10.1126/science.1223012.

Cameron, R. A., Office, D., Matthews, J., Rowley, M., Abbott, J., Simmonds, N. J., Whitty, J. A. and Carr, S. B. (2022) 'Treatment preference among people with cystic fibrosis: The importance of reducing treatment burden', *Chest*, 162(6), pp. 1241–1254, Available at: Elsevier. DOI: 10.1016/j.chest.2022.07.008.

Carnovale, V., Iacotucci, P., Qiao, D., Ferrillo, L., Somma, J., Buonaurio, S., Marcella, d. I., Celardo, A. and Savi, D. (2022a) 'Clinical outcomes of digital health in adults with cystic fibrosis', *Respiratory Medicine*, 202, pp. 106970. DOI: https://doi.org/10.1016/j.rmed.2022.106970 (Accessed 2022/10/01/).

Carnovale, V., Iacotucci, P., Terlizzi, V., Colangelo, C., Ferrillo, L., Pepe, A., Francalanci, M., Taccetti, G., Buonaurio, S., Celardo, A., Salvadori, L., Marsicovetere, G., D'Andria, M., Ferrara, N. and Salvatore, D. (2022b) 'Elexacaftor/tezacaftor/ivacaftor in patients with cystic fibrosis homozygous for the f508del mutation and advanced lung disease: A 48-week observational study', *Journal of Clinical Medicine*, 11(4)*, NLM*. DOI: 10.3390/jcm11041021.

Castellani, C., Duff, A. J. A., Bell, S. C., Heijerman, H. G. M., Munck, A., Ratjen, F., Sermet-Gaudelus, I., Southern, K. W., Barben, J., Flume, P. A., Hodková, P., Kashirskaya, N., Kirszenbaum, M. N., Madge, S., Oxley, H., Plant, B., Schwarzenberg, S. J., Smyth, A. R., Taccetti, G., Wagner, T. O. F., Wolfe, S. P. and Drevinek, P. (2018) 'ECFS best practice guidelines: the 2018 revision', *Journal of Cystic Fibrosis*, 17(2), pp. 153–178. DOI: https://doi.org/10.1016/j.jcf.2018.02.006.

Castellani, C., Southern, K. W., Brownlee, K., Dankert Roelse, J., Duff, A., Farrell, M., Mehta, A., Munck, A., Pollitt, R., Sermet-Gaudelus, I., Wilcken, B., Ballmann, M., Corbetta, C., de Monestrol, I., Farrell, P., Feilcke, M., Férec, C., Gartner, S., Gaskin, K., Hammermann, J., Kashirskaya, N., Loeber, G., Macek, M., Jr., Mehta, G., Reiman, A., Rizzotti, P., Sammon, A., Sands, D., Smyth, A., Sommerburg, O., Torresani, T., Travert, G., Vernooij, A. and Elborn, S. (2009) 'European best practice guidelines for cystic fibrosis neonatal screening', *Journal of Cystic Fibrosis*, 8(3), pp. 153–73*, NLM*. DOI: 10.1016/j.jcf.2009.01.004.

CF START (no date) *CF Start: A Randomised Registry Trial*. Available at: https://www.cfstart.org.uk/ (Accessed: 15 August 2023).

Cheney, J., Vidmar, S., Gailer, N., Wainwright, C. and Douglas, T. A. (2020) 'Health-related quality-of-life in children with cystic fibrosis aged 5-years and associations with health outcomes', *Journal of Cystic Fibrosis*, 19(3), pp. 483–491. DOI: https://doi.org/10.1016/j.jcf.2020.02.022.

Chin, M., Aaron, S. D. and Bell, S. C. (2017) 'The treatment of the pulmonary and extrapulmonary manifestations of cystic fibrosis', *La Presse Médicale*, 46(6, Part 2), pp. e139–e164. DOI: https://doi.org/10.1016/j.lpm.2016.11.030.

Choyce, J., Shaw, K. L., Sitch, A. J., Mistry, H., Whitehouse, J. L. and Nash, E. F. (2017) 'A prospective pilot study of home monitoring in adults with cystic fibrosis (HOME-CF): protocol for a randomised controlled trial', *BMC Pulmonary Medicine*, 17(1), pp. 22. PubMed, Available at: BioMed Central. DOI: 10.1186/s12890-017-0366-x.

Clancy, J. P., Rowe, S. M., Accurso, F. J., Aitken, M. L., Amin, R. S., Ashlock, M. A., Ballmann, M., Boyle, M. P., Bronsveld, I., Campbell, P. W., De Boeck, K., Donaldson, S. H., Dorkin, H. L., Dunitz, J. M., Durie, P. R., Jain, M., Leonard, A., McCoy, K. S., Moss, R. B., Pilewski, J. M., Rosenbluth, D. B., Rubenstein, R. C., Schechter, M. S., Botfield, M., Ordonez, C. L., Spencer-Green, G. T., Vernillet, L., Wisseh, S., Yen, K. and Konstan, M. W. (2012) 'Results of a phase IIa study of VX-809, an investigational CFTR corrector compound, in subjects with cystic fibrosis homozygous for the F508del-CFTR mutation', *Thorax*, 67(1), pp. 12–18. DOI: 10.1136/thoraxjnl-2011-200393.

'Clinical and Functional Translation of CFTR', (2023). Available at: http://www.cftr2.org/resources (Accessed 1 July 2023).

Conway, S., Balfour-Lynn, I. M., De Rijcke, K., Drevinek, P., Foweraker, J., Havermans, T., Heijerman, H., Lannefors, L., Lindblad, A., Macek, M., Madge, S., Moran, M., Morrison, L., Morton, A., Noordhoek, J., Sands, D., Vertommen, A. and Peckham, D. (2014) 'European cystic fibrosis society standards of care: Framework for the cystic fibrosis centre', *Journal of Cystic Fibrosis*, 13(supplement 1), pp. S3–S22. DOI: https://doi.org/10.1016/j.jcf.2014.03.009.

Corey, M., Edwards, L., Levison, H. and Knowles, M. (1997) 'Longitudinal analysis of pulmonary function decline in patients with cystic fibrosis', *The Journal of Pediatrics*, 131(6), pp. 809–814*, NLM*. DOI: 10.1016/s0022-3476(97)70025-8.

Cystic Fibrosis Foundation (1994) 'Microbiology and infectious disease in cystic fibrosis', *Cystic Fibrosis Foundation,* V(I), pp. 25.

Cystic Fibrosis Foundation (2023) *FDA Approves Trikafta for Children Ages 2 Through 5 Years With Certain CF Mutations*. Available at: https://www.cff.org/news/2023-04/trikafta-approval-ages-2-5-mutations (Accessed: 15 August 2023).

Cystic Fibrosis Trust (2009) *Antibiotic Treatment for cystic fibrosis* Available at: https://www.cysticfibrosis.org.uk/sites/default/files/2020-11/Anitbiotic%20Treatment.pdf (Accessed: 18 July 2023).

Cystic Fibrosis Trust (2020a) *Standards of care and good clinical practice for the physiotherapy management of cystic fibrosis* Available at: https://www.cysticfibrosis.org.uk/the-work-we-do/resources-for-cf-professionals/consensus-documents (Accessed: 12 July 2023).

Cystic Fibrosis Trust (2020b) *UK cystic fibrosis registry annual data report 2019*. Available at: https://www.cysticfibrosis.org.uk/the-work-we-do/uk-cf-registry/reporting-and-resources (Accessed: 5 June 2023).

Cystic Fibrosis Trust (2022) *Keeping your lungs healthy*. Available at: https://www.cysticfibrosis.org.uk/sites/default/files/2022-05/Keeping%20your%20lungs%20healthy.pdf (Accessed: 2 February 2023).

Cystic Fibrosis Trust (2023a) *UK cystic fibrosis registry 2022 annual data report*: cysticfibrosis.org.uk. Available at: https://www.cysticfibrosis.org.uk/sites/default/files/2023-10/CFT_2022_Annual_Data_Report_FINAL_v8.pdf (Accessed: 5 June 2023).

Cystic Fibrosis Trust (2023b) *What Is Cystic Fibrosis?* Available at: https://www.cysticfibrosis.org.uk/what-is-cystic-fibrosis/faqs (Accessed: 3 July 2023).

Cystic Fibrosis Trust (no date-a) *Kaftrio*. Available at: https://www.cysticfibrosis.org.uk/what-is-cystic-fibrosis/cystic-fibrosis-care/treatments-and-medication/kaftrio#:~:text=Who%20is%20currently%20eligible%20for,F508del%20and%20any%20other%20mutation. (Accessed: 15 August 2023).

Cystic Fibrosis Trust (no date-b) *Orkambi*. Available at: https://www.cysticfibrosis.org.uk/what-is-cystic-fibrosis/cystic-fibrosis-care/treatments-and-medication/orkambi (Accessed: 16 August 2023).

Dakin, C., Henry, R. L., Field, P. and Morton, J. (2001) 'Defining an exacerbation of pulmonary disease in cystic fibrosis', *Pediatric Pulmonology*, 31(6), pp. 436–442*, NLM*. DOI: 10.1002/ppul.1072.

Daniels, T., Goodacre, L., Sutton, C., Pollard, K., Conway, S. and Peckham, D. (2011) 'Accurate assessment of adherence: Self-report and clinician report vs electronic monitoring of nebulizers', *Chest*, 140(2), pp. 425–432*, NLM*. DOI: 10.1378/chest.09-3074.

Davies, G., Rowbotham, N. J., Smith, S., Elliot, Z. C., Gathercole, K., Rayner, O., Leighton, P. A., Herbert, S., Duff, A. J., Chandran, S., Daniels, T., Nash, E. F. and Smyth, A. R. (2020a) 'Characterising burden of treatment in cystic fibrosis to identify priority areas for clinical trials', *Journal of Cystic Fibrosis*, 19(3), pp. 499–502*, NLM*. DOI: 10.1016/j.jcf.2019.10.025.

Davies, J. C., Cunningham, S., Harris, W. T., Lapey, A., Regelmann, W. E., Sawicki, G. S., Southern, K. W., Robertson, S., Green, Y., Cooke, J. and Rosenfeld, M. (2016) 'Safety, pharmacokinetics, and pharmacodynamics of ivacaftor in patients aged 2-5 years with cystic fibrosis and a CFTR gating mutation (KIWI): an open-label, single-arm study', *The Lancet Respiratory Medicine*, 4(2), pp. 107–115*, NLM*. DOI: 10.1016/s2213-2600(15)00545-7.

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. and 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), pp. 1219–1225, Available at: American Thoracic Society - AJRCCM. DOI: 10.1164/rccm.201301-0153OC.

Davies, J. C., Wainwright, C. E., Sawicki, G. S., Higgins, M. N., Campbell, D., Harris, C., Panorchan, P., Haseltine, E., Tian, S. and Rosenfeld, M. (2020b) 'Ivacaftor in infants aged 4 to <12 months with cystic fibrosis and a gating mutation. Results of a two-part phase 3 clinical trial', *American Journal of Respiratory and Critical Care Medicine*, 203(5), pp. 585–593, Available at: American Thoracic Society - AJRCCM. DOI: 10.1164/rccm.202008-3177OC.

De Boeck, K., Munck, A., Walker, S., Faro, A., Hiatt, P., Gilmartin, G. and Higgins, M. (2014) 'Efficacy and safety of ivacaftor in patients with cystic fibrosis and a non-G551D gating mutation', *Journal of Cystic Fibrosis*, 13(6), pp. 674–680*, NLM*. DOI: 10.1016/j.jcf.2014.09.005.

Del Corral, T., Gómez Sánchez, Á. and López-de-Uralde-Villanueva, I. (2020) 'Test-retest reliability, minimal detectable change and minimal clinically important differences in modified shuttle walk test in children and adolescents with cystic fibrosis', *Journal of Cystic Fibrosis*, 19(3), pp. 442–448. DOI: https://doi.org/10.1016/j.jcf.2019.10.007.

Dixon-Woods, M., Agarwal, S., Jones, D., Young, B. and Sutton, A. (2005) 'Synthesising qualitative and quantitative evidence: a review of possible methods', *Journal of Health Services Research and Policy*, 10(1), pp. 45–53*, NLM*. DOI: 10.1177/135581960501000110.

Djavid, A. R., Thompson, A. E., Irace, A. L., Gusman, E., Altman, K., DiMango, E. A. and Keating, C. L. (2021) 'Efficacy of elexacaftor/tezacaftor/ivacaftor in advanced cystic fibrosis lung disease', *Annals of the American Thoracic Society*, 18(11), pp. 1924–1927*, NLM*. DOI: 10.1513/AnnalsATS.202102-220RL.

Donaldson, S. H., Pilewski, J. M., Griese, M., Cooke, J., Viswanathan, L., Tullis, E., Davies, J. C., Lekstrom-Himes, J. A. and Wang, L. T. (2017) 'Tezacaftor/ivacaftor in subjects with cystic fibrosis and f508del/f508del-cftr or f508del/g551d-cftr', *American Journal of Respiratory and Critical Care Medicine*, 197(2), pp. 214–224, Available at: American Thoracic Society - AJRCCM. DOI: 10.1164/rccm.201704-0717OC.

Döring, G. and Hoiby, N. (2004) 'Early intervention and prevention of lung disease in cystic fibrosis: a European consensus', *Journal of Cystic Fibrosis*, 3(2), pp. 67–91. DOI: https://doi.org/10.1016/j.jcf.2004.03.008.

Doumit, M., Chuang, S., Middleton, P., Selvadurai, H., Sivam, S., Ruseckaite, R., Ahern, S., Mallitt, K. A., Pacey, V., Gray, K. and Jaffe, A. (2023) 'Clinical outcomes of adults and children with cystic fibrosis during the COVID-19 pandemic', *Journal of Cystic Fibrosis*, 22(3), pp. 581–586, Available at: Elsevier. DOI: 10.1016/j.jcf.2022.09.006.

Duckers, J., Lesher, B., Thorat, T., Lucas, E., McGarry, L. J., Chandarana, K. and De Iorio, F. (2021) 'Real-world outcomes of ivacaftor treatment in people with cystic fibrosis: A systematic review', *Journal of Clinical Medicine*, 10(7), pp. 1527. DOI: 10.3390/jcm10071527.

Dwyer, T. J., Daviskas, E., Zainuldin, R., Verschuer, J., Eberl, S., Bye, P. T. P. and Alison, J. A. (2019) 'Effects of exercise and airway clearance (positive expiratory pressure) on mucus clearance in cystic fibrosis: a randomised crossover trial', *European Respiratory Journal*, 53(4), pp. 1801793. DOI: 10.1183/13993003.01793-2018.

Elborn, J. S. (2016) 'Cystic fibrosis', *Lancet*, 388(10059), pp. 2519–2531*, NLM*. DOI: 10.1016/s0140-6736(16)00576-6.

Elkins, M. R., Robinson, M., Rose, B. R., Harbour, C., Moriarty, C. P., Marks, G. B., Belousova, E. G., Xuan, W. and Bye, P. T. P. (2006) 'A controlled trial of long-term inhaled hypertonic saline in patients with cystic fibrosis', *New England Journal of Medicine*, 354(3), pp. 229–240, Available at: Massachusetts Medical Society. DOI: 10.1056/NEJMoa043900.

Ellaffi, M., Vinsonneau, C., Coste, J., Hubert, D., Burgel, P.-R., Dhainaut, J.-F. and Dusser, D. (2005) 'One-year outcome after severe pulmonary exacerbation in adults with cystic fibrosis', *American Journal of Respiratory and Critical Care Medicine*, 171(2), pp. 158–164. DOI: 10.1164/rccm.200405-667OC.

Emerson, J., Rosenfeld, M., McNamara, S., Ramsey, B. and Gibson, R. L. (2002) 'Pseudomonas aeruginosa and other predictors of mortality and morbidity in young children with cystic fibrosis', *Pediatric Pulmonology*, 34(2), pp. 91–100, Available at: John Wiley & Sons, Ltd. DOI: https://doi.org/10.1002/ppul.10127.

European Cystic Fibrosis Society (2021) *ECFSPR annual report 2021*. Available at: https://www.ecfs.eu/sites/default/files/Annual%20Report_2021_09Jun2023.pdf (Accessed: 5 June 2023).

European Medicines Agency (2023a) *Orkambi*. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/orkambi (Accessed: 15 August 2023).

European Medicines Agency (2023b) *Symkevi* Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/symkevi (Accessed: 15 August 2023).

Farrell, P. M., White, T. B., Ren, C. L., Hempstead, S. E., Accurso, F., Derichs, N., Howenstine, M., McColley, S. A., Rock, M., Rosenfeld, M., Sermet-Gaudelus, I., Southern, K. W., Marshall, B. C. and Sosnay, P. R. (2017) 'Diagnosis of Cystic Fibrosis: Consensus Guidelines from the Cystic Fibrosis Foundation', *The Journal of Pediatrics*, 181, pp. S4–S15.e1. DOI: https://doi.org/10.1016/j.jpeds.2016.09.064.

Faulkner, J., Gates, A., Flight, W. G., Bulpett, M., Reade, B. and Hobbs, J. (2022) 'WS10.01 Impact of triple CFTR modulator therapy on airway clearance and nebuliser adherence in adults with cystic fibrosis', *Journal of Cystic Fibrosis*, 21(Supplement 1), pp. S19. DOI: https://doi.org/10.1016/S1569-1993(22)00207-7.

Ferkol, T., Rosenfeld, M. and Milla, C. E. (2006) 'Cystic fibrosis pulmonary exacerbations', *The Journal of Pediatrics*, 148(2), pp. 259–264, Available at: Elsevier. DOI: 10.1016/j.jpeds.2005.10.019.

Flume, P. A., Liou, T. G., Borowitz, D. S., Li, H., Yen, K., Ordoñez, C. L. and Geller, D. E. (2012) 'Ivacaftor in subjects with cystic fibrosis who are homozygous for the f508del-cftr mutation', *Chest*, 142(3), pp. 718–724. DOI: https://doi.org/10.1378/chest.11-2672.

Flume, P. A., Mogayzel, P. J., Robinson, K. A., Goss, C. H., Rosenblatt, R. L., Kuhn, R. J. and Marshall, B. C. (2009a) 'Cystic fibrosis pulmonary guidelines: Treatment of pulmonary exacerbations', *American Journal of Respiratory and Critical Care Medicine*, 180(9), pp. 802–808, Available at: American Thoracic Society - AJRCCM. DOI: 10.1164/rccm.200812-1845PP.

Flume, P. A., Robinson, K. A., Sullivan, B. P., Finder, J. D., Vender, R. L., Willey-Courand, D.-B., White, T. B. and Marshall, B. C. (2009b) 'Cystic fibrosis pulmonary guidelines: Airway clearance therapies', *Respiratory Care*, 54(4), pp. 522. Available at: http://rc.rcjournal.com/content/54/4/522.abstract (Accessed 5 May 2022).

Flume, P. A., Suthoff, E. D., Kosinski, M., Marigowda, G. and Quittner, A. L. (2019) 'Measuring recovery in health-related quality of life during and after pulmonary exacerbations in patients with cystic fibrosis', *Journal of Cystic Fibrosis*, 18(5), pp. 737–742. DOI: https://doi.org/10.1016/j.jcf.2018.12.004.

Flume, P. A., Wainwright, C. E., Elizabeth Tullis, D., Rodriguez, S., Niknian, M., Higgins, M., Davies, J. C. and Wagener, J. S. (2018) 'Recovery of lung function following a pulmonary exacerbation in patients with cystic fibrosis and the G551D-CFTR mutation treated with ivacaftor', *Journal of Cystic Fibrosis*, 17(1), pp. 83–88. DOI: https://doi.org/10.1016/j.jcf.2017.06.002.

Foong, R., Ramsey, K., Harper, A., Turkovic, L., Rosenow, T., Skoric, B., King, L., Davis, M., Clem, C. and Stick, S. (2018) 'The utility of lung clearance index to monitor early lung disease in young children with cystic fibrosis', *Pediatric Pulmonology*, 4(1), pp. 243–244. DOI: 10.1183/23120541.00094-2017.

Foster, C., Eiser, C., Oades, P., Sheldon, C., Tripp, J., Goldman, P., Rice, S. and Trott, J. (2001) 'Treatment demands and differential treatment of patients with cystic fibrosis and their siblings: patient, parent and sibling accounts', *Child: Care, Health and Development*, 27(4), pp. 349–364, Available at: John Wiley & Sons, Ltd. DOI: https://doi.org/10.1046/j.1365-2214.2001.00196.x.

Fuchs, H. J., Borowitz, D. S., Christiansen, D. H., Morris, E. M., Nash, M. L., Ramsey, B. W., Rosenstein, B. J., Smith, A. L. and Wohl, M. E. (1994) 'Effect of aerosolized recombinant human dnase on exacerbations of respiratory symptoms and on pulmonary function in patients with cystic fibrosis', *New England Journal of Medicine*, 331(10), pp. 637–642, Available at: Massachusetts Medical Society. DOI: 10.1056/NEJM199409083311003.

Gaynor, M. and Wood, J. (2018) 'Mechanical insufflation-exsufflation for airway clearance in adults with cystic fibrosis', *Respirology Case Reports*, 6(4), pp. e00307*, NLM*. DOI: 10.1002/rcr2.307.

George, M., Rand-Giovannetti, D., Eakin, M. N., Borrelli, B., Zettler, M. and Riekert, K. A. (2010) 'Perceptions of barriers and facilitators: self-management decisions by older adolescents and adults with CF', *Journal of Cystic Fibrosis*, 9(6), pp. 425–432*, NLM*. DOI: 10.1016/j.jcf.2010.08.016.

Gifford, A. H., Mayer-Hamblett, N., Pearson, K. and 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), pp. 762–767*, NLM*. DOI: 10.1016/j.jcf.2019.11.007 (Accessed Sep).

Gilligan, P. H. (2014) 'Infections in patients with cystic fibrosis: diagnostic microbiology update', *Clinics in Laboratory Medicine*, 34(2), pp. 197–217*, NLM*. DOI: 10.1016/j.cll.2014.02.001.

Gjengedal, E., Rustøen, T., Wahl, A. K. and Hanestad, B. R. (2003) 'Growing up and living with cystic fibrosis: Everyday life and encounters with the health care and social services—a qualitative study', *Advances in Nursing Science*, 26(2), pp. 149–159. DOI: 10.1097/00012272-200304000-00007.

Goss, C. H. and Burns, J. L. (2007) 'Exacerbations in cystic fibrosis. 1: Epidemiology and pathogenesis', *Thorax*, 62(4), pp. 360–367. PubMed, Available at: BMJ Group. DOI: 10.1136/thx.2006.060889.

Granados, A., Chan, C. L., Moheet, A., Vigers, T., Arbeláez, A. M. and Larson Ode, K. (2023) 'The impact of elexacaftor/tezacaftor/ivacaftor on body composition in a small cohort of youth with cystic fibrosis', *Pediatric Pulmonology*, 58(6), pp. 1805–1811*, NLM*. DOI: 10.1002/ppul.26388.

Granger, E., Davies, G. and Keogh, R. H. (2022) 'Treatment patterns in people with cystic fibrosis: have they changed since the introduction of ivacaftor?', *Journal of Cystic Fibrosis*, 21(2), pp. 316–322*, NLM*. DOI: 10.1016/j.jcf.2021.08.014.

Grosse-Onnebrink, J., Mellies, U., Olivier, M., Werner, C. and Stehling, F. (2017) 'Chest physiotherapy can affect the lung clearance index in cystic fibrosis patients', *Pediatric Pulmonology*, 52(5), pp. 625–631*, NLM*. DOI: 10.1002/ppul.23670.

Gur, M., Bar–Yoseph, R., Hanna, M., Abboud, D., Keidar, Z., Palchan, T., Toukan, Y., Masarweh, K., Alisha, I., Zuckerman-Levin, N. and Bentur, L. (2023) 'Effect of Trikafta on bone density, body composition and exercise capacity in CF: A pilot study', *Pediatric Pulmonology*, 58(2), pp. 577–584, Available at: John Wiley & Sons, Ltd. DOI: https://doi.org/10.1002/ppul.26243.

Habib, A. R., Manji, J., Wilcox, P. G., Javer, A. R., Buxton, J. A. and Quon, B. S. (2015) 'A systematic review of factors associated with health-related quality of life in adolescents and adults with cystic fibrosis', *Annals of the American Thoracic Society*, 12(3), pp. 420–428*, NLM*. DOI: 10.1513/AnnalsATS.201408-393OC.

Hakim, F., Kerem, E., Rivlin, J., Bentur, L., Stankiewicz, H., Bdolach-Abram, T. and Wilschanski, M. (2007) 'Vitamins A and E and pulmonary exacerbations in patients with cystic fibrosis', *Journal of Pediatric Gastroenterology and Nutrition*, 45(3), pp. 347–353*, NLM*. DOI: 10.1097/MPG.0b013e31804069e5.

Haq, I., Almulhem, M., Soars, S., Poulton, D. and Brodlie, M. (2022) 'Precision medicine based on CFTR genotype for people with cystic fibrosis', *Pharmacogenomics and Personalized Medicine*, 15, pp. 91–104. DOI: 10.2147/PGPM.S245603.

Haq, I. J., Gray, M. A., Garnett, J. P., Ward, C. and Brodlie, M. (2016) 'Airway surface liquid homeostasis in cystic fibrosis: pathophysiology and therapeutic targets', *Thorax*, 71(3), pp. 284–287*, NLM*. DOI: 10.1136/thoraxjnl-2015-207588.

Hatziagorou, E., Steffen, F., Annalisa, O., Lutz, N., Uros, K., Meir, M.-Z., Andreas, J. and Kris De, B. (2023) 'Risk factors for FEV1 decline in European patients with CF: data from the European Cystic Fibrosis Society Patient Registry (ECFSPR)', *ERJ Open Research*, 9(4). DOI: 10.1183/23120541.00449-2022.

Hebestreit, H., Arets, H. G., Aurora, P., Boas, S., Cerny, F., Hulzebos, E. H., Karila, C., Lands, L. C., Lowman, J. D., Swisher, A. and Urquhart, D. S. (2015) 'Statement on exercise testing in cystic fibrosis', *Respiration*, 90(4), pp. 332–351*, NLM*. DOI: 10.1159/000439057.

Hebestreit, H., Kieser, S., Junge, S., Ballmann, M., Hebestreit, A., Schindler, C., Schenk, T., Posselt, H. G. and Kriemler, S. (2010) 'Long-term effects of a partially supervised conditioning programme in cystic fibrosis', *European Respiratory Journal*, 35(3), pp. 578–583*, NLM*. DOI: 10.1183/09031936.00062409.

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. and McCoy, K. S. (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', *Lancet*, 394(10212), pp. 1940–1948*, NLM*. DOI: 10.1016/s0140-6736(19)32597-8.

Heinz, K. D., Walsh, A., Southern, K. W., Johnstone, Z. and Regan, K. H. (2022) 'Exercise versus airway clearance techniques for people with cystic fibrosis', *The Cochrane Database of Systematic Reviews*, 6(6), Available at: John Wiley & Sons, Ltd. DOI: 10.1002/14651858.CD013285.pub2.

Hewer, S. C. and Smyth, A. R. (2017) 'Antibiotic strategies for eradicating Pseudomonas aeruginosa in people with cystic fibrosis', *The Cochrane Database of Systematic Reveiws*, 4(4), pp. Cd004197*, NLM*. DOI: 10.1002/14651858.CD004197.pub5.

Hewer, S. C. L., Smyth, A. R., Brown, M., Jones, A. P., Hickey, H., Kenna, D., Ashby, D., Thompson, A., Williamson, P. R., , a. and TORPEDO-CF study group (2020) 'Intravenous versus oral antibiotics for eradication of

Pseudomonas aeruginosa in cystic fibrosis (TORPEDO-CF): a randomised controlled trial', *The Lancet Respiratory Medicine*, 8(10), pp. 975–986, Available at: Elsevier. DOI: 10.1016/S2213-2600(20)30331-3.

Hickey, C., Shanahan, P., Ronan, N., Shortt, C., McCarthy, M., Fleming, C., Howlett, C., Cronin, K., O'Donovan, D. and Jennings, R. (2015) 'A retrospective analysis of patient chest physiotherapy practices and adherence to inhaled therapies before and after CFTR modulation with ivacaftor', *Pediatric Pulmonology*, 50(S41), pp. 366. DOI: https://doi.org/10.1002/ppul.23297.

Higham, L., Ahmed, S. and Ahmed, M. (2013) 'Hoping to live a "normal" life whilst living with unpredictable health and fear of death: Impact of cystic fibrosis on young adults', *Journal of Genetic Counseling*, 22(3), pp. 374–383 [https://doi.org/10.1007/s10897-012-9555-1], Available at: John Wiley & Sons, Ltd. DOI: https://doi.org/10.1007/s10897-012-9555-1.

Hind, D., Drabble, S. J., Arden, M. A., Mandefield, L., Waterhouse, S., Maguire, C., Cantrill, H., Robinson, L., Beever, D., Scott, A. J., Keating, S., Hutchings, M., Bradley, J., Nightingale, J., Allenby, M. I., Dewar, J., Whelan, P., Ainsworth, J., Walters, S. J., O'Cathain, A. and Wildman, M. J. (2019) 'Supporting medication adherence for adults with cystic fibrosis: a randomised feasibility study', *BMC Pulmonary Medicine*, 19(1), pp. 77. DOI: 10.1186/s12890-019-0834-6.

Hoen, A. G., Li, J., Moulton, L. A., O'Toole, G. A., Housman, M. L., Koestler, D. C., Guill, M. F., Moore, J. H., Hibberd, P. L., Morrison, H. G., Sogin, M. L., Karagas, M. R. and Madan, J. C. (2015) 'Associations between gut microbial colonization in early life and respiratory outcomes in cystic fibrosis', *The Journal of Pediatrics*, 167(1), pp. 138–147*, NLM*. DOI: 10.1016/j.jpeds.2015.02.049.

Hoppe, J. E., Chilvers, M., Ratjen, F., McNamara, J. J., Owen, C. A., Tian, S., Zahigian, R., Cornell, A. G. and McColley, S. A. (2021) 'Long-term safety of lumacaftor–ivacaftor in children aged 2–5 years with cystic fibrosis homozygous for the F508del-CFTR mutation: a multicentre, phase 3, open-label, extension study.', *The Lancet Respiratory Medicine*, 9(9), pp. 977–988. DOI: 10.1016/S2213-2600(21)00069-2.

Hubert, D., Chiron, R., Camara, B., Grenet, D., Prévotat, A., Bassinet, L., Dominique, S., Rault, G., Macey, J., Honoré, I., Kanaan, R., Leroy, S., Desmazes Dufeu, N. and 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), pp. 388–391, Available at: Elsevier. DOI: 10.1016/j.jcf.2017.03.003.

Jafari, S.-A., Mehdizadeh-Hakkak, A., Kianifar, H.-R., Hebrani, P., Ahanchian, H. and Abbasnejad, E. (2013) 'Effects of probiotics on quality of life in children with cystic fibrosis; a randomized controlled trial', *Iranian Journal of Pediatrics*, 23(6), pp. 669–674. PubMed. Available at: https://pubmed.ncbi.nlm.nih.gov/24910746 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4025125/ (Accessed 22 July 2023).

Jamieson, N., Fitzgerald, D., Singh-Grewal, D., Hanson, C. S., Craig, J. C. and Tong, A. (2014) 'Children's experiences of cystic fibrosis: A systematic review of qualitative studies', *Pediatrics*, 133(6), pp. e1683–e1697. DOI: 10.1542/peds.2014-0009.

Kerem, E., Viviani, L., Zolin, A., MacNeill, S., Hatziagorou, E., Ellemunter, H., Drevinek, P., Gulmans, V., Krivec, U. and Olesen, H. (2014) 'Factors associated with FEV1 decline in cystic fibrosis: analysis of the ECFS patient registry', *European Respiratory Journal*, 43(1), pp. 125–133. DOI: 10.1183/09031936.00166412.

Keyte, R., Egan, H. and Mantzios, M. (2019) 'An exploration into knowledge, attitudes, and beliefs towards risky health behaviours in a paediatric cystic fibrosis population', *Clinical Medicine Insights: Circulatory, Respiratory and Pulmonary Medicine*, 13, pp. 1179548419849427*, NLM*. DOI: 10.1177/1179548419849427.

Keyte, R., Kauser, S., Mantzios, M. and Egan, H. (2022) 'The psychological implications and health risks of cystic fibrosis pre- and post- CFTR modulator therapy', *Chronic Illness*, 0(0), pp. 1–18. DOI: 10.1177/17423953221099042.

Klijn, P. H., Oudshoorn, A., van der Ent, C. K., van der Net, J., Kimpen, J. L. and Helders, P. J. (2004) 'Effects of anaerobic training in children with cystic fibrosis: a randomized controlled study', *Chest*, 125(4), pp. 1299–1305*, NLM*. DOI: 10.1378/chest.125.4.1299.

Knudsen, K. B., Boisen, K. A., Katzenstein, T. L., Mortensen, L. H., Pressler, T., Skov, M. and Jarden, M. (2018) 'Living with cystic fibrosis - a qualitative study of a life coaching intervention', *Patient Preference and Adherence*, 12, pp. 585–594*, NLM*. DOI: 10.2147/ppa.S159306.

Knudsen, K. B., Pressler, T., Mortensen, L. H., Jarden, M., Skov, M., Quittner, A., Katzenstein, T. and Boisen, K. (2016) 'Associations between adherence, depressive symptoms and health-related quality of life in young adults with cystic fibrosis', *SpringerPlus*, 5(1), pp. 1–8. DOI: 10.1186/s40064-016-2862-5.

Konstan, M. W., Morgan, W. J., Butler, S. M., Pasta, D. J., Craib, M. L., Silva, S. J., Stokes, D. C., Wohl, M. E., Wagener, J. S., Regelmann, W. E. and Johnson, C. A. (2007) 'Risk factors for rate of decline in forced expiratory volume in one second in children and adolescents with cystic fibrosis', *The Journal of Pediatrics*, 151(2), pp. 134–139*, NLM*. DOI: 10.1016/j.jpeds.2007.03.006.

Konstan, M. W., VanDevanter, D. R., Rasouliyan, L., Pasta, D. J., Yegin, A., Morgan, W. J. and Wagener, J. S. (2010) 'Trends in the use of routine therapies in cystic fibrosis: 1995-2005', *Pediatric Pulmonology*, 45(12), pp. 1167–1172*, NLM*. DOI: 10.1002/ppul.21315.

Kramer-Golinkoff, E., Camacho, A., Kramer, L. and Taylor-Cousar, J. L. (2022) 'A survey: Understanding the health and perspectives of people with CF not benefiting from CFTR modulators', *Pediatric Pulmonology*, 57(5), pp. 1253–1261, Available at: John Wiley & Sons, Ltd. DOI: https://doi.org/10.1002/ppul.25859.

Kraynack, N. C., Gothard, M. D., Falletta, L. M. and McBride, J. T. (2011) 'Approach to treating cystic fibrosis pulmonary exacerbations varies widely across US CF care centers', *Pediatric Pulmonology*, 46(9), pp. 870–881 [https://doi.org/10.1002/ppul.21442], Available at: John Wiley & Sons, Ltd. DOI: https://doi.org/10.1002/ppul.21442.

Kraynack, N. C. and McBride, J. T. (2009) 'Improving care at cystic fibrosis centers through quality improvement', *Seminars in Respiratory and Critical Care Medicine*, 30(5), pp. 547–558*, NLM*. DOI: 10.1055/s-0029-1238913.

Kreindler, J. L. (2010) 'Cystic fibrosis: Exploiting its genetic basis in the hunt for new therapies', *Pharmacology & Therapeutics*, 125(2), pp. 219–229. DOI: https://doi.org/10.1016/j.pharmthera.2009.10.006.

Lam, J. C., Somayaji, R., Surette, M. G., Rabin, H. R. and Parkins, M. D. (2015) 'Reduction in pseudomonas aeruginosa sputum density during a cystic fibrosis pulmonary exacerbation does not predict clinical response', *BMC Infectious Diseases*, 15, pp. 145. PubMed, Available at: BioMed Central. DOI: 10.1186/s12879-015-0856-5.

Larkin, M., Flowers, P. and Smith, J. A. (2021) *Interpretative Phenomenological Analysis: Theory, Method and Research*: London: SAGE.

Lechtzin, N., West, N., Allgood, S., Wilhelm, E., Khan, U., Mayer-Hamblett, N., Aitken, M. L., Ramsey, B. W., Boyle, M. P., Mogayzel, P. J. and Goss, C. H. (2013) 'Rationale and design of a randomized trial of home electronic symptom and lung function monitoring to detect cystic fibrosis pulmonary exacerbations: The early intervention in cystic fibrosis exacerbation (eICE) trial', *Contemporary Clinical Trials*, 36(2), pp. 460–469. DOI: https://doi.org/10.1016/j.cct.2013.09.004.

Lee, T., Sawicki, G. S., Altenburg, J., Millar, S. J., Geiger, J. M., Jennings, M. T., Lou, Y., McGarry, L. J., Van Brunt, K. and Linnemann, R. W. (2023) 'Effect of elexacaftor/tezacaftor/ivacaftor on annual rate of lung function decline in people with cystic fibrosis', *Journal of Cystic Fibrosis*, 22(3), pp. 402–406. DOI: 10.1016/j.jcf.2022.12.009.

Lim, S. Z. P. and Fitzgerald, D. A. (2015) 'Cystic fibrosis frequently asked questions. Question 3: How do you define a pulmonary exacerbation in cystic fibrosis?', *Paediatric Respiratory Reviews*, 16(4), pp. 249–250*, NLM*. DOI: 10.1016/j.prrv.2015.01.002.

Liou, T. G., Adler, F. R., Fitzsimmons, S. C., Cahill, B. C., Hibbs, J. R. and Marshall, B. C. (2001) 'Predictive 5-year survivorship model of cystic fibrosis', *American Journal of Epidemiology*, 153(4), pp. 345–352*, NLM*. DOI: 10.1093/aje/153.4.345.

Lopes-Pacheco, M. (2020) 'CFTR modulators: The changing face of cystic fibrosis in the era of precision medicine', *Frontiers in Pharmacology*, 10 [Review]. DOI: 10.3389/fphar.2019.01662.

Lopez, A., Daly, C., Vega-Hernandez, G., MacGregor, G. and Rubin, J. L. (2023) 'Elexacaftor/tezacaftor/ivacaftor projected survival and long-term health outcomes in people with cystic fibrosis homozygous for F508del', *Journal of Cystic Fibrosis*, 22(4), pp. 607–614. DOI: https://doi.org/10.1016/j.jcf.2023.02.004 (Accessed 5 July 2023).

Maggie Patricia, M., Nancy, A., George, F. D., Larry, C. L., Felix, R., Ruth, M., Blythe, O. and Jennifer, L. A. (2013) 'Long-term multicentre randomised controlled study of high frequency chest wall oscillation versus positive expiratory pressure mask in cystic fibrosis', *Thorax*, 68(8), pp. 746–751. DOI: 10.1136/thoraxjnl-2012-202915.

Mainz, J. G., Zagoya, C., Polte, L., Naehrlich, L., Sasse, L., Eickmeier, O., Smaczny, C., Barucha, A., Bechinger, L., Duckstein, F., Kurzidim, L., Eschenhagen, P., Caley, L., Peckham, D. and Schwarz, C. (2022) 'Elexacaftor-tezacaftor-ivacaftor treatment reduces abdominal symptoms in cystic fibrosis-early results obtained with the cf-specific cfabd-score', *Frontiers in Pharmacology*, 13, pp. 877118*, NLM*. DOI: 10.3389/fphar.2022.877118.

Majid, M. A. A., Othman, M., Mohamad, S. F., Lim, S. A. H. and Yusof, A. (2017) 'Piloting for interviews in qualitative research: Operationalization and lessons learnt', *International Journal of Academic Research in Business and Social Sciences*, 7(4), pp. 1073–1080. DOI: 10.6007/IJARBSS/v7-i4/2916.

Mall, M. A., Brugha, R., Gartner, S., Legg, J., Moeller, A., Mondejar-Lopez, P., Prais, D., Pressler, T., Ratjen, F. and Reix, P. (2022) 'Efficacy and safety of elexacaftor/tezacaftor/ivacaftor in children 6 through 11 years of age with cystic fibrosis heterozygous for f508del and a minimal function mutation: a phase 3B, randomized, placebo-controlled study', *American Journal of Respiratory and Critical Care Medicine*, 206(11), pp. 1361–1369. DOI: 10.1164/rccm.202202-0392OC.

Malterud, K., Siersma, V. D. and Guassora, A. D. (2015) 'Sample size in qualitative interview studies: Guided by information power', *Qualitative Health Research*, 26(13), pp. 1753–1760, Available at: SAGE Publications Inc. DOI: 10.1177/1049732315617444.

Mantzios, M., Egan, H. and Patchell, C. (2016) 'Can existing knowledge on eating behaviors and obesity support people with cystic fibrosis who are nutritionally compromised?', *Frontiers in Psychology*, 7(1477)*, NLM*. DOI: 10.3389/fpsyg.2016.01477.

Mayer-Hamblett, N., Nichols, D. P., Odem-Davis, K., Riekert, K. A., Sawicki, G. S., Donaldson, S. H., Ratjen, F., Konstan, M. W., Simon, N., Rosenbluth, D. B., Retsch-Bogart, G., Clancy, J. P., VanDalfsen, J. M., Buckingham, R. and Gifford, A. H. (2021) 'Evaluating the impact of stopping chronic therapies after modulator drug therapy in cystic fibrosis: The simplify clinical trial study design', *Annals of the American Thoracic Society*, 18(8), pp. 1397–1405*, NLM*. DOI: 10.1513/AnnalsATS.202010-1336SD.

Mayer-Hamblett, N., Ratjen, F., Russell, R., Donaldson, S. H., Riekert, K. A., Sawicki, G. S., Odem-Davis, K., Young, J. K., Rosenbluth, D. and Taylor-Cousar, J. L. (2022) 'Discontinuation versus continuation of hypertonic saline or dornase alfa in modulator treated people with cystic fibrosis (SIMPLIFY): results from two parallel, multicentre, open-label, randomised, controlled, non-inferiority trials', *The Lancet Respiratory Medicine*, 11(4), pp. 329– 340. DOI: https://doi.org/10.1016/S2213-2600(22)00434-9.

Mayer-Hamblett, N., Retsch-Bogart, G., Kloster, M., Accurso, F., Rosenfeld, M., Albers, G., Black, P., Brown, P., Cairns, A., Davis, S. D., Graff, G. R., Kerby, G. S., Orenstein, D., Buckingham, R. and Ramsey, B. W. (2018) 'Azithromycin for early pseudomonas infection in cystic fibrosis. The optimize randomized trial', *American Journal of Respiratory and Critical Care Medicine*, 198(9), pp. 1177–1187*, NLM*. DOI: 10.1164/rccm.201802-0215OC.

McLeod, C., Wood, J., Schultz, A., Norman, R., Smith, S., Blyth, C. C., Webb, S., Smyth, A. R. and Snelling, T. L. (2020) 'Outcomes and endpoints reported in studies of pulmonary exacerbations in people with cystic fibrosis: A systematic review', *Journal of Cystic Fibrosis*, 19(6), pp. 858– 867. DOI: https://doi.org/10.1016/j.jcf.2020.08.015.

McNamara, J. J., McColley, S. A., Marigowda, G., Liu, F., Tian, S., Owen, C. A., Stiles, D., Li, C., Waltz, D., Wang, L. T. and Sawicki, G. S. (2019) 'Safety, pharmacokinetics, and pharmacodynamics of lumacaftor and ivacaftor combination therapy in children aged 2-5 years with cystic fibrosis homozygous for F508del-CFTR: an open-label phase 3 study', *The Lancet Respiratory Medicine*, 7(4), pp. 325–335*, NLM*. Medline. DOI: 10.1016/S2213-2600(18)30460-0.

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., Rowe, S. M. and Jain, R. (2019) 'Elexacaftor–tezacaftor–ivacaftor for cystic fibrosis with a single phe508del allele', *New England Journal of Medicine*, 381(19), pp. 1809–1819, Available at: Massachusetts Medical Society. DOI: 10.1056/NEJMoa1908639.

Migliorisi, G., Collura, M., Ficili, F., Pensabene, T., Bongiorno, D., Collura, A., Di Bernardo, F. and Stefani, S. (2022) 'Elexacaftor-tezacaftor-ivacaftor as a final frontier in the treatment of cystic fibrosis: Definition of the clinical and microbiological implications in a case-control study', *Pharmaceuticals*, 15(5). DOI: 10.3390/ph15050606.

Milla, C. E., Ratjen, F., Marigowda, G., Liu, F., Waltz, D. and Rosenfeld, M. (2016) '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), pp. 912–920, Available at: American Thoracic Society - AJRCCM. DOI: 10.1164/rccm.201608-1754OC.

Miller, A. C., Harris, L. M., Cavanaugh, J. E., Abou Alaiwa, M., Stoltz, D. A., Hornick, D. B. and Polgreen, P. M. (2022) 'The rapid reduction of infection-related visits and antibiotic use among people with cystic fibrosis after starting elexacaftor-tezacaftor-ivacaftor ', *Clinical Infectious Diseases*, 75(7), pp. 1115–1122. DOI: 10.1093/cid/ciac117.

Milo, F., Ciciriello, F., Alghisi, F. and Tabarini, P. (2023) 'Lived experiences of people with cystic fibrosis that were not eligible for elexacaftor-tezacaftor-ivacaftor (ETI): A qualitative study', *Journal of Cystic Fibrosis*, 22(3), pp. 414–419. DOI: https://doi.org/10.1016/j.jcf.2022.12.007.

Mitchell, R. M., Jones, A. M., Stocking, K., Foden, P. and 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), pp. 874–879*, NLM*. DOI: 10.1136/thoraxjnl-2020-215556.

Mogayzel, P. J., Naureckas, E. T., Robinson, K. A., Mueller, G., Hadjiliadis, D., Hoag, J. B., Lubsch, L., Hazle, L., Sabadosa, K. and Marshall, B. (2013) 'Cystic fibrosis pulmonary guidelines: Chronic medications for maintenance of lung health', *American Journal of Respiratory and Critical Care Medicine*, 187(7), pp. 680–689, Available at: American Thoracic Society - AJRCCM. DOI: 10.1164/rccm.201207-1160OE.

Munck, A., Kerem, E., Ellemunter, H., Campbell, D., Wang, L. T., Ahluwalia, N., Owen, C. A. and Wainwright, C. (2020) 'Tezacaftor/ivacaftor in people with cystic fibrosis heterozygous for minimal function CFTR mutations', *Journal of Cystic Fibrosis*, 19(6), pp. 962–968, Available at: Elsevier. DOI: 10.1016/j.jcf.2020.04.015.

Munn, Z., Peters, M. D. J., Stern, C., Tufanaru, C., McArthur, A. and Aromataris, E. (2018a) 'Systematic review or scoping review? Guidance for authors when choosing between a systematic or scoping review approach', *BMC Medical Research Methodology,* 18(1), pp. 143.

Munn, Z., Stern, C., Aromataris, E., Lockwood, C. and Jordan, Z. (2018b) 'What kind of systematic review should I conduct? A proposed typology and guidance for systematic reviewers in the medical and health sciences', *BMC Medical Research Methodology*, 18(1), pp. 5*, NLM*. DOI: 10.1186/s12874-017-0468-4.

Nap-van der Vlist, M. M., Dalmeijer, G. W., Grootenhuis, M. A., van der Ent, K., Van den Heuvel-Eibrink, M. M., Swart, J. F., van de Putte, E. M. and Nijhof, S. L. (2021) 'Fatigue among children with a chronic disease: A cross-sectional study', *British Medical Journal Paediatrics Open*, 5(1), pp. e000958. DOI: http://dx.doi.org/10.1136/bmjpo-2020-000958.

National Institute for Health and Care Excellence (2013) *Weight management: lifestyle services for overweight or obese children and young people*. Available at: https://www.nice.org.uk/guidance/ph47/chapter/5-Glossary#:~:text=and%20sedentary%20behaviour.-,Body%20mass%20index%20(BMI)%20z%20score,as%20a%20child%20growth%20reference.) (Accessed: 13 August 2023).

Nevitt, S. J., Thornton, J., Murray, C. S. and Dwyer, T. (2020) 'Inhaled mannitol for cystic fibrosis', *The Cochrane Database of Systematic Reviews*, 5(1), Available at: John Wiley & Sons, Ltd. DOI: 10.1002/14651858.CD008649.pub4.

NHS England (2021) *Clinical commissioning urgent policy statement ivacaftor and tezacaftor/ivacaftor for cystic fibrosis: "Off-label" use in patients with named rarer mutations*. Available at: https://www.england.nhs.uk/wp-content/uploads/2020/08/Urgent-policy-statement-CFTR-off-label-rarer-mutations.pdf (Accessed: 15 August 2023).

Nichols, D. P., Donaldson, S. H., Frederick, C. A., Freedman, S. D., Gelfond, D., Hoffman, L. R., Kelly, A., Narkewicz, M. R., Pittman, J. E., Ratjen, F., Sagel, S. D., Rosenfeld, M., Schwarzenberg, S. J., Singh, P. K., Solomon, G. M., Stalvey, M. S., Kirby, S., VanDalfsen, J. M., Clancy, J. P. and Rowe, S. M. (2021) 'PROMISE: Working with the CF community to understand emerging clinical and research needs for those treated with highly effective CFTR modulator therapy', *Journal of Cystic Fibrosis*, 20(2), pp. 205–212. DOI: https://doi.org/10.1016/j.jcf.2021.02.003.

Nichols, D. P., Durmowicz, A. G., Field, A., Flume, P. A., VanDevanter, D. R. and Mayer-Hamblett, N. (2019) 'Developing inhaled antibiotics in cystic fibrosis: Current challenges and opportunities', *Annals of the American Thoracic Society*, 16(5), pp. 534–539*, NLM*. DOI: 10.1513/AnnalsATS.201812-863OT.

Nichols, D. P., Odem-Davis, K., Cogen, J. D., Goss, C. H., Ren, C. L., Skalland, M., Somayaji, R. and Heltshe, S. L. (2020) 'Pulmonary outcomes associated with long-term azithromycin therapy in cystic fibrosis', *American Journal of Respiratory and Critical Care Medicine*, 201(4), pp. 430–437*, NLM*. DOI: 10.1164/rccm.201906-1206OC.

Nichols, D. P., Paynter, A. C., Heltshe, S. L., Donaldson, S. H., Frederick, C. A., Freedman, S. D., Gelfond, D., Hoffman, L. R., Kelly, A., Narkewicz, M. R., Pittman, J. E., Ratjen, F., Rosenfeld, M., Sagel, S. D., Schwarzenberg, S. J., Singh, P. K., Solomon, G. M., Stalvey, M. S., Clancy, J. P., Kirby, S., Van Dalfsen, J. M., Kloster, M. H., Rowe, S. M. and group, P. S. (2022) 'Clinical effectiveness of elexacaftor/tezacaftor/ivacaftor in people with cystic fibrosis: A clinical trial', *American Journal of Respiratory and Critical Care Medicine*, 205(5), pp. 529–539*, NLM*. Medline. DOI: 10.1164/rccm.202108-1986OC.

Nicolais, C. J., Bernstein, R., Saez-Flores, E., McLean, K. A., Riekert, K. A. and Quittner, A. L. (2019) 'Identifying factors that facilitate treatment adherence in cystic fibrosis: Qualitative analyses of interviews with parents and adolescents', *Journal of Clinical Psychology in Medical Settings*, 26(4), pp. 530–540. DOI: 10.1007/s10880-018-9598-z.

Olivier, M., Kavvalou, A., Welsner, M., Hirtz, R., Straßburg, S., Sutharsan, S., Stehling, F. and Steindor, M. (2023) 'Real-life impact of highly effective CFTR modulator therapy in children with cystic fibrosis', *Frontiers in Pharmacology*, 14, pp. 1176815*, NLM*. DOI: 10.3389/fphar.2023.1176815.

Ong, T. and Ramsey, B. W. (2023) 'Cystic Fibrosis: A Review', *The Journal of the American Medical Association*, 329(21), pp. 1859–1871*, NLM*. DOI: 10.1001/jama.2023.8120.

Orkambi (2023) *History of Orkambi*. Available at: https://www.orkambi.com/orkambi-history (Accessed: 15 August 2023).

Ouzzani, M., Hammady, H., Fedorowicz, Z. and Elmagarmid, A. (2016) 'Rayyan—a web and mobile app for systematic reviews', *Systematic Reviews*, 5(210), pp. 1–10. DOI: https://doi.org/10.1186/s13643-016-0384-4

Paff, T., van der Schee, M. P., Daniels, J. M., Pals, G., Postmus, P. E., Sterk, P. J. and Haarman, E. G. (2013) 'Exhaled molecular profiles in the assessment of cystic fibrosis and primary ciliary dyskinesia', *Journal of Cystic Fibrosis*, 12(5), pp. 454–460*, NLM*. DOI: 10.1016/j.jcf.2012.12.010.

Page, A., Goldenberg, A. and Matthews, A. L. (2022) 'Lived experiences of individuals with cystic fibrosis on CFTR-modulators', *BMC Pulmonary Medicine*, 22(1), pp. 42. DOI: 10.1186/s12890-022-01825-2.

Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., Shamseer, L., Tetzlaff, J. M., Akl, E. A., Brennan, S. E., Chou, R., Glanville, J., Grimshaw, J. M., Hróbjartsson, A., Lalu, M. M., Li, T., Loder, E. W., Mayo-Wilson, E., McDonald, S., McGuinness, L. A., Stewart, L. A., Thomas, J., Tricco, A. C., Welch, V. A., Whiting, P. and Moher, D. (2021) 'The PRISMA 2020 statement: An updated guideline for reporting systematic reviews', *International Journal of Surgery*, 88, pp. 105906. DOI: https://doi.org/10.1016/j.ijsu.2021.105906.

Parkins, M. D. and Floto, R. A. (2015) 'Emerging bacterial pathogens and changing concepts of bacterial pathogenesis in cystic fibrosis', *Journal of Cystic Fibrosis*, 14(3), pp. 293–304*, NLM*. DOI: 10.1016/j.jcf.2015.03.012.

Paterson, S. L., Barry, P. J. and Horsley, A. R. (2020) 'Tezacaftor and ivacaftor for the treatment of cystic fibrosis', *Expert Review of Respiratory Medicine*, 14(1), pp. 15–30, Available at: Taylor & Francis. DOI: 10.1080/17476348.2020.1682998.

Petersen, M. C., Begnel, L., Wallendorf, M. and 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), pp. 265–271. DOI: https://doi.org/10.1016/j.jcf.2021.11.012.

Quanjer, P. H., Stanojevic, S., Cole, T. J., Baur, X., Hall, G. L., Culver, B. H., Enright, P. L., Hankinson, J. L., Ip, M. S., Zheng, J. and Stocks, J. (2012) 'Multi-ethnic reference values for spirometry for the 3-95-yr age range: the

global lung function 2012 equations', *European Respiratory Journal*, 40(6), pp. 1324–1343*, NLM*. DOI: 10.1183/09031936.00080312.

Quittner, A. L., Goldbeck, L., Abbott, J., Duff, A., Lambrecht, P., Solé, A., Tibosch, M. M., Brucefors, A. B., Yüksel, H. and Catastini, P. (2014a) 'Prevalence of depression and anxiety in patients with cystic fibrosis and parent caregivers: results of The International Depression Epidemiological Study across nine countries', *Thorax*, 69(12), pp. 1090–1097. DOI: 10.1136/thoraxjnl-2014-205983.

Quittner, A. L., Opipari, L. C., Espelage, D. L., Carter, B., Eid, N. and Eigen, H. (1998) 'Role strain in couples with and without a child with a chronic illness: associations with marital satisfaction, intimacy, and daily mood', *Health Psychology*, 17(2), pp. 112–124*, NLM*. DOI: 10.1037//0278-6133.17.2.112 (Accessed Mar).

Quittner, A. L., Saez-Flores, E. and Barton, J. D. (2016) 'The psychological burden of cystic fibrosis', *Current Opinion in Pulmonary Medicine* 22(2), pp. 187–191*, NLM*. DOI: 10.1097/mcp.0000000000000244.

Quittner, A. L., Zhang, J., Marynchenko, M., Chopra, P. A., Signorovitch, J., Yushkina, Y. and Riekert, K. A. (2014b) 'Pulmonary medication adherence and health-care use in cystic fibrosis', *Chest*, 146(1), pp. 142–151. DOI: 10.1378/chest.13-1926.

Radtke, T., Smith, S., Nevitt, S. J., Hebestreit, H. and Kriemler, S. (2022) 'Physical activity and exercise training in cystic fibrosis', *The Cochrane Database of Systematic Reviews*, 8(8), pp. Cd002768*, NLM*. DOI: 10.1002/14651858.CD002768.pub5.

Ramsey, B. W. and Boat, T. F. (1994) 'Outcome measures for clinical trials in cystic fibrosis. Summary of a Cystic Fibrosis Foundation consensus conference', *The Journal of Pediatrics*, 124(2), pp. 177–192. PubMed. DOI: 10.1016/s0022-3476(94)70301-9.

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. and Elborn, J. S. (2011) 'A CFTR potentiator in patients with cystic fibrosis and the G551D mutation', *New England Journal of Medicine*, 365(18), pp. 1663–1672*, NLM*. DOI: 10.1056/NEJMoa1105185.

Ramsey, B. W., Pepe, M. S., Quan, J. M., Otto, K. L., Montgomery, A. B., Williams-Warren, J., Vasiljev-K, M., Borowitz, D., Bowman, C. M., Marshall, B. C., Marshall, S. and Smith, A. L. (1999) 'Intermittent administration of inhaled tobramycin in patients with cystic fibrosis', *New England Journal of Medicine*, 340(1), pp. 23–30, Available at: Massachusetts Medical Society. DOI: 10.1056/NEJM199901073400104.

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

Ratjen, F., Hug, C., Marigowda, G., Tian, S., Huang, X., Stanojevic, S., Milla, C. E., Robinson, P. D., Waltz, D., Davies, J. C. and and VX14-809-109 investigator group (2017) 'Efficacy and safety of lumacaftor and ivacaftor in patients aged 6-11 years with cystic fibrosis homozygous for F508del-CFTR: a randomised, placebo-controlled phase 3 trial', *The Lancet Respiratory Medicine*, 5(7), pp. 557–567*, NLM*. Medline. DOI: 10.1016/S2213-2600(17)30215-1.

Rosenfeld, M., Emerson, J., Williams-Warren, J., Pepe, M., Smith, A., Montgomery, A. B. and Ramsey, B. (2001) 'Defining a pulmonary exacerbation in cystic fibrosis', *Journal of Pediatrics*, 139(3), pp. 359–365. DOI: https://doi.org/10.1067/mpd.2001.117288.

Rosenfeld, M., Ratjen, F., Brumback, L., Daniel, S., Rowbotham, R., McNamara, S., Johnson, R., Kronmal, R., Davis, S. D. and ISIS Study Group (2012) 'Inhaled hypertonic saline in infants and children younger than 6 years with cystic fibrosis: the isis randomized controlled trial', *Journal of the American Medical Association*, 307(21), pp. 2269–2277. DOI: 10.1001/jama.2012.5214.

Rosenfeld, M., Wainwright, C. E., Higgins, M., Wang, L. T., McKee, C., Campbell, D., Tian, S., Schneider, J., Cunningham, S. and Davies, J. C. (2018) 'Ivacaftor treatment of cystic fibrosis in children aged 12 to <24 months and with a CFTR gating mutation (ARRIVAL): a phase 3 single-arm study', *The Lancet Respiratory Medicine*, 6(7), pp. 545–553*, NLM*. DOI: 10.1016/s2213-2600(18)30202-9.

Rowbotham, N. J., Sherie, S., Zoe, C. E., Belinda, C., Lorna, J. A., Katherine, C., Lucy, A. and Alan Robert, S. (2023) 'A refresh of the top 10 research priorities in cystic fibrosis', *Thorax*, 78, pp. 840–843. DOI: 10.1136/thorax-2023-220100.

Rowbotham, N. J., Smith, S., Leighton, P. A., Rayner, O. C., Gathercole, K., Elliott, Z. C., Nash, E. F., Daniels, T., Duff, A. J. A., Collins, S., Chandran, S., Peaple, U., Hurley, M. N., Brownlee, K. and Smyth, A. R. (2018) 'The top 10 research priorities in cystic fibrosis developed by a partnership between people with CF and healthcare providers', *Thorax*, 73(4), pp. 388–390*, NLM*. DOI: 10.1136/thoraxjnl-2017-210473.

Rowbotham, N. J., Smith, S. J., Davies, G., Daniels, T., Elliott, Z. C., Gathercole, K., Rayner, O. C. and Smyth, A. R. (2020) 'Can exercise replace airway clearance techniques in cystic fibrosis? A survey of patients and healthcare professionals', *Journal of Cystic Fibrosis*, 19(4), pp. e19–e24. DOI: https://doi.org/10.1016/j.jcf.2019.10.026.

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. and Davies, J. C. (2017) 'Tezacaftor–ivacaftor in residual-function heterozygotes with cystic fibrosis', *New England Journal of Medicine*, 377(21), pp. 2024–2035, Available at: Massachusetts Medical Society. DOI: 10.1056/NEJMoa1709847.

Rubin, J. L., Thayer, S., Watkins, A., Wagener, J. S., Hodgkins, P. S. and Schechter, M. S. (2017) 'Frequency and costs of pulmonary exacerbations in patients with cystic fibrosis in the United States', *Current Medical Research and Opinion*, 33(4), pp. 667–674*, NLM*. DOI: 10.1080/03007995.2016.1277196.

Sagel, S. D., Khan, U., Jain, R., Graff, G., Daines, C. L., Dunitz, J. M., Borowitz, D., Orenstein, D. M., Abdulhamid, I., Noe, J., Clancy, J. P., Slovis, B., Rock, M. J., McCoy, K. S., Strausbaugh, S., Livingston, F. R., Papas, K. A. and Shaffer, M. L. (2018) 'Effects of an antioxidant-enriched multivitamin in cystic fibrosis. A randomized, controlled, multicenter clinical trial', *American Journal of Respiratory and Critical Care Medicine*, 198(5), pp. 639–647*, NLM*. DOI: 10.1164/rccm.201801-0105OC.

Saglam, M., Vardar-Yagli, N., Savci, S., Inal-Ince, D., Aribas, Z., Bosnak-Guclu, M., Arikan, H., Calik-Kutukcu, E. and Gunes-Yalcin, E. (2016) 'Six minute walk test versus incremental shuttle walk test in cystic fibrosis', *Pediatrics International*, 58(9), pp. 887–893 [https://doi.org/10.1111/ped.12919], Available at: John Wiley & Sons, Ltd. DOI: https://doi.org/10.1111/ped.12919.

Saiman, L., Marshall, B. C., Mayer-Hamblett, N., Burns, J. L., Quittner, A. L., Cibene, D. A., Coquillette, S., Fieberg, A. Y., Accurso, F. J., Campbell, P. W. and Macrolide Study Group (2003) 'Azithromycin in patients with cystic fibrosis chronically infected with pseudomonas aeruginosa: A randomized controlled trial', *Journal of the American Medical Association*, 290(13), pp. 1749–1756. DOI: 10.1001/jama.290.13.1749.

Sanders, D. B., Bittner, R. C., Rosenfeld, M., Redding, G. J. and Goss, C. H. (2011) 'Pulmonary exacerbations are associated with subsequent FEV1 decline in both adults and children with cystic fibrosis', *Pediatric Pulmonology*, 46(4), pp. 393–400*, NLM*. DOI: 10.1002/ppul.21374.

Sanders, D. B., Bittner, R. C. L., Rosenfeld, M., Hoffman, L. R., Redding, G. J. and Goss, C. H. (2010a) 'Failure to recover to baseline pulmonary function after cystic fibrosis pulmonary exacerbation', *American Journal of Respiratory and Critical Care Medicine*, 182(5), pp. 627–632. PubMed, Available at: American Thoracic Society. DOI: 10.1164/rccm.200909-1421OC.

Sanders, D. B., Hoffman, L. R., Emerson, J., Gibson, R. L., Rosenfeld, M., Redding, G. J. and Goss, C. H. (2010b) 'Return of FEV1 after pulmonary exacerbation in children with cystic fibrosis', *Pediatric Pulmonology*, 45(2), pp. 127–134, Available at: John Wiley & Sons, Ltd. DOI: 10.1002/ppul.21117.

Santuzzi, C. H., Liberato, F. M. G., Morau, S. A. C., de Oliveira, N. F. F. and Nascimento, L. R. (2020) 'Adherence and barriers to general and respiratory exercises in cystic fibrosis', *Pediatric Pulmonology*, 55(10), pp. 2646–2652, Available at: John Wiley & Sons, Ltd. DOI: https://doi.org/10.1002/ppul.24912.

Sawicki, G. S., Heller, K. S., Demars, N. and Robinson, W. M. (2015) 'Motivating adherence among adolescents with cystic fibrosis: Youth and parent perspectives', *Pediatric Pulmonology*, 50(2), pp. 127–136 [https://doi.org/10.1002/ppul.23017], Available at: John Wiley & Sons, Ltd. DOI: https://doi.org/10.1002/ppul.23017.

Sawicki, G. S., Ren, C. L., Konstan, M. W., Millar, S. J., Pasta, D. J. and Quittner, A. L. (2013) 'Treatment complexity in cystic fibrosis: Trends over time and associations with site-specific outcomes', *Journal of Cystic Fibrosis*, 12(5), pp. 461–467. DOI: https://doi.org/10.1016/j.jcf.2012.12.009.

Sawicki, G. S., Sellers, D. E. and Robinson, W. M. (2008) 'Self-reported physical and psychological symptom burden in adults with cystic fibrosis', *Journal of Pain and Symptom Management*, 35(4), pp. 372–380*, NLM*. DOI: 10.1016/j.jpainsymman.2007.06.005.

Sawicki, G. S., Sellers, D. E. and Robinson, W. M. (2009) 'High treatment burden in adults with cystic fibrosis: challenges to disease self-management', *Journal of Cystic Fibrosis*, 8(2), pp. 91–96. PubMed. DOI: 10.1016/j.jcf.2008.09.007.

Saynor, Z. L., Cunningham, S., Morrison, L., Main, E., Vogiatzis, I., Reid, S. and Urquhart, D. (2023) 'Exercise as airway clearance therapy (ExACT) in cystic fibrosis: a UK-based e-Delphi survey of patients, caregivers and health professionals', *Thorax*, 78(1), pp. 88–91*, NLM*. DOI: 10.1136/thorax-2022-219213.

Schaedel, C., de Monestrol, I., Hjelte, L., Johannesson, M., Kornfält, R., Lindblad, A., Strandvik, B., Wahlgren, L. and Holmberg, L. (2002) 'Predictors of deterioration of lung function in cystic fibrosis', *Pediatric Pulmonology*, 33(6), pp. 483–491, Available at: John Wiley & Sons, Ltd. DOI: https://doi.org/10.1002/ppul.10100.

Schmid-Mohler, G., Caress, A.-L., Spirig, R., Benden, C. and Yorke, J. (2019) '"Thrust out of normality"—How adults living with cystic fibrosis experience pulmonary exacerbations: A qualitative study', *Journal of Clinical Nursing*, 28, pp. 190–200. DOI: https://doi.org/10.1111/jocn.14646.

Schneiderman-Walker, J., Pollock, S. L., Corey, M., Wilkes, D. D., Canny, G. J., Pedder, L. and Reisman, J. J. (2000) 'A randomized controlled trial of a 3-year home exercise program in cystic fibrosis', *The Journal of Pediatrics*, 136(3), pp. 304–310*, NLM*. DOI: 10.1067/mpd.2000.103408.

Schütz, K., Pallenberg, S. T., Kontsendorn, J., DeLuca, D., Sukdolak, C., Minso, R., Büttner, T., Wetzke, M., Dopfer, C., Sauer-Heilborn, A., Ringshausen, F. C., Junge, S., Tümmler, B., Hansen, G. and Dittrich, A.-M. (2023) 'Spirometric and anthropometric improvements in response to elexacaftor/tezacaftor/ivacaftor depending on age and lung disease severity', *Frontiers in Pharmacology*, 14 [Original Research]. DOI: 10.3389/fphar.2023.1171544.

Scotet, V., L'Hostis, C. and Férec, C. (2020) 'The changing epidemiology of cystic fibrosis: Incidence, survival and impact of the cftr gene discovery', *Genes*, 11(6), pp. 589*, NLM*. DOI: 10.3390/genes11060589.

Secunda, K., Jovanovic, B., Rowe, S., Heltshe, S. and Jain, M. (2019) 'Is there a gender'' gap'' in the response to ivacaftor in cystic fibrosis patients?', *American Thoracic Society International Conference abstarct*, pp. A4329. DOI: https://doi.org/10.1164/ajrccm-conference.2019.199.1_MeetingAbstracts.A4329.

Sepahzad, A., Morris-Rosendahl, D. J. and Davies, J. C. (2021) 'Cystic fibrosis lung disease modifiers and their relevance in the new era of precision medicine', *Genes*, 12(4), pp. 562. DOI: doi: 10.3390/genes12040562.

Sheikh, S., Britt, R. D. J., Ryan-Wenger, N. A., Khan, A. Q., Lewis, B. W., Gushue, C., Ozuna, H., Jaganathan, D., McCoy, K. and Kopp, B. T. (2023) 'Impact of elexacaftor–tezacaftor–ivacaftor on bacterial colonization and inflammatory responses in cystic fibrosis', *Pediatric Pulmonology*, 58(3), pp. 825–833, Available at: John Wiley & Sons, Ltd. DOI: https://doi.org/10.1002/ppul.26261.

Sheppard, D. N. and Welsh, M. J. (1999) 'Structure and function of the CFTR chloride channel', *Physiological Reviews*, 79(supplement 1), pp. S23–S45*, NLM*. DOI: 10.1152/physrev.1999.79.1.S23.

Shteinberg, M., Haq, I. J., Polineni, D. and Davies, J. C. (2021) 'Cystic fibrosis', *Lancet*, 397(10290), pp. 2195–2211*, NLM*. DOI: 10.1016/s0140-6736(20)32542-3.

Shteinberg, M. and Taylor-Cousar, J. L. (2020) 'Impact of CFTR modulator use on outcomes in people with severe cystic fibrosis lung disease', *European Respiratory Review*, 29(155), pp. 190112. DOI: 10.1183/16000617.0112-2019.

Singh, S. J., Morgan, M. D., Scott, S., Walters, D. and Hardman, A. E. (1992) 'Development of a shuttle walking test of disability in patients with chronic airways obstruction', *Thorax*, 47(12), pp. 1019–1024*, NLM*. DOI: 10.1136/thx.47.12.1019.

Singh, S. J., Puhan, M. A., Andrianopoulos, V., Hernandes, N. A., Mitchell, K. E., Hill, C. J., Lee, A. L., Camillo, C. A., Troosters, T., Spruit, M. A., Carlin, B. W., Wanger, J., Pepin, V., Saey, D., Pitta, F., Kaminsky, D. A., McCormack, M. C., MacIntyre, N., Culver, B. H., Sciurba, F. C., Revill, S. M., Delafosse, V. and Holland, A. E. (2014) 'An official systematic review of the European Respiratory Society/American Thoracic Society: measurement properties of field walking tests in chronic respiratory disease', *European Respiratory Journal*, 44(6), pp. 1447–1478*, NLM*. DOI: 10.1183/09031936.00150414.

Slatter, A., Francis, S. A., Smith, F. and Bush, A. (2004) 'Supporting parents in managing drugs for children with cystic fibrosis', *British Journal of Nursing*, 13(19), pp. 1135–1139*, NLM*. DOI: 10.12968/bjon.2004.13.19.16318.

Smith, B. A., Modi, A. C., Quittner, A. L. and Wood, B. L. (2010) 'Depressive symptoms in children with cystic fibrosis and parents and its effects on adherence to airway clearance', *Pediatric Pulmonology*, 45(8), pp. 756–763*, NLM*. DOI: 10.1002/ppul.21238.

Smith, S. and Rowbotham, N. J. (2022) 'Inhaled anti-pseudomonal antibiotics for long-term therapy in cystic fibrosis', *The Cochrane Database of Systematic Reviews*, 11(11), Available at: John Wiley & Sons, Ltd. DOI: 10.1002/14651858.CD001021.pub4.

Song, J. T., Desai, S., Franciosi, A. N., Dagenais, R. V. E. and Quon, B. S. (2022) 'Research letter: The impact of elexacaftor/tezacaftor/ivacaftor on adherence to nebulized maintenance therapies in people with cystic fibrosis', *Journal of Cystic Fibrosis*, 21(6), pp. 1080–1081, Available at: Netherlands: Elsevier B.V. DOI: 10.1016/j.jcf.2022.05.005.

South, K., Smaldone, A., Sadeghi, H., Piane, V., Kowal, R., Wei, L. and George, M. (2023) 'Parent and adolescent perceptions of cystic fibrosis management responsibility: A mixed-methods study', *Pediatric Pulmonology*, 58(8), pp. 2340– 2351, Available at: John Wiley & Sons, Ltd. DOI: https://doi.org/10.1002/ppul.26494.

Southern, K. 2021. A randomised open-label trial to assess change in respiratory function for people with cystic fibrosis (pwCF) established on triple combination therapy (Kaftrio™) after rationalisation of nebulised mucoactive therapies (the CF STORM trial).

Steinberg, L., Graham, S., O'brien, L., Woolard, J., Cauffman, E. and Banich, M. (2009) 'Age differences in future orientation and delay discounting', *Child development*, 80(1), pp. 28–44. DOI: 10.1111/j.1467-8624.2008.01244.x

Suthoff, E., Mainz, J. G., Cox, D. W., Thorat, T., Grossoehme, D. H., Fridman, M., Sawicki, G. S. and Rosenfeld, M. (2019) 'Caregiver burden due to pulmonary exacerbations in patients with cystic fibrosis', *Journal of Pediatrics*, 215, pp. 164–171*, NLM*. DOI: 10.1016/j.jpeds.2019.08.038.

Swisher, A. K. and Erickson, M. (2008) 'Perceptions of physical activity in a group of adolescents with cystic fibrosis', *Cardiopulmonary Physical Therapy Journal*, 19(4), pp. 107–113*, NLM*. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2845233/ (Accessed 1 May 2022).

Symdeko (no date) *What is SYMDEKO?* Available at: https://www.symdeko.com/ (Accessed: 15 August 2023).

Tate, S., MacGregor, G., Davis, M., Innes, J. A. and Greening, A. P. (2002) 'Airways in cystic fibrosis are acidified: detection by exhaled breath condensate', *Thorax*, 57(11), pp. 926. DOI: 10.1136/thorax.57.11.926.

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. and Elborn, J. S. (2017) 'Tezacaftor–ivacaftor in patients with cystic fibrosis homozygous for phe508del', *New England Journal of Medicine*, 377(21), pp. 2013–2023, Available at: Massachusetts Medical Society. DOI: 10.1056/NEJMoa1709846.

Thomas, J. and Harden, A. (2008) 'Methods for the thematic synthesis of qualitative research in systematic reviews', *BMC Medical Research Methodology*, 8(1), pp. 45. DOI: 10.1186/1471-2288-8-45.

Tomaszek, L., Dębska, G., Cepuch, G., Kulpa, M., Pawlik, L. and Broniatowska, E. (2019) 'Evaluation of quality of life predictors in adolescents and young adults with cystic fibrosis', *Heart & Lung*, 48(2), pp. 159–165. DOI: https://doi.org/10.1016/j.hrtlng.2018.08.003.

Tracy, S. J. (2010) 'Qualitative quality: Eight "big-tent" criteria for excellent qualitative research', *Qualitative Inquiry*, 16(10), pp. 837–851, Available at: SAGE Publications Inc. DOI: 10.1177/1077800410383121.

Treggiari, M. M., Rosenfeld, M., Mayer-Hamblett, N., Retsch-Bogart, G., Gibson, R. L., Williams, J., Emerson, J., Kronmal, R. A. and Ramsey, B. W. (2009) 'Early anti-pseudomonal acquisition in young patients with cystic fibrosis: Rationale and design of the EPIC clinical trial and observational study', *Contemporary Clinical Trials*, 30(3), pp. 256–268. DOI: 10.1016/j.cct.2009.01.003.

Tricco, A. C., Lillie, E., Zarin, W., O'Brien, K. K., Colquhoun, H., Levac, D., Moher, D., Peters, M. D. J., Horsley, T., Weeks, L., Hempel, S., Akl, E. A., Chang, C., McGowan, J., Stewart, L., Hartling, L., Aldcroft, A., Wilson, M. G., Garritty, C., Lewin, S., Godfrey, C. M., Macdonald, M. T., Langlois, E. V., Soares-Weiser, K., Moriarty, J., Clifford, T., Tunçalp, Ö. and Straus, S. E. (2018) 'PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation', *Annals of Internal Medicine*, 169(7), pp. 467-473, Available at: American College of Physicians. DOI: 10.7326/M18-0850 (Accessed 15 June 2023).

Urquhart, D. S., Cunningham, S., Taylor, E., Vogiatzis, I., Allen, L., Lewis, S., Neilson, A. R., Soilemezi, D., Akooji, N. and Saynor, Z. L. (2022) 'Exercise as an airway clearance technique in people with cystic fibrosis (ExACT-CF): Rationale and study protocol for a randomised pilot trial [version 1; peer review: 2 approved]', *NIHR Open Research*, 2(64) [study protocol]. DOI: https://doi.org/10.3310/nihropenres.13347.1.

Vandeleur, M., Walter, L. M., Armstrong, D. S., Robinson, P., Nixon, G. M. and Horne, R. S. (2017a) 'What keeps children with cystic fibrosis awake at night?', *Journal of Cystic Fibrosis*, 16(6), pp. 719–726. DOI: https://doi.org/10.1016/j.jcf.2017.04.012.

Vandeleur, M., Walter, L. M., Armstrong, D. S., Robinson, P., Nixon, G. M. and Horne, R. S. C. (2017b) 'How well do children with cystic fibrosis sleep? An actigraphic and questionnaire-based study', *The Journal of Pediatrics*, 182, pp. 170–176. DOI: https://doi.org/10.1016/j.jpeds.2016.11.069.

VanDevanter, D. R. and Konstan, M. W. (2012) 'Outcome measures for clinical trials assessing treatment of cystic fibrosis lung disease', *Journal of Clinical Investigation*, 2(2), pp. 163–175*, NLM*. DOI: 10.4155/cli.11.174.

VanDevanter, D. R., Morris, N. J. and Konstan, M. W. (2016) 'IV-treated pulmonary exacerbations in the prior year: An important independent risk factor for future pulmonary exacerbation in cystic fibrosis', *Journal of Cystic Fibrosis*, 15(3), pp. 372–379. DOI: https://doi.org/10.1016/j.jcf.2015.10.006.

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. and Boyle, M. P. (2015) 'Lumacaftor–ivacaftor in patients with cystic fibrosis homozygous for phe508del cftr', *New England Journal of Medicine*, 373(3), pp. 220–231, Available at: Massachusetts Medical Society. DOI: 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. and 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), pp. 708–713*, NLM*. DOI: 10.1016/j.jcf.2019.06.009.

Wang, A., Lee, M., Keller, A., Jian, S., Lowe, K., Finklea, J. D. and Jain, R. (2023) 'Sex differences in outcomes of people with cystic fibrosis treated with elexacaftor/tezacaftor/ivacaftor', *Journal of Cystic Fibrosis*, 8(56). DOI: https://doi.org/10.1016/j.jcf.2023.05.009.

Ward, N., Stiller, K. and Holland, A. E. (2019) 'Exercise is commonly used as a substitute for traditional airway clearance techniques by adults with cystic fibrosis in Australia: a survey', *Journal of Physiotherapy*, 65(1), pp. 43–50*, NLM*. DOI: 10.1016/j.jphys.2018.11.006.

Wark, P. and McDonald, V. M. (2018) 'Nebulised hypertonic saline for cystic fibrosis', *The Cochrane Database of Systematic Reviews*, 9(9), pp. Cd001506*, NLM*. DOI: 10.1002/14651858.CD001506.pub4.

Waters, V. and Ratjen, F. (2015) 'Pulmonary exacerbations in children with cystic fibrosis', *Annals of the American Thoracic Society*, 12 (supplement 2), pp. S200–S206*, NLM*. DOI: 10.1513/AnnalsATS.201502-098AW.

Wiesel, V., Aviram, M., Mei-Zahav, M., Dotan, M., Prais, D., Cohen-Cymberknoh, M., Gur, M., Bar-Yoseph, R., Livnat, G., Goldbart, A., Hazan, G., Hazan, I. and Golan-Tripto, I. (2023) 'Eradication of Nontuberculous Mycobacteria in People with Cystic Fibrosis Treated with Elexacaftor/Tezacaftor/Ivacaftor: A Multicenter Cohort Study', *Journal of Cystic Fibrosis*, S1569-1993(23). DOI: 10.1016/j.jcf.2023.05.003.

Williams, B., Mukhopadhyay, S., Dowell, J. and Coyle, J. (2007) 'Problems and solutions: Accounts by parents and children of adhering to chest physiotherapy for cystic fibrosis', *Disability and Rehabilitation*, 29(14), pp. 1097–1105, Available at: Taylor & Francis. DOI: 10.1080/09638280600948060.

Wollsching-Strobel, M., Dieninghoff, D., Emrich, L. F., Kroppen, D., Majorski, D. S., Mathes, T., Magnet, F. S., Schwarz, S. B., Crieé, C. and Windisch, W. (2022) 'Impact of elexacaftor/tezacaftor/ivacaftor combination therapy on lung function in adults with cystic fibrosis: Beyond FEV1', *European Respiratory Journal*, 60, pp. 369. DOI: 10.1183/13993003.congress-2022.369.

Wolter, J., Seeney, S., Bell, S., Bowler, S., Masel, P. and McCormack, J. (2002) 'Effect of long term treatment with azithromycin on disease parameters in cystic fibrosis: a randomised trial', *Thorax*, 57(3), pp. 212–216*, NLM*. DOI: 10.1136/thorax.57.3.212.

Yang, C. and Montgomery, M. (2021) 'Dornase alfa for cystic fibrosis', *The Cochrane Database of Systematic Reviews*, 2021(3), Available at: John Wiley & Sons, Ltd. DOI: 10.1002/14651858.CD001127.pub5.

Yardley, L. (2000) 'Dilemmas in qualitative health research', *Psychology & Health*, 15(2), pp. 215–228, Available at: Routledge. DOI: 10.1080/08870440008400302.

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. and Rowe, S. M. (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), pp. 1522–1532. DOI: 10.1164/rccm.202102-0509OC.

Ziaian, T., Sawyer, M. G., Reynolds, K. E., Carbone, J. A., Clark, J. J., Baghurst, P. A., Couper, J. J., Kennedy, D., Martin, A. J., Staugas, R. E. and French, D. J. (2006) 'Treatment burden and health-related quality of life of children with diabetes, cystic fibrosis and asthma', *Journal of Paediatrics and Child Health*, 42(10), pp. 596–600 [https://doi.org/10.1111/j.1440-1754.2006.00943.x], Available at: John Wiley & Sons, Ltd. DOI: https://doi.org/10.1111/j.1440-1754.2006.00943.x.

Zielenski, J., Rozmahel, R., Bozon, D., Kerem, B., Grzelczak, Z., Riordan, J. R., Rommens, J. and Tsui, L. C. (1991) 'Genomic DNA sequence of the cystic fibrosis transmembrane conductance regulator (CFTR) gene', *Genomics*, 10(1), pp. 214–228*, NLM*. DOI: 10.1016/0888-7543(91)90503-7.

Appendices

Appendix A. Patient information sheets (PIS)

The Newcastle upon Tyne Hospitals NHS Foundation Trust | THE great north CHILDREN'S HOSPITAL | Newcastle University

PARTICIPANT INFORMATION SHEET FOR YOUNG PEOPLE (11-15 years)

Study title

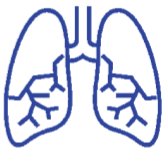
Qualitative study to explore the impact of modulator drugs on attitudes and opinions towards physiotherapy and nebulised treatment in children and young people with cystic fibrosis- TEMPO STUDY.

This study is part of Ph.D. project

- We would like you to help us with our research study. Before you decide, it is important for you to understand what the study is about and what will happen to you if you take part. Please read this leaflet carefully and ask us about anything that you do not understand.

What is the study for?

This study is trying to hear your views on the impact of CFTR modulator therapy (for example Orkambi, Symkevi or Kaftrio) on other treatments in the future, especially chest physiotherapy and nebulisers. The results of this work will help us to understand more about what children and young people think and may help us to reduce the load of the treatment in the future.



Why have I been chosen to take part?

You are under 18 years old; you have cystic fibrosis and you are taking a CFTR modulator drug.

What will happen if I take part?

We would like to simply ask you and your parents or guardian some questions. We would take about 60 minutes of your time to ask questions about your experience with the physiotherapy treatment after starting the CFTR modulator medicine and your opinions on reducing the load of treatment.

Is there anything else to be worried about if I take part?

There is nothing else required of you. We will take some information from your clinical notes about your care, but no extra clinic visits or changes in your diet or lifestyle is needed.

If we find out something that we think is important about your health that may be relevant to your care we will talk to your mum, dad or carer.

What will happen to my data?

The information we collect about you will be labelled only with your study number. Your name will be stored separately and safely. Only the nurse and

doctor will know who you are and we will remove anything from your comments and opinions that could identify you (anonymised).

Do I have to take part?

No! It is entirely up to you. We would like you to read this information sheet. You can take time to think it over, and ask any further questions

If you do decide to take part:

- You will be asked to sign a form to say that you agree to take part (consent form), your parent or guardian will also sign a form
- You will be given this information sheet and a copy of your signed consent form to keep.

You are free to stop taking part at any time during the research without giving a reason. If you withdraw from the study, it will not affect any treatment you might need in the future.

What happens when the research study stops?

We will collect all the information together and we will decide if it is useful in helping decrease the load of the treatment for young people with cystic fibrosis in the future.

Contact for further information

If you have any questions, your parents or guardian can contact the study team at any time and they know how to do this.

Thank you for reading this information leaflet.

The Newcastle upon Tyne Hospitals NHS
NHS Foundation Trust

THE great north CHILDREN'S HOSPITAL

Newcastle University

Qualitative study to explore the impact of modulator drugs on attitudes and opinions towards physiotherapy and nebulised treatment in children and young people with cystic fibrosis - the TEMPO study

This study is part of Ph.D. project

This information sheet is intended for young people aged 16–18 years with cystic fibrosis

Investigators: Dr Malcolm Brodlie, Consultant in Paediatric Respiratory Medicine, Great North Children's Hospital,
Mrs Maryam Almulhem, PhD student at Newcastle University.

Thank you for agreeing to be contacted about taking part in an interview. This is completely optional. Before you decide whether to take part, it is important for you to understand why the research is being done and what it will involve. Please take the time to read the following information carefully. One of our team can go through this information with you and answer any questions that you may have.

Why are you interviewing people?

We would like to hear people's views and experiences of the impact of receiving CFTR (Cystic fibrosis transmembrane conductance regulator) modulator drugs (for example Orkambi, Symkevi or Kaftrio) and the need for and attitudes towards other established treatments, especially physiotherapy and nebulisers. The information we receive will help us learn more about the impact of treatment with modulator drugs on the burden of other treatments and this will inform approaches to cystic fibrosis care moving forwards in the post-modulator era and the most relevant questions to be addressed by future clinical research.

Why have I been invited?

You are being invited to take part in this study because you are looked after by the Great North Children's Hospital cystic fibrosis team, and you are taking a modulator drug. You can help us find some answers that will help us understand the burden of treatment that you experience.

Do I have to take part?

No. It is up to you to decide if you want to take part. You can take time to think it over, and ask any further questions. Your decision will not affect your care and if you change

your mind you can withdraw from the interview at any time. As you will see below all interviews will be treated anonymously (not named or identified) and do not affect the care that you receive at all.

What do I have to do?

If you are interested in taking part please complete the *'consent to contact'* form, and please ensure you fill in your telephone number.

What happens next?

We want to speak to as many people as we can, but we might not be able to contact everyone. If we do contact you, a researcher from Newcastle University will contact you first, usually by telephone. They will answer any questions you have and agree a date and time with you to do the interview. This interview can be on the telephone or video call (whichever is more convenient for you and depending on COVID-19 guidance). Your interviewer will go through a consent form, over the phone. This is to show that you understand what the study is about, that you are happy to be interviewed and that you are happy for us to record the interview.

What will happen during the interview?

The interview will last approximately 60 minutes. The interviewer will ask some questions about your background and specifically about your thoughts on reducing the number of physical therapy and nebulised treatments after the start of the modulator drugs. The interviewer is a clinical PhD student at Newcastle University who is supervised by Dr Malcolm Brodlie, Consultant in Paediatric Respiratory Medicine, and is independent of the hospitals and your GP. The interview will be audio recorded.

Why do you record interviews?

We record the audio (sound) of the interviews as it is difficult to take notes of what people say, listen carefully and think all at the same time! After the interview the recording will be listened to carefully and every word that both you and the interviewer say will be typed down. This will be done by the researcher. We will then use this written record to help us remember what people said.

What will happen if I don't want to carry on with the interview study?

You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have. We need to manage your records in specific ways for the research to be reliable. This means that we won't be able to let you see or change the data we hold about you. You can find out more about how we use your information by asking one of the research team or the sponsors data protection officer

(details at the end of this document).

Will my taking part in the study be kept private?

Yes. We will need to use information from you for this research project. This information will include your name and contact details. People will use this information to do the research or to check your records to make sure that the research is being done properly. People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead. We will keep all information about you safe and secure. Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study.

Privately the researchers will also look at your records to note down essential clinical information, for example which medicines you are on, and what nebulisers and physiotherapy you do. This will also be noted down anonymously (not named or identified).

Any documents, recordings of your voice and interview transcripts (written version) will be kept securely at Newcastle University. We will remove anything from the transcription that could identify you. We may use quotes from your interview in publications and presentations but will take care to ensure that you or other people mentioned in your interviews cannot be identified when we do this. Anonymised (not named or identified) transcripts (written out versions) will be kept to help future research. This may include sharing the transcripts with other researchers who are interested in doing their own analyses of the data.

If you tell us something in the interview that makes the researcher think either you or someone else is at risk of harm, we may need to tell someone else. We would tell you before we did this.

Are there any benefits to helping with the interview?

Although there are no direct benefits to you personally, we hope that you find being interviewed an interesting experience. Your interview will be part of research that may help us better care for children and young people with cystic fibrosis.

Are there any disadvantages to helping with the interview?

The main disadvantage is the time it will take; an interview usually lasts about an hour. It may involve talking about personal things relating to treatments, which you may find a bit difficult, but our interviewer is well trained and used to hearing these kinds of things

Has anyone reviewed this study?

All research carried out in the NHS is looked at by an independent group of people called a Research Ethics Committee. This is to protect your safety, rights, dignity and respect.

How is the study being funded?

This study is being funded as part of an academic PhD project.

What will happen to the results of the study?

Anonymised (not named or identified) results of the research will be kept by the research team for 5 years after the study completion. Findings from the study may be published in medical journals. This may include direct quotations. However, personal or identifiable information about you or anyone mentioned in your interview will not be available from what is written.

Will I learn the results of the study?

If you are interested, we can give you a summary of the results after the study has finished. Please let the research team know if you would like to receive this.

Where can I get more information?

If you require any further information regarding the study, you can contact the investigators who are based at the Great North Children's Hospital.

What if there are any problems?

If you have any concerns about any aspect of the study, you can speak to any of the researchers. If you prefer to raise your concerns with someone not involved in your care, you can contact the Patient Advice and Liaison Service (PALS). This service is private and can be contacted on Freephone: 0800 032 0202 Alternatively, if you wish to make a formal complaint you can contact the Patient Relations Department through any of the details below: Telephone: 0191 223 1382 or 0191 223 1454 Email: nuth.patient.relations@nhs.net Address: Patient Relations Department The Newcastle upon Tyne Hospitals NHS Foundation Trust The Freeman Hospital Newcastle upon Tyne NE7 7DN. Newcastle University have provided indemnity for the design, management and conduct of the study.

Contacts

Research contact

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Thank you for reading this information sheet

The Newcastle upon Tyne Hospitals NHS
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Newcastle University

Qualitative study to explore the impact of modulator drugs on attitudes and opinions towards physiotherapy and nebulised treatment in children and young people with cystic fibrosis – the TEMPO study

This study is part of Ph.D. project

This information sheet is intended for healthcare professionals who are involved in the care of children and young people with cystic fibrosis

Investigators: Mrs Maryam Almulhem, PhD student at Newcastle University.
Dr Malcolm Brodlie, Consultant in Paediatric Respiratory Medicine, Great North Children's Hospital.

Thank you for agreeing to be contacted about taking part in an interview. This is completely optional. Before you decide whether to take part, it is important for you to understand why the research is being done and what it will involve. Please take the time to read the following information carefully. One of our team can go through this information with you and answer any questions you may have.

Why are you interviewing people?
We would like to hear people's views and experiences of the impact of CFTR modulator therapy and the need for and adherence with physiotherapy and nebulised treatments. The information we receive will help us learn more about the impact of treatment with modulator drugs on treatment burden, with special focus on chest physiotherapy and nebulisers, that will inform approaches to CF care in the post-modulator era and the most relevant questions to be addressed by future clinical research.

Why have I been invited?
You are being invited to take part in this study because you have experience of caring for a children with cystic fibrosis on CFTR modulator drugs.

Do I have to take part?
No. It is up to you and to decide if you want to take part. You can take time to think it over, and ask any further questions. You can withdraw from the interview at any time.

What do I have to do?
If you are interested in taking part, please complete the *'consent to contact form'*, making sure you fill in your telephone number.

What happens next?
We want to speak to as many people as we can, but we might not be able to contact

everyone. If we do contact you, a researcher from Newcastle University will contact you first, usually by telephone. They will answer any questions you have and agree a date and time with you to do the interview. This interview can be on the telephone or video call or in person (whichever is more convenient for you and depending on COVID-19 restrictions). Your interviewer will go through a consent form, over the phone or in person. This is to show that you understand what the study is about, that you are happy to be interviewed and that you are happy for us to record the interview.

What will happen during the interview?
The interview will last approximately 60 minutes. The interviewer will ask some questions about your background and specifically about your thoughts on de-escalation of physiotherapy treatment after children are established on CFTR modulators. The interviewer is employed by Newcastle University and is independent of the clinical team, but is supervised by Dr Malcolm Brodlie. The interview will be audio recorded.

Why do you record interviews?
We record the interviews as it is difficult to take notes of what people say, listen carefully and think all at the same time! After the interview the recording will be listened to carefully and every word that both you and the interviewer say will be typed down. This will be done by the interviewer themselves. We will then use this written record to help us remember what people said.

What will happen if I don't want to carry on with the interview study?
You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have. We need to manage your records in specific ways for the research to be reliable. This means that we won't be able to let you see or change the data we hold about you. You can find out more about how we use your information by asking one of the research team or the sponsors data protection officer (details at the end of this document).

Will my taking part in the study be kept confidential?
Yes.
We will need to use information from you for this research project. This information will include your name, clinical role in the cystic fibrosis team and contact details. People will use this information to do the research or to check your records to make sure that the research is being done properly. People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead. We will keep all information about you safe and secure. Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study.
Any documents, recordings of your voice and interview transcripts (written out version) will be kept securely at Newcastle University. We will remove anything from the transcription that could identify you (anonymised). We may use quotes from your

interview in publications and presentations but will take care to ensure that you, or other people mentioned in your interviews cannot be identified when we do this. Anonymised transcripts (written out versions) will be kept to help future research. This may include sharing the transcripts with other researchers who are interested in doing their own analyses of the data.
If you tell us something in the interview that makes the researcher, think either you or someone else is at risk of harm, we may need to tell someone else. We would tell you before we did this.

Are there any benefits to helping with the interview?
Although there are no direct benefits to you personally, we hope that you find being interviewed an interesting experience. Your interview will be part of research that may help us better care for children with cystic fibrosis.

Are there any disadvantages to helping with the interview?
The main disadvantage is the time it will take; an interview usually lasts about an hour. The interview will cover cystic fibrosis care in general and will not be about specific patients and is unlikely to touch on upsetting or sensitive topics.

Has anyone reviewed this study?
All research carried out in the NHS is looked at by an independent group of people called a Research Ethics Committee. This is to protect your safety, rights, dignity, and respect.

How is the study being funded?
This study is being funded as part of a PhD project.

What will happen to the results of the study?
Anonymised results of the research will be kept by the research team for 5 years after the study completion. Findings from the study may be published in medical journals. This may include direct quotations. However, personal or identifiable information about you or anyone mentioned in your interview will not be available from what is written.

Will I learn the results of the study?
If you are interested, we can give you a copy of the results after the study has finished. Please let the research team know if you would like to receive this.

Where can I get more information?
If you require any further information regarding the study, you can contact the investigators who are based at the Great North Children's Hospital.

What if there are any problems?
If you have any concerns about any aspect of the study, you can speak to any of the researchers. If you prefer to raise your concerns with someone not involved in your care,

you can contact the Patient Advice and Liaison Service (PALS). This service is confidential and can be contacted on Freephone: 0800 032 0202 Alternatively, if you wish to make a formal complaint you can contact the Patient Relations Department through any of the details below: Telephone: 0191 223 1382 or 0191 223 1454 Email: nuth.patient.relations@nhs.net Address: Patient Relations Department The Newcastle upon Tyne Hospitals NHS Foundation Trust The Freeman Hospital Newcastle upon Tyne NE7 7DN. Newcastle University have provided indemnity for the design, management and conduct of the study.

Contacts

Research Contacts

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The Newcastle upon Tyne Hospitals NHS
NHS Foundation Trust

THE great north CHILDREN'S HOSPITAL

Newcastle University

Qualitative study to explore the impact of modulator drugs on attitudes and opinions towards physiotherapy and nebulised treatment in children and young people with cystic fibrosis - the TEMPO study

This study is part of Ph.D. project

This information sheet is intended for the parents/guardians of children with cystic fibrosis

Investigators: Dr Malcolm Brodlie, Consultant in Paediatric Respiratory Medicine, Great North Children's Hospital,
Mrs Maryam Almulhem, PhD student at Newcastle University.

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Why are you interviewing people?

We would like to hear people's views and experiences of the impact of receiving CFTR modulator drugs (for example Orkambi, Symkevi or Kaftrio) and the need for and attitudes towards other established treatments, especially physiotherapy and nebulisers. The information we receive will help us learn more about the impact of treatment with modulator drugs on the burden of other treatments and this will inform approaches to cystic fibrosis care moving forwards in the post-modulator era and the most relevant questions to be addressed by future clinical research.

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Why have I been invited?

You are being invited to take part in this study because you have experience of caring for a child with cystic fibrosis who is receiving a CFTR modulator drug.

Do I have to take part?

No. It is up to you to decide if you want to take part. You can take time to think it over, and ask any further questions. Your decision will not affect your child's care and if you change your mind you can withdraw from the interview at any time. As you will see below all interviews will be treated anonymously (not named or identified) and do not affect the care that your child receives at all.

What do I have to do?

If you are interested in taking part please complete the *'consent to contact'* form, and please ensure you fill in your telephone number.

What happens next?

We want to speak to as many people as we can, but we might not be able to contact everyone. If we do contact you, a researcher from Newcastle University will contact you first, usually by telephone. They will answer any questions you have and agree a date and time with you to do the interview. This interview can be on the telephone or video call (whichever is more convenient for you). Your interviewer will go through a consent form, over the phone. This is to show that you understand what the study is about, that you are happy to be interviewed and that you are happy for us to record the interview.

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The interview will last approximately 60 minutes. The interviewer will ask some questions about your background and specifically about your thoughts on reducing the number of physical therapy and nebulised treatments after the start of the modulator drugs. The interviewer is a clinical PhD student at Newcastle University who is supervised by Dr Malcolm Brodlie, Consultant in Paediatric Respiratory Medicine, and is independent of the hospitals and your GP. The interview will be audio recorded.

Why do you record interviews?

We record the audio (sound) of the interviews as it is difficult to take notes of what people say, listen carefully and think all at the same time! After the interview the recording will be listened to carefully and every word that both you and the interviewer say will be typed down. This will be done by the researcher. We will then use this written record to help us remember what people said.

What will happen if I don't want to carry on with the interview study?

You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have. We need to manage your records in specific ways for the research to be reliable. This means that we won't be able to let you see or change the data we hold about you. You can find out more about how we use your information by asking one of the research team or the sponsors data protection officer (details at the end of this document).

Will my taking part in the study be kept private?

Yes.

We will need to use information from you for this research project. This information will

include your name and contact details. People will use this information to do the research or to check your records to make sure that the research is being done properly. People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead. We will keep all information about you safe and secure. Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study.

Privately the researchers will also look at your child's records to note down essential clinical information, for example which medicines they are on, what nebulisers and physiotherapy they do. This will also be noted down anonymously (not named or identified).

Any documents, recordings of your voice and interview transcripts (written out version) will be kept securely at Newcastle University. We will remove anything from the transcription that could identify you (anonymised). We may use quotes from your interview in publications and presentations but will take care to ensure that you, your child, or other people mentioned in your interviews cannot be identified when we do this. Anonymised (not named or identified) transcripts (written out versions) will be kept to help future research. This may include sharing the transcripts with other researchers who are interested in doing their own analyses of the data.

If you tell us something in the interview that makes the researcher think either you or someone else is at risk of harm, we may need to tell someone else. We would tell you before we did this.

Are there any benefits to helping with the interview?

Although there are no direct benefits to you personally, we hope that you find being interviewed an interesting experience. Your interview will be part of research that may help us better care for children with cystic fibrosis.

Are there any disadvantages to helping with the interview?

The main disadvantage is the time it will take; an interview usually lasts about an hour. Talking about personal things, which you may find a bit difficult, but our interviewer is well trained and used to hearing these kinds of things

Has anyone reviewed this study?

All research carried out in the NHS is looked at by an independent group of people called a Research Ethics Committee. This is to protect your safety, rights, dignity and respect.

How is the study being funded?

This study is being funded as part of an academic PhD project.

What will happen to the results of the study?

Anonymised (not named or identified) results of the research will be kept by the research team for 5 years after the study completion. Findings from the study may be published in medical journals. This may include direct quotations. However, personal or identifiable information about you or anyone mentioned in your interview will not be available from what is written.

Will I learn the results of the study?

If you are interested, we can give you a summary of the results after the study has finished. Please let the research team know if you would like to receive this.

Where can I get more information?

If you require any further information regarding the study, you can contact the investigators who are based at the Great North Children's Hospital.

What if there are any problems?

If you have any concerns about any aspect of the study, you can speak to any of the researchers. If you prefer to raise your concerns with someone not involved in your care, you can contact the Patient Advice and Liaison Service (PALS). This service is private and can be contacted on Freephone: 0800 032 0202 Alternatively, if you wish to make a formal complaint you can contact the Patient Relations Department through any of the details below: Telephone: 0191 223 1382 or 0191 223 1454 Email: nuth.patient.relations@nhs.net Address: Patient Relations Department The Newcastle upon Tyne Hospitals NHS Foundation Trust The Freeman Hospital Newcastle upon Tyne NE7 7DN. Newcastle University have provided indemnity for the design, management and conduct of the study.

Contacts

Research Contacts:

Dr Malcolm Brodlie
Consultant in Paediatric Respiratory Medicine
Level 3, Clinical Resource Building
Queen Victoria Road
Newcastle upon Tyne
NE1 4LP
Telephone 0191 2825089

Mrs Maryam Almulhem
Medical school, Newcastle University
Framlington place
Newcastle upon Tyne
NE2 4HH
email: m.m.s.almulhem2@ncl.ac.uk

Appendix B. Consent to contact form.

Qualitative study to explore the impact of modulator drugs on attitudes and opinions towards physiotherapy and nebulised treatment in children and young people with cystic fibrosis- the TEMPO study

Agreement to contact form

If you are interested in taking part in the study and wish to discuss your involvement further or indeed wish to go ahead and arrange for an interview, we need your agreement to contact you (ideally by telephone).

By completing the form below you are not agreeing to take part in the interview. You are only agreeing to being contacted by one of our researchers.

Name: .....

Address: .....

.....

.....

Post code: .....

Telephone: .....

Please give the number where you would prefer to be contacted (Home, Work, Mobile)

When is the best time for us to telephone you? .....

I agree to being contacted by one of the researchers involved in the above study in order to discuss my further involvement and/ or to arrange a suitable appointment for an interview

_____	_____	_____
Name	Date	Signature

Please return this form to us using the stamped addressed envelope included.

Thank you for taking the time to read through this information and considering taking part in this study.

Appendix C. Invitation letter

Malcolm Brodlie

Honorary Consultant in Paediatric Respiratory Medicine

Level 3, Clinical Resource Building

Great North Children's Hospital

Royal Victoria Infirmary

Queen Victoria Road

Newcastle upon Tyne

NE1 4LP

United Kingdom

Secretary: Sandy Burlison ☎ +44 191 2820807

Dear

I am writing to inform you about a research study that you may be interested in. This study will form part of a PhD degree, awarded by Newcastle University. The student involved is Mrs Maryam Almulhem who is working with Dr Malcolm Brodlie.

Along with this letter, please find attached an information sheet that will tell you about the research study, what it would involve and how to take part in the research if you wish. We are interested in listening to people's views on the impact of CFTR modulator drugs (e.g. Kaftrio) on physiotherapy and nebulised treatments.

If you are interested in being involved with the research, please complete the enclosed form, and return it to us in the stamped, addressed envelope enclosed. We will then contact you to arrange a convenient time for your interview, which will be done by a videocall.

Alternatively, if you have any questions you can get in touch with Maryam Almulhem and let her know the best time to contact you by either:

- Mobile number 07361421377.
- E-mailing on (m.m.s.almulhem2@ncl.ac.uk)

If the recruitment for this study does not go as planned and we have not heard from you, we may contact you again by letter to see if you are interested in the study. If you are not interested in taking part or do not wish to be contacted, please let us know.

If you have any questions about the research, do not hesitate to contact Malcolm Brodlie or the research team.

Many thanks for considering this

Malcolm Brodlie

Honorary Consultant in Paediatric Respiratory Medicine

Maryam Almulhem

PhD Student

The Newcastle upon Tyne Hospitals NHS Foundation Trust | THE great north CHILDREN'S HOSPITAL | Newcastle University

Qualitative study to explore the impact of modulator drugs on attitudes and opinions towards physiotherapy and nebulised treatment in children and young people with cystic fibrosis – the TEMPO study

Telephone or Videocall Interview Assent - Checklist and Script for Children 11-15 years

TO BE COMPLETED BY RESEARCHER: researcher to initial chosen boxes and sign the form

Participant identification number:
Researcher initials:

SECTION 1 – BEFORE recording is started

Researcher to make introductions and follow the points below **BEFORE** the recorder is switched on:

Researcher to initial box when complete:

1	Check the patient has seen and read the Patient Information Sheet version _____ dated _____ (please complete)	
2	Check with the patient if they have any questions	
3	Ask the patient if they are happy to be interviewed for this study	
4	Check they understand that the interview will be audio recorded	

SECTION 2 – AUDIO-RECORDER SWITCHED ON

Researcher to switch on the recorder and explain to the patient and/or parent/guardian:

"What I'll now do is to read a series of questions and ask you to say whether you agree with each one by saying yes or no. There are six questions. Are you ok for me to continue?"

CONTINUE TO PAGE 2

Researcher to initial box when complete:

1.	Ask ''have you read the Participant Information Sheet version _____ dated _____?''	
2.	Ask "did you understand everything in the information sheet?"	
3.	Ask "have you had the chance to ask questions about the study and are you happy with the answers given?"	
4.	Ask "do you understand that you do not have to take part in this interview and you can ask to stop the interview at any time?"	
5.	Ask "do you agree to take part in an interview and for me to audio record the interview?"	
6.	Explain "Thank you, that's the last consent question.''	

- **SWITCH OFF RECORDER**

Name of person taking consent	Date	Signature

The Newcastle upon Tyne Hospitals NHS Foundation Trust | THE great north CHILDREN'S HOSPITAL | Newcastle University

Qualitative study to explore the impact of modulator drugs on attitudes and opinions towards physiotherapy and nebulised treatment in children and young people with cystic fibrosis – the TEMPO study

Telephone or Videocall Interview Consent – Checklist and Script for 16 -18 years old

TO BE COMPLETED BY RESEARCHER: researcher to initial chosen boxes and sign the form

Participant identification number:
Researcher initials:

SECTION 1 – BEFORE recording is started

Researcher to make introductions and follow the points below **BEFORE** the recorder is switched on:

Researcher to initial box when complete:

1	Check the patient has seen and read the Patient Information Sheet version _____ dated _____ (please complete)	
2	Check with the patient if they have any questions	
3	Ask the patient if they are happy to be interviewed for this study	
4	Check they understand that the interview will be audio recorded	

SECTION 2 – AUDIO-RECORDER SWITCHED ON

Researcher to switch on the recorder and explain to the patient and/or parent/guardian:

"What I'll now do is to read a series of questions and ask you to say whether you agree with each one by saying yes or no. There are eight questions. Are you ok for me to continue?"

CONTINUE TO PAGE 2

		Researcher to initial box when complete:
1.	Ask ''have you read the Participant Information Sheet version _____ dated _____?''	
2.	Ask "did you understand everything in the information sheet?"	
3.	Ask "have you had the chance to ask questions about the study and are you happy with the answers given?"	
4.	Ask "do you understand that you do not have to take part in this interview and you can ask to stop the interview at any time?"	
5.	Ask "do you agree to take part in an interview and for me to audio record the interview?"	
6.	Ask "Do you understand that after the study, anonymised extracts from the interview will be kept to help future research and may be shared with other researchers and organisations? This means that data may also be used for purposes not related to this study, but it will not be possible to identify you from these data."	
7.	Ask "Do you agree to the information provided in the interview being managed by Newcastle University and that this consent form and data collected during the interview may be looked at by responsible individuals from The Newcastle upon Tyne Hospitals NHS Foundation Trust or its representatives or from ethical authorities"	
8.	Explain "Thank you, that's the last consent question.''	

- **SWITCH OFF RECORDER**

Name of person taking consent	Date	Signature

Qualitative study to explore the impact of modulator drugs on attitudes and opinions towards physiotherapy and nebulised treatment in children and young people with cystic fibrosis – the TEMPO study

TELEPHONE or VIDEOCALL INTERVIEW CONSENT – CHECKLIST AND SCRIPT

TO BE COMPLETED BY RESEARCHER: researcher to initial chosen boxes and sign the form

Participant identification number:
Researcher initials:

SECTION 1 – BEFORE recording is started

Researcher to make introductions and follow the points below **BEFORE** the recorder is switched on:

Researcher to initial box when complete:

1	Check the patient has seen and read the Patient Information Sheet version _____ dated _____ (please complete)	
2	Check with the patient if they have any questions	
3	Ask the patient if they are happy to be interviewed for this study	
4	Check they understand that the interview will be audio recorded	

SECTION 2 – AUDIO-RECORDER SWITCHED ON

Researcher to switch on the recorder and explain to the patient and/or parent/guardian:

"What I'll now do is to read a series of questions and ask you to say whether you agree with each one by saying yes or no. There are six questions. Are you ok for me to continue?"

CONTINUE TO PAGE 2

1.	Ask ''have you read the Participant Information Sheet version _____ dated _____?''	
2.	Ask "did you understand everything in the information sheet?"	
3.	Ask "have you had the chance to ask questions about the study and are you happy with the answers given?"	
4.	Ask "do you understand that you do not have to take part in this interview and you can ask to stop the interview at any time?"	
5.	Ask "do you agree to take part in an interview and for me to audio record the interview?"	
6.	Ask "Do you understand that after the study, anonymised extracts from the interview will be kept to help future research and may be shared with other researchers and organisations? This means that data may also be used for purposes not related to this study, but it will not be possible to identify you from these data."	
7.	Ask "Do you agree to the information provided in the interview being managed by Newcastle University and that this consent form and data collected during the interview may be looked at by responsible individuals from The Newcastle upon Tyne Hospitals NHS Foundation Trust or its representatives or from ethical authorities"	
8.	Explain "Thank you, that's the last consent question.''	

Researcher to initial box when complete:

- **SWITCH OFF RECORDER**

_____ _____ _____

Name of person taking consent | Date | Signature

The Newcastle upon Tyne Hospitals NHS Foundation Trust | THE great north CHILDREN'S HOSPITAL | Newcastle University

Qualitative study to explore the impact of modulator drugs on attitudes and opinions towards physiotherapy and nebulised treatment in children and young people with cystic fibrosis – the TEMPO study

TELEPHONE or VIDEOCALL INTERVIEW CONSENT – CHECKLIST AND SCRIPT

TO BE COMPLETED BY RESEARCHER: researcher to initial chosen boxes and sign the form

Participant identification number:

Researcher initials:

SECTION 1 – BEFORE recording is started

Researcher to make introductions and follow the points below **BEFORE** the recorder is switched on:

Researcher to initial box when complete:

1	Check the patient has seen and read the Healthcare Professional Participant Information Sheet version _____ dated _____ (please complete)	
2	Check with the healthcare professional if they have any questions	
3	Ask the healthcare professional if they are happy to be interviewed for this study	
4	Check they understand that the interview will be audio recorded	

SECTION 2 – AUDIO-RECORDER SWITCHED ON

Researcher to switch on the recorder and explain to the healthcare professional:

"What I'll now do is to read a series of questions and ask you to say whether you agree with each one by saying yes or no. There are six questions. Are you ok for me to continue?"

CONTINUE TO PAGE 2

Researcher to initial box when complete:

1.	Ask "have you read the Healthcare Professionals Participant Information Sheet version _____ dated _____?"	
2.	Ask "did you understand everything in the information sheet?"	
3.	Ask "have you had the chance to ask questions about the study and are you happy with the answers given?"	
4.	Ask "do you understand that you do not have to take part in this interview and you can ask to stop the interview at any time?"	
5.	Ask "do you agree to take part in an interview and for me to audio record the interview?"	
6.	Ask "Do you understand that after the study, anonymised extracts from the interview will be kept to help future research and may be shared with other researchers and organisations? This means that data may also be used for purposes not related to this study, but it will not be possible to identify you from these data."	
7.	Ask "Do you agree to the information provided in the interview being managed by Newcastle University and that this consent form and data collected during the interview may be looked at by responsible individuals from The Newcastle upon Tyne Hospitals NHS Foundation Trust or its representatives or from ethical authorities"	
8.	Ask "do you agree to be contacted about a second follow up interview in the future (only if this is required to clarify any points)?"	
9.	Explain "Thank you, that's the last consent question."	

- **SWITCH OFF RECORDER**

_____	_____	_____
Name of person taking consent	Date	Signature

Participant Identification Number:

HEALTHCARE PROFESSIONAL CONSENT FORM

Qualitative study to explore the impact of modulator drugs on attitudes and opinions towards physiotherapy and nebulised treatment in children and young people with cystic fibrosis – the TEMPO study

	*Please **initial** each box if you agree*
1. I confirm that I have read and understood the Healthcare Professional Participant Information Sheet version ..... dated ..... for the above study and have had the opportunity to consider the information and to contact or be contacted by the research team to discuss any queries	
2. I understand that I do not have to take part in this project and do not have to give a reason for declining participation. I am free to withdraw my consent at any time. My decision whether to participate or not will not affect clinical relationships or legal rights	
3. I agree to the information I provide in the interview to be audio recorded and used for research purposes, and that anonymised parts of my interview may be published or presented	
4. I understand that the information collected may be used to support other research in the future, and may be shared anonymously with other researchers	
5. I agree to the information provided in the interview being managed by Newcastle University and that this consent form and data collected during the interview may be looked at by responsible individuals from The Newcastle upon Tyne Hospitals NHS Foundation Trust or its representatives or from ethical authorities	
6. I agree to take part in the interview	

----------	----------	----------
Name of participant	Date	Signature
----------	----------	----------
Name of person consenting	Date	Signature

Appendix E. Interview guideline

Young people with cystic fibrosis aged 12-18 years on Kaftrio.

We are interested in how you look after your CF and how you feel about the treatments after starting on Kaftrio (ETI).

A. <u>Before being on a ETI drug:</u>

1. what was your daily treatment routine?

Prompts:

- How did you feel about this routine especially physiotherapy and nebuliser?
- Who did you turn to for help? Example.

2. How would you describe your daily life (e.g. going to school, playing sport, going out, travel)?
3. What was the worst CF treatment in your opinion? Why?

B. <u>After starting on ETI:</u>

4. What are the changes you notice after starting ETI?

Prompts:

- symptoms
- treatments
- complaints
- adherence
- expectations
- What's the reason behind this change?
- How did it make you feel when you see these changes?

5. How would you describe the impact of this treatment on your daily (social) life (e.g. going to school, playing sport, going out, travel)?

C. <u>Simplifying the treatment</u>.

6. What do you think about the idea of doing less physiotherapy after starting ETI?

Prompts:

- Do you think you still need to do physiotherapy? Why?
- If you could stop one nebuliser, what would it be?

D. <u>Conclusion.</u>

7. What questions would you like future research studies to focus on to help CF population in the future?
8. To me the main points from this interview have been (Summarise the main points from the interview) Have I missed anything?
9. Is there anything else that you would like to comment on about the modulators, load of treatment, physiotherapy or nebulisers that we haven't discussed today?

2

Parents or guardians of children or young people with CF:

A. <u>Before starting on ETI:</u>

1. Can you talk me through what a typical day in your child's life involved?

Prompts:

- What is your role when it comes to physiotherapy for your child? Does anyone else assist you with caretaking?
- What was the worst treatment in your opinion?

2. Could you describe the impact of this on your child's day-to-day life (going to school, playing, travel)?

B. <u>After starting on ETI:</u>

3. What are the things that changed after starting ETI in your child's life?

Prompts:

- symptoms
- treatments
- complaints
- adherence
- social life
- What's the reason behind this change?
- How did it make you feel when you see these changes?

4. How do you currently feel about the level of support you have now in caring for your child?

C. <u>Simplifying the treatment</u>.

5. How do you feel about the idea of simplifying the physiotherapy after starting ETI?

Prompts:

- What do you expect after ETI in terms of physiotherapy?
- If you could stop one nebuliser, what would it be?

D. <u>Conclusion.</u>

6. What questions would you like future research studies in this area to address?
7. To me the main points from this interview have been (Summarise the main points from the interview) Have I missed anything?
8. Is there anything else that you would like to comment on about the modulators, burden of treatment, physiotherapy or nebulisers that we haven't discussed today?

Healthcare professionals

A. <u>Before the introduction of ETI:</u>

1. What is your role on the CF team? How long have you been working with CF?

Prompts:

- In your view, how important is physiotherapy for CF patients?
- How do you help CF patients to manage their treatment? Especially physiotherapy.

B. <u>After the introduction of ETI:</u>

2. What is the difference you notice after the ETI on CF practice?

Prompts:

- Importance of physiotherapy
- Dealing with patients/family
- Challenges

3. What's the impact of Kaftrio on the workload?

C. <u>Simplifying the treatment</u>

4. How do you feel about simplifying physio treatment?

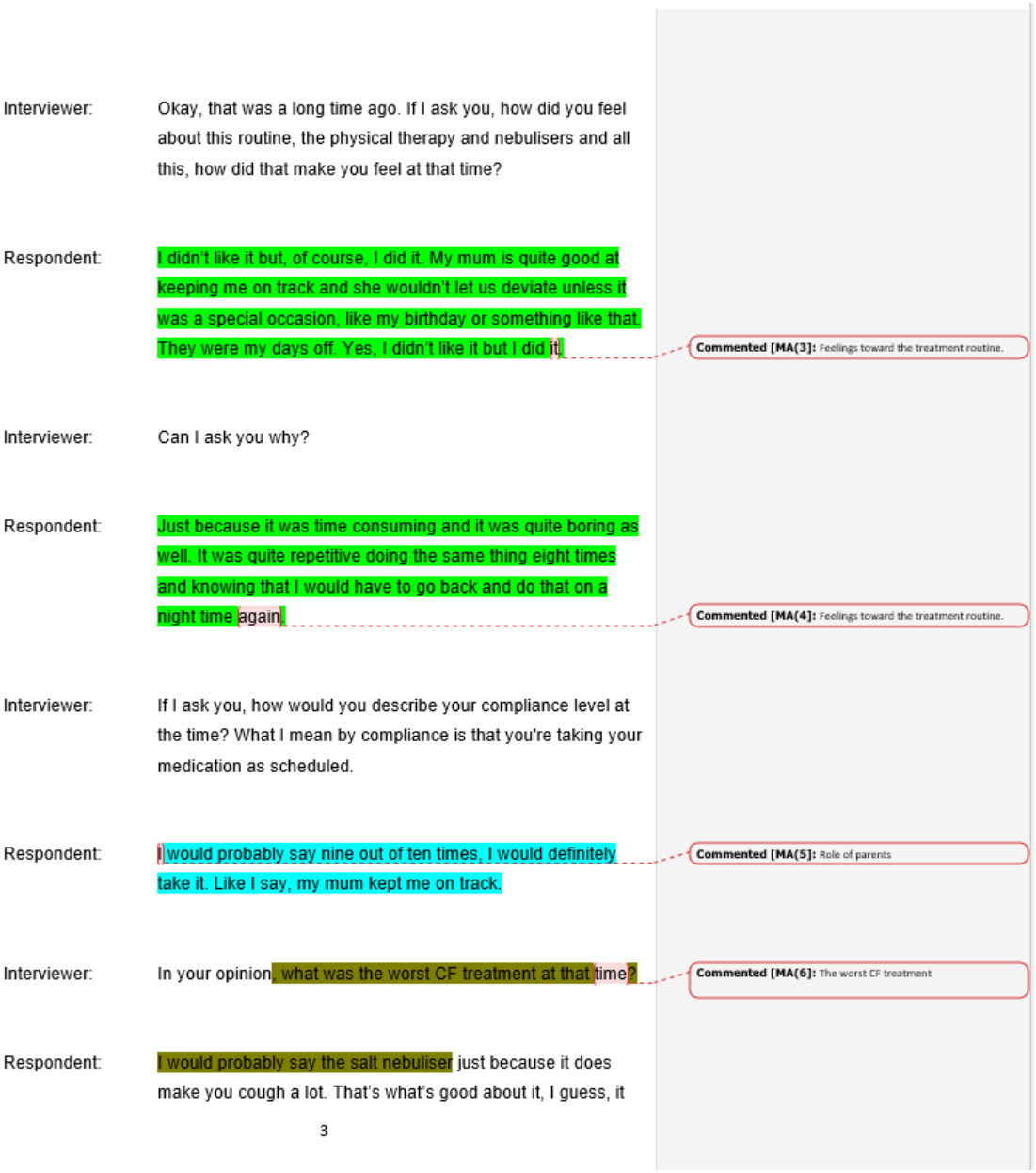
Prompts:

- Advantages/disadvantages?
- What type of physio treatment do you think can be stopped? Nebulisers?

D. <u>Conclusion:</u>

5. What questions would you like future research studies to address in this area?
6. To me the main points from this interview have been (Summarise the main points from the interview) Have I missed anything?
7. Is there anything else that you would like to comment on about the modulators, burden of treatment, physiotherapy or nebulisers that we haven't discussed today?

Appendix F. Examples of transcription



Interviewer: Okay, that was a long time ago. If I ask you, how did you feel about this routine, the physical therapy and nebulisers and all this, how did that make you feel at that time?

Respondent: I didn't like it but, of course, I did it. My mum is quite good at keeping me on track and she wouldn't let us deviate unless it was a special occasion, like my birthday or something like that. They were my days off. Yes, I didn't like it but I did it.

Commented [MA(3]: Feelings toward the treatment routine.

Interviewer: Can I ask you why?

Respondent: Just because it was time consuming and it was quite boring as well. It was quite repetitive doing the same thing eight times and knowing that I would have to go back and do that on a night time again.

Commented [MA(4]: Feelings toward the treatment routine.

Interviewer: If I ask you, how would you describe your compliance level at the time? What I mean by compliance is that you're taking your medication as scheduled.

Respondent: I would probably say nine out of ten times, I would definitely take it. Like I say, my mum kept me on track.

Commented [MA(5]: Role of parents

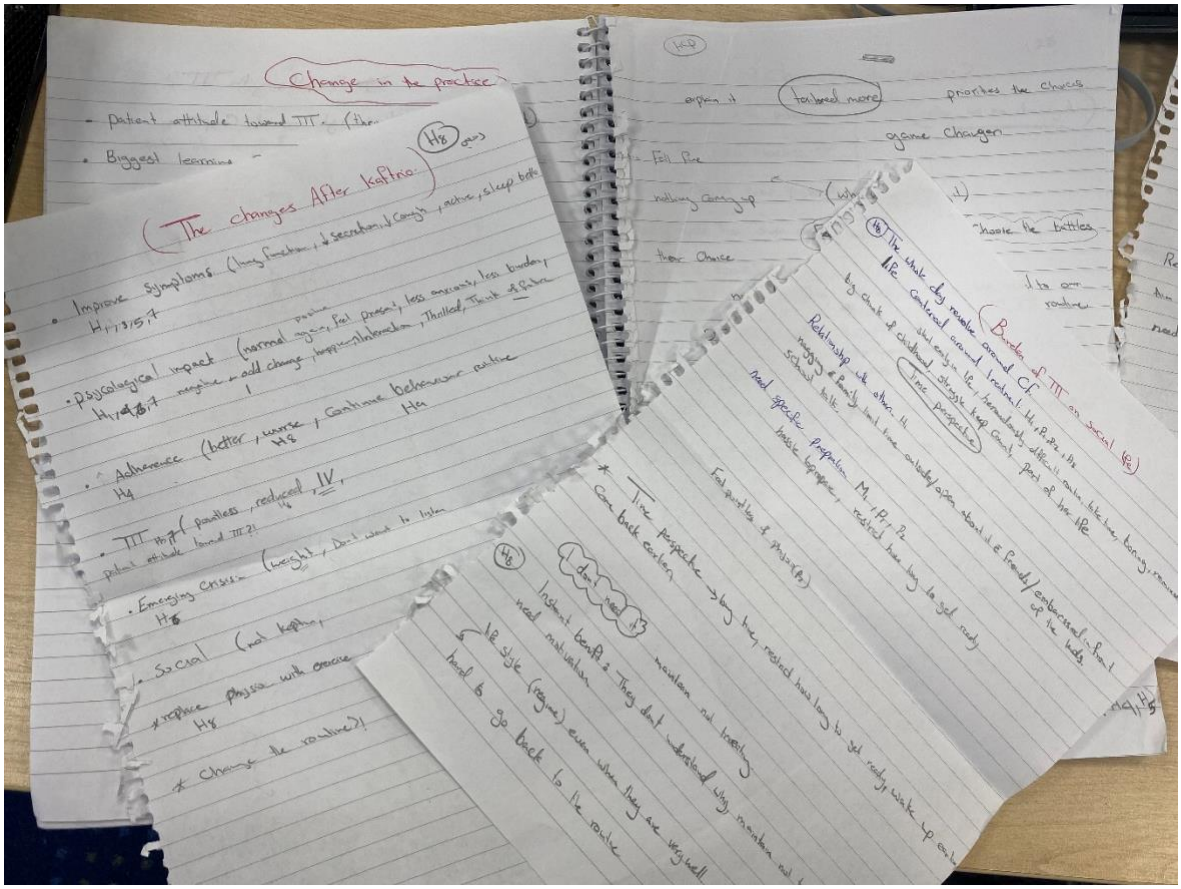
Interviewer: In your opinion, what was the worst CF treatment at that time?

Commented [MA(6]: The worst CF treatment

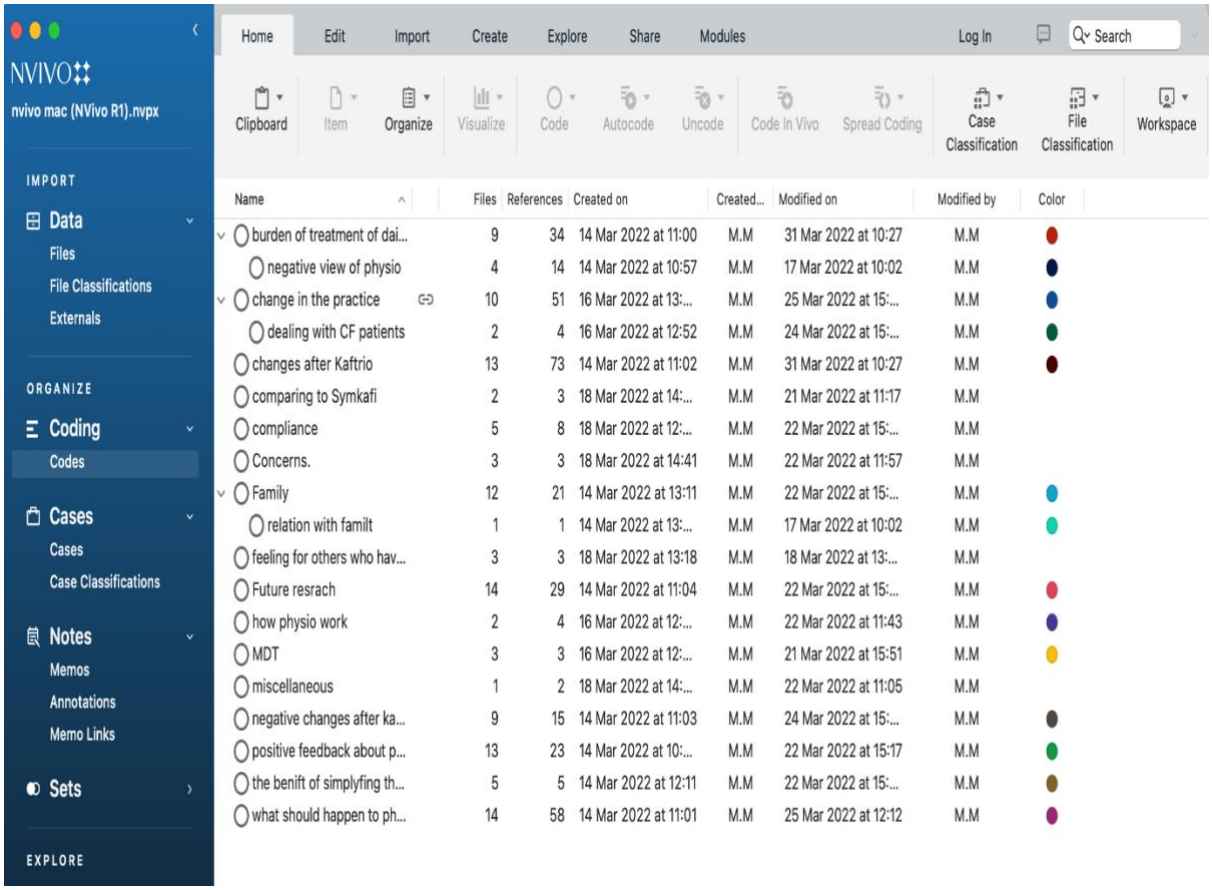
Respondent: I would probably say the salt nebuliser just because it does make you cough a lot. That's what's good about it, I guess, it

3

Appendix G. Initial Coding using notes.



Appendix H. NVIVO coding



Name	Files	References	Created on	Created...	Modified on	Modified by	Color
burden of treatment of dai...	9	34	14 Mar 2022 at 11:00	M.M	31 Mar 2022 at 10:27	M.M	
negative view of physio	4	14	14 Mar 2022 at 10:57	M.M	17 Mar 2022 at 10:02	M.M	
change in the practice	10	51	16 Mar 2022 at 13:...	M.M	25 Mar 2022 at 15:...	M.M	
dealing with CF patients	2	4	16 Mar 2022 at 12:52	M.M	24 Mar 2022 at 15:...	M.M	
changes after Kaftrio	13	73	14 Mar 2022 at 11:02	M.M	31 Mar 2022 at 10:27	M.M	
comparing to Symkafi	2	3	18 Mar 2022 at 14:...	M.M	21 Mar 2022 at 11:17	M.M	
compliance	5	8	18 Mar 2022 at 12:...	M.M	22 Mar 2022 at 15:...	M.M	
Concerns.	3	3	18 Mar 2022 at 14:41	M.M	22 Mar 2022 at 11:57	M.M	
Family	12	21	14 Mar 2022 at 13:11	M.M	22 Mar 2022 at 15:...	M.M	
relation with familt	1	1	14 Mar 2022 at 13:...	M.M	17 Mar 2022 at 10:02	M.M	
feeling for others who hav...	3	3	18 Mar 2022 at 13:18	M.M	18 Mar 2022 at 13:...	M.M	
Future resrach	14	29	14 Mar 2022 at 11:04	M.M	22 Mar 2022 at 15:...	M.M	
how physio work	2	4	16 Mar 2022 at 12:...	M.M	22 Mar 2022 at 11:43	M.M	
MDT	3	3	16 Mar 2022 at 12:...	M.M	21 Mar 2022 at 15:51	M.M	
miscellaneous	1	2	18 Mar 2022 at 14:...	M.M	22 Mar 2022 at 11:05	M.M	
negative changes after ka...	9	15	14 Mar 2022 at 11:03	M.M	24 Mar 2022 at 15:...	M.M	
positive feedback about p...	13	23	14 Mar 2022 at 10:...	M.M	22 Mar 2022 at 15:17	M.M	
the benift of simplyfing th...	5	5	14 Mar 2022 at 12:11	M.M	22 Mar 2022 at 15:...	M.M	
what should happen to ph...	14	58	14 Mar 2022 at 11:01	M.M	25 Mar 2022 at 12:12	M.M	

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

Dr Malcolm Brodlie
Level 3 Clinical Resource Building
Royal Victoria Infirmary
Newcastle upon Tyne
NE1 4LPN/A

Email: approvals@hra.nhs.uk
HCRW.approvals@wales.nhs.uk

04 October 2021

Dear Dr Brodlie

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**Qualitative study to explore the impact of modulator drugs on attitudes and opinions towards physiotherapy and nebulised treatment in children and young people with cystic fibrosis.**
IRAS project ID:	**299610**
REC reference:	**21/EM/0210**
Sponsor	**Newcastle Joint Research Office**

I am pleased to confirm that **HRA and Health and Care Research Wales (HCRW) Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

Please now work with participating NHS organisations to confirm capacity and capability, in line with the instructions provided in the "Information to support study set up" section towards the end of this letter.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?
HRA and HCRW Approval does not apply to NHS/HSC organisations within Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report (including this letter) have been sent to the coordinating centre of each participating nation. The relevant national coordinating function/s will contact you as appropriate.

Appendix J. Guidance on distress case

The Newcastle upon Tyne Hospitals NHS
NHS Foundation Trust

THE great north CHILDREN'S HOSPITAL

Newcastle University

Guidance that will be followed to identify and minimise any distress to participants during interviews.

Prior to commencing interviews:

There will be thorough preparation and discussion of the topics and questions between the student and supervisor to ensure there is awareness of any potential areas of distress that may be encountered.

Before conducting the first formal interview, the student will meet with their supervisor to discuss procedures that are in place in case a participant becomes distressed during an interview. The supervisor will also ensure the student feels prepared for the interview. The supervisor must be satisfied that the researcher is competent in conducting interviews before giving approval for the commencement of data collection.

Students will inform their supervisor when they are completing all interviews and in turn the supervisor will ensure the student has a means of contacting them when they are conducting interviews.

During the interviews:

At the beginning of the interview the student will remind the participants that they can stop the interview at any time, that they can choose not to answer questions, and that there are no right or wrong answers to questions (so there is no fear of 'saying the wrong thing').

Once the interview begins, the researcher will be required to be aware of any potential indications of distress (e.g., withdrawing, visible upset, declining to answer numerous questions, shifting in seat, looking away from the interviewer, asking for the interview to end) and should air on the side of caution in all instances. If there is even the slightest indication that participants might be distressed the student must immediately follow the procedure below:

1) The recording will be immediately stopped and the participant will be asked if they are ok. At this point the participant will be asked if they want to take a break/end the interview/continue talking – the participant's decision will be final. If the participant decides to take a break and continue with

the interview, confirmation will be sought that the participant is actually comfortable continuing and they will be reminded there is no penalty for withdrawing.

2) If the participant wishes to continue but remains distressed, the interviewer will make the decision to draw the interview to an end. At this point, the interviewer will commit to providing the participant with an opportunity to talk and ensure the participant is not visibly distressed when leaving the interview.

3) If the participant remains distressed and the researcher does not feel capable of managing the situation, they will contact the CI who will be available at all times during interviews by phone contact. Depending on the situation, the CI will either provide guidance to the student, speak directly to the participant over the phone, or make attempts to go and meet with the researcher and the participant.

4) If the participant has become distressed at any point in the interview, the student will ensure the participant has the contact details of the rest of the research and clinical team and remind them that they are free to contact any member of the research or clinical team if there is anything further they would like to discuss.

6) Following the interview, the student will debrief the interview with the CI and (if necessary) other senior members of the research team. A written record of the incident and the procedures followed will be made.

NHS
The Newcastle upon Tyne Hospitals
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REF: LOA/LR

24th November 2021

Sent by email only to: m.m.s.almulhem2@newcastle.ac.uk
Maryam Almulhem

Dear Maryam

Letter of access for research (Research Project No: 09939)

This letter confirms your right of access to conduct research through The Newcastle upon Tyne Hospitals NHS Foundation Trust for the purpose and on the terms and conditions set out below. This right of access commences on **22nd November 2021** and ends on **23 September 2023** unless terminated earlier in accordance with the clauses below.

Renewal of this agreement is your responsibility; if you wish to extend this study please apply by the **23 June 2023.**

You have a right of access to conduct such research as confirmed in writing in the letter of permission for research from this NHS organisation. Please note that you cannot start the research until the Principal Investigator for the research project has received a letter from us giving permission to conduct the project.

The information supplied about your role in research at The Newcastle upon Tyne Hospitals NHS Foundation Trust has been reviewed and you do not require an honorary research contract with this NHS organisation. We are satisfied that such pre-engagement checks as we consider necessary have been carried out.

You are considered to be a legal visitor to The Newcastle upon Tyne Hospitals NHS Foundation Trust premises. You are not entitled to any form of payment or access to other benefits provided by this NHS organisation to employees and this letter does not give rise to any other relationship between you and this NHS organisation, in particular that of an employee.

While undertaking research through The Newcastle upon Tyne Hospitals NHS Foundation Trust, you will remain accountable to your employer **Newcastle University** but you are required to follow the reasonable instructions of

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PROSPERO
International prospective register of systematic reviews

A systematic review of the definition of pulmonary exacerbations in people with cystic fibrosis

Citation

Maryam Almulhem, Chris Ward, Robert Gray, Malcolm Brodlie. A systematic review of the definition of pulmonary exacerbations in people with cystic fibrosis. PROSPERO 2020 CRD42020161128 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020161128

Review question

What definitions are used for pulmonary exacerbation in people of different age groups with cystic fibrosis (CF)?

Searches

The following electronic bibliographic databases: Embase, MEDLINE, Cochrane Library, Scopus, and CINAHL. There will be no restrictions on the type of study design, as a variety of study designs are required to meet the objective of this review. Reference tracking of screened studies will be also conducted to gather information from additional sources. Duplications will be removed and this process will be reported on PRISMA flow diagram.

(Definition* OR "defined as" OR "consensus statement") AND (Pulmonary exacerbation*) AND (cystic fibrosis) [1990-2019]/ AND [english]

Types of study to be included

There will be no restriction for type of study and study design eligible for inclusion in the review.

Condition or domain being studied [1 change]

People with cystic fibrosis who experience pulmonary exacerbation.

Participants/population [1 change]

The population being studied are people with cystic fibrosis. Inclusion criteria: Human studies reporting a definition for pulmonary exacerbation in people with cystic fibrosis in different age groups. Studies published in English between 1990-2019 with full text available. Exclusion criteria: Studies that do not report a definition for pulmonary exacerbation. Studies which were not published in English or where full text is not available.

Intervention(s), exposure(s) [1 change]

Cystic Fibrosis CF is one of the most common life-limiting genetic disorders worldwide affecting over 80, 000 children and adults. Although CF is a multisystem disorder, it is lung disease that is responsible for the vast majority of morbidity and mortality in people with CF. The natural history of CF lung disease involves exacerbations and periods of greater stability. We know that pulmonary exacerbations are important for a number of reasons:

• Clinically exacerbations may be associated with sustained reductions in lung function and adverse longer term clinical

outcomes

• For individual patients they are associated with increased symptoms and limitations on usual activities

• For society and health care providers they are associated with substantial financial cost.

Perhaps surprisingly, there is no agreed definition of what constitutes a pulmonary exacerbation in people with CF. The age of a person with CF is relevant and no single definition is likely to be appropriate across all ages. Adults with CF are more likely to experience severe exacerbations treated with IV antibiotics in hospital where as less severe exacerbations in children are often treated as an outpatient with oral antibiotics.

By reviewing definitions used in the literature we aim to develop a standardised definition for each age group for use in future clinical research and practice.

Comparator(s)/control

Not applicable

Context

No restrictions.

Main outcome(s)

Definition of pulmonary exacerbation in people with cystic fibrosis.

Measures of effect

None

Additional outcome(s)

None

Measures of effect

Not applicable

Data extraction (selection and coding) [1 change]

One reviewer will work on extracted data by title and abstract. Then two reviewers will work independently to extract data from the full text. Any disagreement will be resolved by discussion, and if required a third reviewer will be included. A piloting spreadsheet form will be designed to extract the following data: author(s) name, title, citation, year, country, setting, study objective, study design and type of publication, population characteristics (e.g. age), result(s), and definition of pulmonary exacerbation. This form will be used independently by the two reviewers to extract the data. Any discrepancies between the two reviewers will be fixed by discussion, and if needed a third reviewer's opinion will be considered.

Risk of bias (quality) assessment [1 change]

The purpose of this review is to purely study definitions of pulmonary exacerbations used in the literature, not to extract data and therefore the quality and risk of bias in individual studies does not require assessment.

Strategy for data synthesis [2 changes]

The definitions used for pulmonary exacerbation in studies will be pooled and then summarised. A summary of all included studies will be presented in evidence tables according to the type of study and relevant age range. Narrative synthesis and thematic analysis of the review findings will be conducted. All the findings will be synthesised to generate a single standardised definition of pulmonary exacerbation for each age group.

Analysis of subgroups or subsets

Definition of pulmonary exacerbation in people with cystic fibrosis in different age groups:

1- 0-2 years

2- 2-6 years

3- 7-12 years

4- > 12 years

Contact details for further information

Maryam Almulhem

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Organisational affiliation of the review

Newcastle University

https://www.ncl.ac.uk/

Review team members and their organisational affiliations [1 change]

Mrs Maryam Almulhem. Newcastle University

Dr Chris Ward. Newcastle University

Dr Robert Gray. University of Edinburgh

Dr Malcolm Brodlie. Newcastle University

Collaborators

. European Cystic Fibrosis Society Pulmonary Exacerbation Working Group

Type and method of review

Systematic review

Anticipated or actual start date

06 January 2020

Anticipated completion date

30 October 2020

Funding sources/sponsors

Newcastle University

Conflicts of interest

Language

English

Country

England

Stage of review

Review Ongoing

Subject index terms status

Subject indexing assigned by CRD

Subject index terms

Cystic Fibrosis; Humans; Lung; Records; Respiratory Tract Infections

Date of registration in PROSPERO

05 February 2020

Date of first submission

13 December 2019

Stage of review at time of this submission

Full protocol PRISMA

Review title:

A scoping review of the definition of pulmonary exacerbations in people with cystic fibrosis

- Review question

What definitions are reported for pulmonary exacerbation in people of different age groups with cystic fibrosis (CF) in the literature?

- Search Strategy

The following electronic bibliographic databases: Embase, MEDLINE, Cochrane Library, Scopus, and CINAHL. The review will be restricted to primary research including clinical trials and prospective observational studies, as a variety of study designs are required to meet the objective of this review. Duplications will be removed, and this process will be reported on PRISMA-ScR flow diagram.
(cystic fibrosis") AND (Pulmonary exacerbation*) [1990-2022]/ AND [English]

- Condition or domain being studied

People with cystic fibrosis who experience pulmonary exacerbation.

- Participants/population

The population being studied are people with cystic fibrosis in all ages.

Inclusion criteria: Human primary studies reporting a definition for pulmonary exacerbation in people with cystic fibrosis in different age groups. Studies published in English between 1990-2022.

Exclusion criteria: study designs including secondary resource studies such as review articles and retrospective studies, In vivo and In vitro studies, and case studies.

Studies that do not report a definition for pulmonary exacerbation. Studies which were not published in English or published out of the included date.

- Intervention(s), exposure(s).

Cystic Fibrosis CF is one of the most common life-limiting genetic disorders worldwide affecting over 80, 000 children and adults. Although CF is a multisystem disorder, it is lung disease that is responsible for the vast majority of morbidity and mortality in people with CF. The natural history of CF lung disease involves exacerbations and periods of greater stability. We know that pulmonary exacerbations are important for a number of reasons:

• Clinically exacerbations may be associated with sustained reductions in lung function and adverse longer term clinical outcomes
• For individual patients they are associated with increased symptoms and limitations on

usual activities
• For society and health care providers they are associated with substantial financial cost.

Perhaps surprisingly, there is no agreed definition of what constitutes a pulmonary exacerbation in people with CF. The age of a person with CF is relevant and no single definition is likely to be appropriate across all ages. Adults with CF are more likely to experience severe exacerbations treated with IV antibiotics in hospital whereas less severe exacerbations in children are often treated as an outpatient with oral antibiotics. By reviewing definitions used in the literature we aim to develop a standardised definition for each age group for use in future clinical research and practice.

- Comparator(s)/control

Not applicable.

- Types of study to be included

Primary research, including clinical trials and prospective observational studies, will be included. Studies published as a full article or in-press will be considered.

- Context

No restrictions.

- Main outcome(s)

Definition of pulmonary exacerbation in people with cystic fibrosis.

- Additional outcome(s)

Signs and symptoms reported in the definitions of pulmonary exacerbation.

- Data charting (selection and coding)

Primary reviewer will work on extracted data by title and abstract. Then primary reviewer will work to extract data from the full text. A second reviewer will screen 10% of the included articles to ensure accuracy. Any disagreement will be resolved by discussion, and if required a third reviewer will be included. A piloting chart form will be designed to extract the following data: author(s) name, title, citation, study design and type of publication, population characteristics (e.g., age), and definition of pulmonary exacerbation.

- Risk of bias (quality) assessment

The purpose of this review is to purely study definitions of pulmonary exacerbations used in the literature, not to extract data and therefore the quality and risk of bias in individual studies does not require assessment.

- Strategy for data synthesis

The definitions used for pulmonary exacerbation in studies will be pooled and then summarised using a thematic qualitative synthesis. Narrative synthesis and thematic analysis of the review findings will be conducted. All the findings will be synthesised to generate a single standardised definition of pulmonary exacerbation for each age group.

- Analysis of subgroups or subsets

Definition of pulmonary exacerbation in people with cystic fibrosis in different age groups:

1- paediatric (< 18 years old)

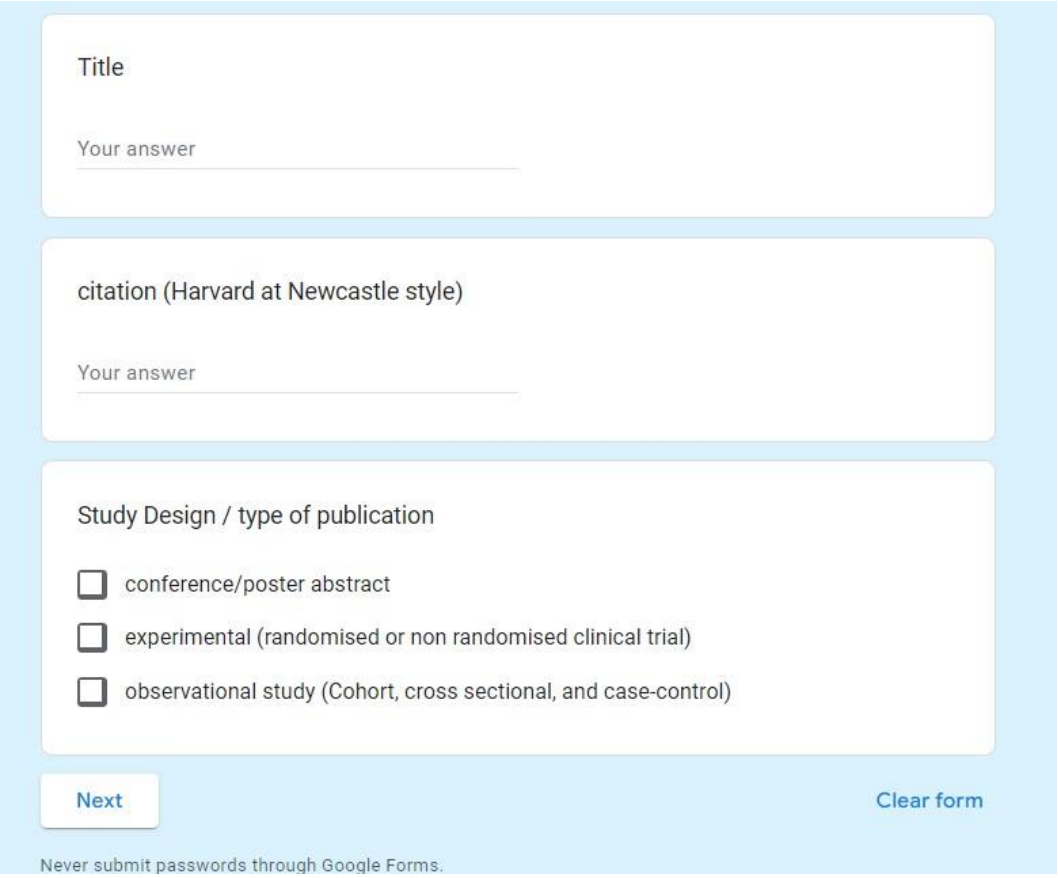
2- Adult (≥ 18 years old).

3- Mixed age group.

- Keywords

Cystic fibrosis, CF, Exacerbation.

Appendix N. Data charting form



Population characteristics (e.g. age)

- [ ] adult 18 and pluse
- [ ] paediatric (less than 18)
- [ ] both
- [ ] Other: _____

Free text of the definition of pulmonary exacerbation

Your answer

Most common symtoms/signs used

- [ ] sputum
- [ ] cough
- [ ] lung function
- [ ] weight/appetite
- [ ] chest sounds
- [ ] CXR changes
- [ ] fever
- [ ] dyspnoea
- [ ] chest pain
- [ ] hemoptysis
- [ ] sinus pain/tendernss
- [ ] Malesia, fatigue, or lethargy.
- [ ] absenteeism
- [ ] Oxygen saturation
- [ ] increase RR
- [ ] decrease exercise tolerance
- [ ] Laboratory findings
- [ ] tachycardia, blood pressure
- [ ] sore throat

Appendix O. Full list of included articles in the scoping review

Title	citation (Harvard at Newcastle style)
1. Combination antibiotic susceptibility testing to treat exacerbations of cystic fibrosis associated with multiresistant bacteria: a randomised, double-blind, controlled clinical trial	Aaron, S. D., Vandemheen, K. L., Ferris, W., Fergusson, D., Tullis, E., Haase, D., Berthiaume, Y., Brown, N., Wilcox, P., Yozghatlian, V., Bye, P., Bell, S., Chan, F., Rose, B., Jeanneret, A., Stephenson, A., Noseworthy, M., Freitag, A., Paterson, N. and Doucette, S. (2005) 'Combination antibiotic susceptibility testing to treat exacerbations of cystic fibrosis associated with multiresistant bacteria: a randomised, double-blind, controlled clinical trial', Lancet, 366(9484), pp. 463-471.
2. What defines a pulmonary exacerbation? The perceptions of adults with cystic fibrosis	Abbott, J., Holt, A., Hart, A., Morton, A. M., MacDougall, L., Pogson, M., Milne, G., Rodgers, H. C. and Conway, S. P. (2009) 'What defines a pulmonary exacerbation? The perceptions of adults with cystic fibrosis', Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society, 8(5), pp. 356-9.
3. Patient indicators of a pulmonary exacerbation: preliminary reports from school aged children map onto those of adults	Abbott, J., Holt, A., Morton, A. M., Hart, A., Milne, G., Wolfe, S. P. and Conway, S. P. (2012) 'Patient indicators of a pulmonary exacerbation: preliminary reports from school aged children map onto those of adults', Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society, 11(3), pp. 180-6.
4. Denufosol tetrasodium in patients with cystic fibrosis and normal to mildly impaired lung function	Accurso, F. J., Moss, R. B., Wilmott, R. W., Anbar, R. D., Schaberg, A. E., Durham, T. A. and Ramsey, B. W. (2011) 'Denufosol tetrasodium in patients with cystic fibrosis and normal to mildly impaired lung function', American Journal of Respiratory & Critical Care Medicine, 183(5), pp. 627-634.
5. Evaluation of once daily tobramycin versus the traditional three time daily for the treatment of acute pulmonary exacerbations in adult cystic fibrosis patients	Al Ansari, N. A., Foweraker, J., Mackeown, D. and Bilton, D. (2006) 'Evaluation of once daily tobramycin versus the traditional three time daily for the treatment of acute pulmonary exacerbations in adult cystic fibrosis patients', Qatar Medical Journal, 15(1), pp. 34-38.
6. The Effect of a Comprehensive, Intensive Inpatient Treatment Program on Lung Function and Exercise Capacity in Patients With Cystic Fibrosis	Alison, J. A., Donnelly, P. M., Lennon, M., Parker, S., Torzillo, P., Mellis, C. and Bye, P. T. (1994) 'The effect of a comprehensive, intensive inpatient treatment program on lung function and exercise capacity in patients with cystic fibrosis', Physical Therapy, 74(6), pp. 583-3.
7. Comparison of biosimilar Tigerase and Pulmozyme in long-term symptomatic therapy of patients with cystic fibrosis and severe pulmonary impairment (subgroup analysis of a Phase III randomized open-label clinical trial	Amelina, E. L., Krasovsky, S. A., Akhtyamova-Givirovskaya, N. E., Kashirskaya, N. Y., Abdulganieva, D. I., Asherova, I. K., Zilber, I. E., Kozyreva, L. S., Kudelya, L. M., Ponomareva, N. D., Revel-Muroz, N. P., Reutskaya, E. M., Stepanenko, T. A., Seitova, G. N., Ukhanova, O. P., Magnitskaya, O. V., Kudlay, D. A., Markova, O. A. and Gapchenko, E. V. (2021) 'Comparison of biosimilar Tigerase and Pulmozyme in long-term symptomatic therapy of patients with cystic fibrosis and severe pulmonary impairment (subgroup analysis of a Phase III randomized open-label clinical trial (NCT04468100))', PloS one, 16(12), pp. e0261410.
8. Routine spirometry in cystic fibrosis patients: impact on pulmonary exacerbation diagnosis and FEV1 decline	Aquino, C. S. B. d., Rodrigues, J. C. and Silva-Filho, L. V. R. F. d. (2022) 'Routine spirometry in cystic fibrosis patients: impact on pulmonary exacerbation diagnosis and FEV1 decline', Jornal brasileiro de pneumologia : publicacao oficial da Sociedade Brasileira de Pneumologia e Tisilogia, 48(3), pp. e20210237.
9. Comparison of cystic fibrosis exacerbations requiring oral or intravenous antibiotics.	Baker, E. H., Burgess, J. C., Bilton, D., Hodson, M. E., Gyi, K. M. and Srivastava, S. A. (2010) 'Comparison of cystic fibrosis exacerbations requiring oral or intravenous antibiotics', Pediatric pulmonology, 45(SUPPL. 33), pp. 376-377.

10. Multicenter Randomized Controlled Trial of Withdrawal of Inhaled Corticosteroids in Cystic Fibrosis	Balfour-Lynn, I. M., Lees, B., Hall, P., Phillips, G., Khan, M., Flather, M. and Elborn, J. S. (2006) 'Multicenter randomized controlled trial of withdrawal of inhaled corticosteroids in cystic fibrosis', American Journal of Respiratory & Critical Care Medicine, 173(12), pp. 1356-1362.
11. Body fat percentage is a risk factor for exacerbations in adults with cystic fibrosis	Baran, E., Butti, F., Hendriksen, B., Granero, N., D'Ascenzo, V., Pistorio, V., Volta, L., Menna, L. and Garcia, G. (2016) 'Body fat percentage is a risk factor for exacerbations in adults with cystic fibrosis', Journal of Cystic Fibrosis, 15(Supplement 1), pp. S102.
12. Quantification of MRI T2-weighted High Signal Volume in Cystic Fibrosis: A Pilot Study	Benlala, I., Hocke, F., Macey, J., Bui, S., Berger, P., Laurent, F. and Dournes, G. (2020) 'Quantification of MRI T2-weighted High Signal Volume in Cystic Fibrosis: A Pilot Study', Radiology, 294(1), pp. 186-196.
13. Volumetric quantification of lung MR signal intensities using ultrashort TE as an automated score in cystic fibrosis	Benlala, I., Point, S., Leung, C., Berger, P., Woods, J. C., Raherison, C., Laurent, F., Macey, J. and Dournes, G. (2020) 'Volumetric quantification of lung MR signal intensities using ultrashort TE as an automated score in cystic fibrosis', European Radiology, 30(10), pp. 5479-5488.
14. Inhaled dry powder mannitol in cystic fibrosis: an efficacy and safety study	Bilton, D., Robinson, P., Cooper, P., Gallagher, C. G., Kolbe, J., Fox, H., Jaques, A. and Charlton, B. (2011) 'Inhaled dry powder mannitol in cystic fibrosis: an efficacy and safety study', The European respiratory journal, 38(5), pp. 1071-80.
15. Predictors of pulmonary exacerbations in patients with cystic fibrosis infected with multi-resistant bacteria	Block, J. K., Vandemheen, K. L., Tullis, E., Fergusson, D., Doucette, S., Haase, D., Berthiaume, Y., Brown, N., Wilcox, P., Bye, P., Bell, S., Noseworthy, M., Pedder, L., Freitag, A., Paterson, N. and Aaron, S. D. (2006) 'Predictors of pulmonary exacerbations in patients with cystic fibrosis infected with multi-resistant bacteria', Thorax, 61(11), pp. 969-74.
16. Quality of life in clinically stable adult cystic fibrosis out-patients: Associations with daytime sleepiness and sleep quality	Bouka, A., Tiede, H., Liebich, L., Dumitrascu, R., Hecker, C., Reichenberger, F., Mayer, K., Seeger, W. and Schulz, R. (2012) 'Quality of life in clinically stable adult cystic fibrosis out-patients: associations with daytime sleepiness and sleep quality', Respiratory medicine, 106(9), pp. 1244-9.
17. Reliability, Repeatability, and Sensitivity	Bradley, J., Howard, J., Wallace, E., Elborn, S., Bradley, J., Howard, J., Wallace, E. and Elborn, S. (2000) 'Reliability, repeatability, and sensitivity of the modified shuttle test in adult cystic fibrosis', CHEST, 117(6), pp. 1666-1671.
18. Quality of life and healthcare utilisation in cystic fibrosis: A multicentre study	Bradley, J. M., Blume, S. W., Balp, M.-M., Honeybourne, D. and Elborn, J. S. (2013) 'Quality of life and healthcare utilisation in cystic fibrosis: a multicentre study', The European respiratory journal, 41(3), pp. 571-7.
19. Impact of recent pulmonary exacerbations on quality of life in patients with cystic fibrosis	Britto, M. T., Kotagal, U. R., Hornung, R. W., Atherton, H. D., Tsevat, J., Wilmott, R. W., Britto, M. T., Kotagal, U. R., Hornung, R. W., Atherton, H. D., Tsevat, J. and Wilmott, R. W. (2002) 'Impact of recent pulmonary exacerbations on quality of life in patients with cystic fibrosis', CHEST, 121(1), pp. 64-72.
20. Computed Tomography Correlates with Pulmonary Exacerbations in Children with Cystic Fibrosis	Brody, A. S., Sucharew, H., Campbell, J. D., Millard, S. P., Molina, P. L., Klein, J. S., Quan, J., Brody, A. S., Sucharew, H., Campbell, J. D., Millard, S. P., Molina, P. L., Klein, J. S. and Quan, J. (2005) 'Computed tomography correlates with pulmonary exacerbations in children with cystic fibrosis', American Journal of Respiratory & Critical Care Medicine, 172(9), pp. 1128-1132.
21. Lack of efficacy of Lactobacillus GG in reducing pulmonary exacerbations and hospital admissions in children with cystic fibrosis: A randomised placebo controlled trial	Bruzzese, E., Raia, V., Ruberto, E., Scotto, R., Giannattasio, A., Bruzzese, D., Cavicchi, M. C., Francalanci, M., Colombo, C., Faelli, N., Dacco, V., Magazzu, G., Costa, S., Lucidi, V., Majo, F. and Guarino, A. (2018) 'Lack of efficacy of Lactobacillus GG in reducing pulmonary exacerbations and hospital admissions in children with cystic fibrosis: A randomised placebo controlled trial', Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society, 17(3), pp. 375-382.
22. Effect of Lactobacillus GG supplementation on pulmonary exacerbations in patients with cystic fibrosis: A pilot study	Bruzzese, E., Raia, V., Spagnuolo, M. I., Volpicelli, M., De Marco, G., Maiuri, L. and Guarino, A. (2007) 'Effect of Lactobacillus GG

	supplementation on pulmonary exacerbations in patients with cystic fibrosis: a pilot study', Clinical Nutrition, 26(3), pp. 322-328.
23. a patient-reported outcome measure	Button, B. M., Wilson, L. M., Burge, A. T., Kimmel, L., Finlayson, F., Williams, E., Talbot, A., Tierney, A., King, S., Holland, A. E., Keating, D., Kotsimbos, T. and Wilson, J. W. (2021) 'The AWESCORE, a patient-reported outcome measure: Development, feasibility, reliability, validity and responsiveness for adults with cystic fibrosis', ERJ Open Research, 7(3), pp. 00120-2021.
24. Prospective evaluation of respiratory exacerbations in children with cystic fibrosis from newborn screening to 5 years of age	Byrnes, C. A., Vidmar, S., Cheney, J. L., Carlin, J. B., Armstrong, D. S., Cooper, P. J., Grimwood, K., Moodie, M., Robertson, C. F., Rosenfeld, M., Tiddens, H. A. and Wainwright, C. E. (2013) 'Prospective evaluation of respiratory exacerbations in children with cystic fibrosis from newborn screening to 5 years of age', Thorax, 68(7), pp. 643-651.
25. Clinical outcomes of digital health in adults with cystic fibrosis	Carnovale, V., Iacotucci, P., Qiao, D., Ferrillo, L., Somma, J., Buonaurio, S., Marcella, d. I., Celardo, A. and Savi, D. (2022) 'Clinical outcomes of digital health in adults with cystic fibrosis', Respiratory medicine, 202, pp. 106970.
26. Factors predicting 6-min walking test indexes in adults with cystic fibrosis	Carpio, C., Lerin, M., Torres, I., Fernandez-Velilla, M., Garcia Rio, F., Alvarez-Sala, R. and Prados, C. (2022) 'Factors predicting 6-min walking test indexes in adults with cystic fibrosis', Science and Sports, 37(5-6), pp. 438-445.
27. Indoor air pollution exposure is associated with greater morbidity in cystic fibrosis	Carson, S. W., Psoter, K., Koehler, K., Siklosi, K. R., Montemayor, K., Toporek, A., West, N. E., Lechtzin, N., Hansel, N. N., Collaco, J. M. and Merlo, C. A. (2022) 'Indoor air pollution exposure is associated with greater morbidity in cystic fibrosis', Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society, 21(2), pp. e129-e135.
28. A prospective pilot study of home monitoring in adults with cystic fibrosis (HOME-CF): protocol for a randomised controlled trial	Choyce, J., Shaw, K. L., Sitch, A. J., Mistry, H., Whitehouse, J. L. and Nash, E. F. (2017) 'A prospective pilot study of home monitoring in adults with cystic fibrosis (HOME-CF): protocol for a randomised controlled trial', BMC Pulmonary Medicine, 17, pp. 1-7.
29. Detection and monitoring of lung inflammation in cystic fibrosis during respiratory tract exacerbation using diffusion-weighted magnetic resonance imaging	Ciet, P., Bertolo, S., Ros, M., Andrinopoulou, E. R., Tavano, V., Lucca, F., Feiweier, T., Krestin, G. P., Tiddens, H. A. W. M. and Morana, G. (2017) 'Detection and monitoring of lung inflammation in cystic fibrosis during respiratory tract exacerbation using diffusion-weighted magnetic resonance imaging', The European respiratory journal, 50(1).
30. Pulmonary function in hospitalized infants and toddlers with cystic fibrosis	Clayton, R. G., Sr., Diaz, C. E., Bashir, N. S., Panitch, H. B., Schidlow, D. V. and Allen, J. L. (1998) 'Pulmonary function in hospitalized infants and toddlers with cystic fibrosis', The Journal of pediatrics, 132(3 Pt 1), pp. 405-8.
31. How abnormal is the normal? Clinical characteristics of CF patients with normal FEV1	Cohen-Cymberknoh, M., Ben Meir, E., Gartner, S., Reiter, J., Spangenberg, A., Garriga, L., Eisenstadt, I., Israeli, T., Tsabari, R., Shoseyov, D., Gileles-Hillel, A., Breuer, O., Simanovsky, N. and Kerem, E. (2021) 'How abnormal is the normal? Clinical characteristics of CF patients with normal FEV1', Pediatric pulmonology, 56(7), pp. 2007-2013.
32. Comparison of Functional Free-Breathing Pulmonary 1H and Hyperpolarized 129Xe Magnetic Resonance Imaging in Pediatric Cystic Fibrosis	Couch, M. J., Munidasa, S., Rayment, J. H., Voskrebenzev, A., Seethamraju, R. T., Vogel-Claussen, J., Ratjen, F. and Santyr, G. (2021) 'Comparison of Functional Free-Breathing Pulmonary 1H and Hyperpolarized 129Xe Magnetic Resonance Imaging in Pediatric Cystic Fibrosis', Academic Radiology, 28(8), pp. e209-e218.
33. Antibiotic therapy and effects of respiratory physiotherapy techniques in cystic fibrosis patients treated for acute lung exacerbations: an experimental study	da Silva Santos, C. I., de Oliveira Ribeiro, M. A. G., Morcillo, A. M., Ribeiro, A. F. and Ribeiro, J. D. (2010) 'Antibiotic therapy and Effects of Respiratory Physiotherapy Techniques Cystic Fibrosis Patients Treated for Acute Lung Exacerbation: an Experimental Study', Archivos de bronconeumologia, 46(6), pp. 310-316.
34. Efficacy and safety of ivacaftor in patients aged 6 to 11 years with cystic fibrosis with a G551D mutation	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. and 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 & Critical Care Medicine, 187(11), pp. 1219-1225.
35. Computed tomography	Davis, S. D., Fordham, L. A., Brody, A. S., Noah, T. L., Retsch-Bogart, G. Z., Qaqish, B. F., Yankaskas, B. C., Johnson, R. C., Leigh, M. W., Davis, S. D., Fordham, L. A., Brody, A. S., Noah, T. L., Retsch-Bogart, G. Z., Qaqish, B. F., Yankaskas, B. C., Johnson, R. C. and Leigh, M. W. (2007) 'Computed tomography reflects lower airway inflammation and tracks changes in early cystic fibrosis', American Journal of Respiratory & Critical Care Medicine, 175(9), pp. 943-950.
36. A randomised trial of hypertonic saline during hospitalisation for exacerbation of cystic fibrosis	Dentice, R. L., Elkins, M. R., Middleton, P. G., Bishop, J. R., Wark, P. A. B., Dorahy, D. J., Harmer, C. J., Honghua, H., Bye, P. T. P. and Hu, H. (2016) 'A randomised trial of hypertonic saline during hospitalisation for exacerbation of cystic fibrosis', Thorax, 71(2), pp. 141-147.
37. Effect of esomeprazole versus placebo on pulmonary exacerbations in cystic fibrosis	Dimango, E., Walker, P., Keating, C., Berdella, M., Robinson, N., Langfelder-Schwind, E., Levy, D. and Liu, X. (2014) 'Effect of esomeprazole versus placebo on pulmonary exacerbations in cystic fibrosis', BMC Pulmonary Medicine, 14(1), pp. 21-21.
38. The effect of infective exacerbations on sleep and neurobehavioral function in cystic fibrosis	Dobbin, C. J., Bartlett, D., Melehan, K., Grunstein, R. R., Bye, P. T. P., Dobbin, C. J., Bartlett, D., Melehan, K., Grunstein, R. R. and Bye, P. T. P. (2005) 'The effect of infective exacerbations on sleep and neurobehavioral function in cystic fibrosis', American Journal of Respiratory & Critical Care Medicine, 172(1), pp. 99-104.
39. Six-Minute Walk Test Results Predict Risk of Hospitalization for Youths with Cystic Fibrosis: A 5-Year Follow-Up Study	Donadio, M. V. F., Heinzmann-Filho, J. P., Vendrusculo, F. M., Frasson, P. X. H. and Marostica, P. J. C. (2017) 'Six-Minute Walk Test Results Predict Risk of Hospitalization for Youths with Cystic Fibrosis: A 5-Year Follow-Up Study', Journal of Pediatrics, 182, pp. 204-209.e1.
40. The modified shuttle test as a predictor of risk for hospitalization in youths with cystic fibrosis: A two-year follow-up study: Modified shuttle test as a predictor of hospitalization	Donadio, M. V. F., Vendrusculo, F. M., Campos, N. E., Becker, N. A., de Almeida, I. S., Queiroz, K. C. V., Leite, L. R. and Aquino, E. S. (2021) 'The modified shuttle test as a predictor of risk for hospitalization in youths with cystic fibrosis: A two-year follow-up study: Modified shuttle test as a predictor of hospitalization', Journal of Cystic Fibrosis, 20(4), pp. 648-654.
41. Non-invasive ventilation used as an adjunct to airway clearance treatments improves lung function during an acute exacerbation of cystic fibrosis: a randomised trial	Dwyer, T. J., Robbins, L., Kelly, P., Piper, A. J., Bell, S. C. and Bye, P. T. P. (2015) 'Non-invasive ventilation used as an adjunct to airway clearance treatments improves lung function during an acute exacerbation of cystic fibrosis: a randomised trial', Journal of Physiotherapy (Elsevier), 61(3), pp. 142-147.
42. Aerosolized lancovutide in adolescents (≥12 years) and adults with cystic fibrosis – a randomized trial	Eber, E., Trawinska-Bartnicka, M., Sands, D., Bellon, G., Mellies, U., Bolbás, K., Quattrucci, S., Mazurek, H., Widmann, R., Schoergenhofer, C., Jilma, B. and Ratjen, F. (2021) 'Aerosolized lancovutide in adolescents (≥12 years) and adults with cystic fibrosis – a randomized trial', Journal of Cystic Fibrosis, 20(1), pp. 61-67.
43. Empire-CF study: A phase 2 clinical trial of leukotriene A4 hydrolase inhibitor acebilustat in adult subjects with cystic fibrosis	Elborn, J. S., Konstan, M. W., Taylor-Cousar, J. L., Fajac, I., Horsley, A., Sutharsan, S., Aaron, S. D., Daines, C. L., Uluer, A., Downey, D. G., Lucidi, V. V., Ahuja, S., Springman, E., Mershon, J., Grosswald, R. and Rowe, S. M. (2021) 'Empire-CF study: A phase 2 clinical trial of leukotriene A4 hydrolase inhibitor acebilustat in adult subjects with cystic fibrosis', Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society, 20(6), pp. 1026-1034.
44. A controlled trial of long-term inhaled hypertonic saline in patients with cystic fibrosis	Elkins, M. R., Robinson, M., Rose, B. R., Harbour, C., Moriarty, C. P., Marks, G. B., Belousova, E. G., Xuan, W. and Bye, P. T. P. (2006) 'A controlled trial of long-term inhaled hypertonic saline in patients with cystic fibrosis', The New England journal of medicine, 354(3), pp. 229-40.
45. Cough in adult cystic fibrosis: Diagnosis and response to fundoplication	Fathi, H., Moon, T., Donaldson, J., Jackson, W., Sedman, P. and Morice, A. H. (2009) 'Cough in adult cystic fibrosis: Diagnosis and response to fundoplication', Cough, 5(1).

46. A phase 3, multi-center, multinational, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of levofloxacin inhalation solution (APT-1026) in stable cystic fibrosis patients	Flume, P. A., VanDevanter, D. R., Morgan, E. E., Dudley, M. N., Loutit, J. S., Bell, S. C., Kerem, E., Fischer, R., Smyth, A. R., Aaron, S. D., Conrad, D., Geller, D. E. and Elborn, J. S. (2016) 'A phase 3, multi-center, multinational, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of levofloxacin inhalation solution (APT-1026) in stable cystic fibrosis patients', Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society, 15(4), pp. 495-502.
47. The utility of lung clearance index to monitor early lung disease in young children with cystic fibrosis	Foong, R. E., Ramsey, K. A., Harper, A. J., Turkovic, L., Rosenow, T., Skoric, B., King, L., Davis, M., Clem, C., Stick, S. M., Davis, S. D., Ranganathan, S. and Hall, G. (2018) 'The utility of lung clearance index to monitor early lung disease in young children with cystic fibrosis', Pediatric pulmonology, 53(Supplement 2), pp. 243-244.
48. Pregnancy and cystic fibrosis: a case-controlled study	Frangolias, D. D., Nakielna, E. M., Wilcox, P. G., Frangolias, D. D., Nakielna, E. M. and Wilcox, P. G. (1997) 'Pregnancy and cystic fibrosis: a case-controlled study', CHEST, 111(4), pp. 963-969.
49. Longitudinal course of clinical lung clearance index in children with cystic fibrosis	Frauchiger, B. S., Binggeli, S., Yammine, S., Spycher, B., Kruger, L., Ramsey, K. A. and Latzin, P. (2021) 'Longitudinal course of clinical lung clearance index in children with cystic fibrosis', The European respiratory journal, 58(1).
50. Effect of aerosolized recombinant human DNase on exacerbations of respiratory symptoms and on pulmonary function in patients with cystic fibrosis	Fuchs, H. J., Borowitz, D. S., Christiansen, D. H., Morris, E. M., Nash, M. L., Ramsey, B. W., Rosenstein, B. J., Smith, A. L. and Wohl, M. E. (1994) 'Effect of aerosolized recombinant human DNase on exacerbations of respiratory symptoms and on pulmonary function in patients with cystic fibrosis. The Pulmozyme Study Group', The New England journal of medicine, 331(10), pp. 637-42.
51. Time Free From Hospitalization in Children and Adolescents With Cystic Fibrosis: Findings From FEV1, Lung Clearance Index and Peak Work Rate	Gambazza, S., Mariani, A., Brivio, A., Carta, F., Blardone, C., Lisiero, S., Russo, M. and Colombo, C. (2022) 'Time Free From Hospitalization in Children and Adolescents With Cystic Fibrosis: Findings From FEV1, Lung Clearance Index and Peak Work Rate', Frontiers in Pediatrics, 10, pp. 926248.
52. Comparison of Flutter device and chest physical therapy in the treatment of cystic fibrosis pulmonary exacerbation.	Gondor, M., Nixon, P. A., Mutich, R., Rebovich, P. and Orenstein, D. M. (1999) 'Comparison of Flutter device and chest physical therapy in the treatment of cystic fibrosis pulmonary exacerbation', Pediatric pulmonology, 28(4), pp. 255-60.
53. Advancing patient reported outcomes in children with cystic fibrosis	Goss, C. H., Dellon, E. P., Lymp, J. F., Gibson, R., McNamara, S., Thompson, V. V., Rebovich, P., Ramsey, B. w. and Orenstein, D. M. (2011) 'Advancing patient reported outcomes in children with cystic fibrosis', Pediatric pulmonology, 46(SUPPL. 34), pp. 294-295.
54. Time spent vs episodes completed: Differences in self-reported treatment activity in surveys of CF adults	Graham, D., O'Donnell, H. K., Sellers, D. E., Sawicki, G. S., Robinson, W. M. and Dill, E. J. (2015) 'Time spent vs episodes completed: Differences in self-reported treatment activity in surveys of CF adults', Pediatric pulmonology, 50(SUPPL. 41), pp. 433.
55. Chest physiotherapy can affect the lung clearance index in cystic fibrosis patients	Grosse-Onnebrink, J., Mellies, U., Olivier, M., Werner, C. and Stehling, F. (2017) 'Chest physiotherapy can affect the lung clearance index in cystic fibrosis patients', Pediatric pulmonology, 52(5), pp. 625-631.
56. Pilot study of vitamin D supplementation in adults with cystic fibrosis pulmonary exacerbation: A randomized, controlled trial	Grossmann, R. E., Zughaier, S. M., Kumari, M., Seydafkan, S., Lyles, R. H., Liu, S., Sueblinvong, V., Schechter, M. S., Stecenko, A. A., Ziegler, T. R. and Tangpricha, V. (2012) 'Pilot study of vitamin D supplementation in adults with cystic fibrosis pulmonary exacerbation: A randomized, controlled trial', Dermato-Endocrinology, 4(2), pp. 191-197.
57. The use of ivacaftor in CFTR mutations resulting in residual functioning protein	Guigui, S., Wang, J. and Cohen, R. I. (2016) 'The use of ivacaftor in CFTR mutations resulting in residual functioning protein', Respiratory Medicine Case Reports, 19, pp. 193-195.
58. The clinical benefits of long-term supplementation with omega-3 fatty acids in cystic fibrosis patients - A pilot study	Hanssens, L., Thiebaut, I., Lefevre, N., Malfroot, A., Knoop, C., Duchateau, J. and Casimir, G. (2016) 'The clinical benefits of long-term supplementation with omega-3 fatty acids in cystic fibrosis patients - A

	pilot study', Prostaglandins, leukotrienes, and essential fatty acids, 108, pp. 45-50.
59. Use of lung clearance index to assess the response to intravenous treatment in cystic fibrosis	Hatziagorou, E., Avramidou, V., Kirvassilis, F. and Tsanakas, J. (2015) 'Use of lung clearance index to assess the response to intravenous treatment in cystic fibrosis', Hippokratia, 19(1), pp. 47-52.
60. Pain is a common problem affecting clinical outcomes in adults with cystic fibrosis	Hayes, M., Yaster, M., Haythornthwaite, J. A., Riekert, K. A., Nelson McMillan, K., White, E., Mogayzel, P. J., Jr., Lechtzin, N., Hayes, M., Yaster, M., Haythornthwaite, J. A., Riekert, K. A., Nelson McMillan, K., White, E., Mogayzel, P. J., Jr. and Lechtzin, N. (2011) 'Pain is a common problem affecting clinical outcomes in adults with cystic fibrosis', CHEST, 140(6), pp. 1598-1603.
61. Cohort study of sleep quality in adult patients with acute pulmonary exacerbations of cystic fibrosis	Henderson, D., Moore, V., MacMorran, K., Castellini, J., Hay, K., Keegan, V., Reid, D., Curtin, D. and Tay, G. (2022) 'Cohort study of sleep quality in adult patients with acute pulmonary exacerbations of cystic fibrosis', Internal Medicine Journal, 52(1), pp. 63-68.
62. Supporting medication adherence for adults with cystic fibrosis: a randomised feasibility study	Hind, D., Drabble, S. J., Arden, M. A., Mandefield, L., Waterhouse, S., Maguire, C., Cantrill, H., Robinson, L., Beever, D., Scott, A. J., Keating, S., Hutchings, M., Bradley, J., Nightingale, J., Allenby, M. I., Dewar, J., Whelan, P., Ainsworth, J., Walters, S. J. and O'Cathain, A. (2019) 'Supporting medication adherence for adults with cystic fibrosis: a randomised feasibility study', BMC Pulmonary Medicine, 19(1), pp. N.PAG-N.PAG.
63. Exhaled nitric oxide is not elevated in the inflammatory airways diseases of cystic fibrosis and bronchiectasis	Ho, L. P., Innes, J. A. and Greening, A. P. (1998) 'Exhaled nitric oxide is not elevated in the inflammatory airways diseases of cystic fibrosis and bronchiectasis', The European respiratory journal, 12(6), pp. 1290-4.
64. Non-invasive ventilation assists chest physiotherapy in adults with acute exacerbations of cystic fibrosis	Holland, A. E., Denehy, L., Ntoumenopoulos, G., Naughton, M. T. and Wilson, J. W. (2003) 'Non-invasive ventilation assists chest physiotherapy in adults with acute exacerbations of cystic fibrosis', Thorax, 58(10), pp. 880-4.
65. Intravenous antibiotic use and exacerbation events in an adult cystic fibrosis centre: A prospective observational study	Hoo, Z. H., Bramley, N. R., Curley, R., Edenborough, F. P., Walters, S. J., Campbell, M. J. and Wildman, M. J. (2019) 'Intravenous antibiotic use and exacerbation events in an adult cystic fibrosis centre: A prospective observational study', Respiratory medicine, 154, pp. 109-115.
66. Pulmonary exacerbations and clinical outcomes in a longitudinal cohort of infants and preschool children with cystic fibrosis	Hoppe, J. E., Wagner, B. D., Sagel, S. D., Accurso, F. J. and Zemanick, E. T. (2017) 'Pulmonary exacerbations and clinical outcomes in a longitudinal cohort of infants and preschool children with cystic fibrosis', BMC Pulmonary Medicine, 17, pp. 1-8.
67. Defining and identifying early-onset lung disease in cystic fibrosis with cumulative clinical characteristics	Huang, L., Lai, H. J., Antos, N., Rock, M. J., Asfour, F., Howenstine, M., Gaffin, J. M. and Farrell, P. M. (2022) 'Defining and identifying early-onset lung disease in cystic fibrosis with cumulative clinical characteristics', Pediatric pulmonology, 57(10), pp. 2363-2373.
68. Real-World Long-Term Ivacaftor for Cystic Fibrosis in France: Clinical Effectiveness and Healthcare Resource Utilization	Hubert, D., Marguet, C., Benichou, J., DeSouza, C., Payen-Champenois, C., Kinnman, N., Chandarana, K., Munck, A., Fajac, I., Ramel, S., Vigneron, P., Storni, V., Remus, N., Durieu, L. B. I., Laurans, M., Troussier, C. R. F., Huet, M. L. D. F., Pin, I., Payet, B. C. A., Languepin, J., Danner-Boucher, I., Mankikian, M. A. J., Wizla, N., Cosson, L., Mittaine, E. D. M., Reix, P., Dufeu, N., David, V., Bui, T. L. S., Chiron, R., Grenet, D., Chedevergne, F., Belleguic, C. and Mely, L. (2021) 'Real-World Long-Term Ivacaftor for Cystic Fibrosis in France: Clinical Effectiveness and Healthcare Resource Utilization', Pulmonary Therapy, 7(2), pp. 455-468.
69. Effects of Probiotics on Quality of Life in Children with Cystic Fibrosis; A Randomized Controlled Trial	Jafari, S.-A., Mehdizadeh-Hakkak, A., Kianifar, H.-R., Hebrani, P., Ahanchian, H. and Abbasnejad, E. (2013) 'Effects of Probiotics on Quality of Life in Children with Cystic Fibrosis; A Randomized Controlled Trial', Iranian Journal of Pediatrics, 23(6), pp. 669-674.

70. A novel respiratory symptom scoring system for CF pulmonary exacerbations	Jarad, N. A. and Sequeiros, I. M. (2012) 'A novel respiratory symptom scoring system for CF pulmonary exacerbations', QJM : monthly journal of the Association of Physicians, 105(2), pp. 137-43.
71. Sleep Phase Delay in Cystic Fibrosis: A Potential New Manifestation of Cystic Fibrosis Transmembrane Regulator Dysfunction	Jensen, J. L., Jones, C. R., Kartsonaki, C., Packer, K. A., Adler, F. R. and Liou, T. G. (2017) 'Sleep Phase Delay in Cystic Fibrosis: A Potential New Manifestation of Cystic Fibrosis Transmembrane Regulator Dysfunction', CHEST, 152(2), pp. 386-393.
72. Productivity loss associated with pulmonary exacerbations among patients with cystic fibrosis and caregivers	Johnson, B., Bhanegaonkar, A., Hassan, M., Bonafede, M., Limone, B., Unni, S. and Brixner, D. (2017) 'Productivity loss associated with pulmonary exacerbations among patients with cystic fibrosis and caregivers', Journal of Managed Care and Specialty Pharmacy, 23(3-A SUPPL.), pp. S50.
73. Cystic fibrosis clinical score: a new scoring system to evaluate acute pulmonary exacerbation	Kanga, J., Kuhn, R., Craigmyle, L., Haverstock, D. and Church, D. (1999) 'Cystic fibrosis clinical score: a new scoring system to evaluate acute pulmonary exacerbation', Clinical therapeutics, 21(8), pp. 1343-56.
74. Prospective evaluation of vascular changes in acute respiratory infections in children with cystic fibrosis	Kartal Ozturk, G., Eski, A., Celebi Celik, F., Conkar, S., Gulen, F., Demir, E. and Keskinoglu, A. (2020) 'Prospective evaluation of vascular changes in acute respiratory infections in children with cystic fibrosis', Turkish journal of medical sciences, 50(4), pp. 1007-1014.
75. The ease of breathing test tracks clinical changes in cystic fibrosis	Kazmerski, T. and Orenstein, D. M. (2012) 'The ease of breathing test tracks clinical changes in cystic fibrosis', Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society, 11(5), pp. 383-6.
76. Pain impacts on quality of life and interferes with treatment in adults with cystic fibrosis	Kelemen, L., Lee, A. L., Button, B. M., Presnell, S., Wilson, J. W. and Holland, A. E. (2012) 'Pain Impacts on Quality of Life and Interferes with Treatment in Adults with Cystic Fibrosis', Physiotherapy Research International, 17(3), pp. 132-141.
77. Ataluren for the treatment of nonsense-mutation cystic fibrosis: a randomised, double-blind, placebo-controlled phase 3 trial	Kerem, E., Konstan, M. W., De Boeck, K., Accurso, F. J., Sermet-Gaudelus, I., Wilschanski, M., Elborn, J. S., Melotti, P., Bronsveld, I., Fajac, I., Malfroot, A., Rosenbluth, D. B., Walker, P. A., McColley, S. A., Knoop, C., Quattrucci, S., Rietschel, E., Zeitlin, P. L., Barth, J., Elfring, G. L., Welch, E. M., Branstrom, A., Spiegel, R. J., Peltz, S. W., Ajayi, T. and Rowe, S. M. (2014) 'Ataluren for the treatment of nonsense-mutation cystic fibrosis: a randomised, double-blind, placebo-controlled phase 3 trial', The Lancet. Respiratory medicine, 2(7), pp. 539-47.
78. Physical activity in adults with cystic fibrosis receiving intravenous antibiotics in hospital and in the community	Khiroya, H., Pound, R., Qureshi, U., Brown, C., Barrett, J., Rashid, R., Whitehouse, J. L., Turner, A. M. and Nash, E. F. (2014) 'Physical activity in adults with cystic fibrosis receiving intravenous antibiotics in hospital and in the community', Open Respiratory Medicine Journal, 9(1), pp. 15-21.
79. 18F-fluorodeoxyglucose-PET/CT imaging of lungs in patients with cystic fibrosis	Klein, M., Cohen-Cymberknoh, M., Armoni, S., Shoseyov, D., Chisin, R., Orevi, M., Freedman, N., Kerem, E., Klein, M., Cohen-Cymberknoh, M., Armoni, S., Shoseyov, D., Chisin, R., Orevi, M., Freedman, N. and Kerem, E. (2009) '18F-fluorodeoxyglucose-PET/CT imaging of lungs in patients with cystic fibrosis', CHEST, 136(5), pp. 1220-1228.
80. A randomized double blind, placebo controlled phase 2 trial of BIIL 284 BS (an LTB4 receptor antagonist) for the treatment of lung disease in children and adults with cystic fibrosis	A randomized double blind, placebo controlled phase 2 trial of BIIL 284 BS (an LTB4 receptor antagonist) for the treatment of lung disease in children and adults with cystic fibrosis
81. Efficacy and safety of ataluren in patients with nonsense-mutation cystic fibrosis not receiving chronic inhaled aminoglycosides: The international, randomized, double-blind, placebo-controlled Ataluren Confirmatory Trial in Cystic Fibrosis (ACT CF)	Konstan, M. W., VanDevanter, D. R., Rowe, S. M., Wilschanski, M., Kerem, E., Sermet-Gaudelus, I., DiMango, E., Melotti, P., McIntosh, J. and De Boeck, K. (2020) 'Efficacy and safety of ataluren in patients with nonsense-mutation cystic fibrosis not receiving chronic inhaled aminoglycosides: The international, randomized, double-blind, placebo-controlled Ataluren Confirmatory Trial in Cystic Fibrosis (ACT CF)', Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society, 19(4), pp. 595-601.

82. Concentration of fractional excretion of nitric oxide (FENO): A potential airway biomarker of restored CFTR function	Kotha, K., Szczesniak, R. D., Naren, A. P., Fenchel, M. C., Duan, L. L., McPhail, G. L. and Clancy, J. P. (2015) 'Concentration of fractional excretion of nitric oxide (FENO): A potential airway biomarker of restored CFTR function', Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society, 14(6), pp. 733-40.
83. Clinical validation of digital biomarkers for paediatric patients with asthma and cystic fibrosis: potential for clinical trials and clinical care	Kruizinga, M. D., Essers, E., Stuurman, F. E., Yavuz, Y., de Kam, M. L., Zhuparris, A., Janssens, H. M., Groothuis, I., Sprij, A. J., Nuijsink, M., Cohen, A. F. and Driessen, G. J. A. (2022) 'Clinical validation of digital biomarkers for paediatric patients with asthma and cystic fibrosis: potential for clinical trials and clinical care', The European respiratory journal, 59(6).
84. Radioaerosol Assessment of Lung Improvement in Cystic Fibrosis Patients Treated for Acute Pulmonary Exacerbations	Laube, B. L., Chang, D. Y., Blask, A. N. and Rosenstein, B. J. (1992) 'Radioaerosol assessment of lung improvement in cystic fibrosis patients treated for acute pulmonary exacerbations', CHEST, 101(5), pp. 1302-1308.
85. The Association Between Pain and Clinical Outcomes in Adolescents With Cystic Fibrosis	Lechtzin, N., Allgood, S., Hong, G., Riekert, K., Haythornthwaite, J. A., Mogayzel, P., Hankinson, J. and Yaster, M. (2016) 'The Association Between Pain and Clinical Outcomes in Adolescents With Cystic Fibrosis', Journal of Pain & Symptom Management, 52(5), pp. 681-687.
86. Rationale and design of a randomized trial of home electronic symptom and lung function monitoring to detect cystic fibrosis pulmonary exacerbations: the early intervention in cystic fibrosis exacerbation (eICE) trial	Lechtzin, N., West, N., Allgood, S., Wilhelm, E., Khan, U., Mayer-Hamblett, N., Aitken, M. L., Ramsey, B. W., Boyle, M. P., Mogayzel, P. J., Jr. and Goss, C. H. (2013) 'Rationale and design of a randomized trial of home electronic symptom and lung function monitoring to detect cystic fibrosis pulmonary exacerbations: the early intervention in cystic fibrosis exacerbation (eICE) trial', Contemporary clinical trials, 36(2), pp. 460-9.
87. Bronchiectasis on chest computed tomography (CT) is a strong predictor of respiratory tract exacerbations in cystic fibrosis (CF)	Loeve, M., Gerbrands, K., Hop, W., Rosenfeld, M. and Tiddens, H. (2009) 'Bronchiectasis on chest computed tomography (CT) is a strong predictor of respiratory tract exacerbations in cystic fibrosis (CF)', Journal of Thoracic Imaging, 24(3), pp. w13.
88. Asymmetric dimethylarginine and related metabolites in exhaled breath condensate of children with cystic fibrosis	Lucca, F., Da Dalt, L., Ros, M., Gucciardi, A., Pirillo, P., Naturale, M., Perilongo, G., Giordano, G. and Baraldi, E. (2018) 'Asymmetric dimethylarginine and related metabolites in exhaled breath condensate of children with cystic fibrosis', The clinical respiratory journal, 12(1), pp. 140-148.
89. Lung function in 3-5-year-old children with cystic fibrosis	Mayer, O. H., Jawad, A. F., McDonough, J. and Allen, J. (2008) 'Lung function in 3-5-year-old children with cystic fibrosis', Pediatric pulmonology, 43(12), pp. 1214-23.
90. Evaluating the impact of stopping chronic therapies after modulator drug therapy in cystic fibrosis: The SIMPLIFY clinical trial study design	Mayer-Hamblett, N., Nichols, D. P., Odem-Davis, K., Riekert, K. A., Sawicki, G. S., Donaldson, S. H., Ratjen, F., Konstan, M. W., Simon, N., Rosenbluth, D. B., Retsch-Bogart, G., Clancy, J. P., Van Dalfsen, J. M., Buckingham, R. and Gifford, A. H. (2021) 'Evaluating the impact of stopping chronic therapies after modulator drug therapy in cystic fibrosis: The SIMPLIFY clinical trial study design', Annals of the American Thoracic Society, 18(8), pp. 1397-1405.
91. Azithromycin for Early Pseudomonas Infection in Cystic Fibrosis. The OPTIMIZE Randomized Trial	Mayer-Hamblett, N., Retsch-Bogart, G., Kloster, M., Accurso, F., Rosenfeld, M., Albers, G., Black, P., Brown, P., Cairns, A., Davis, S. D., Graff, G. R., Kerby, G. S., Orenstein, D., Buckingham, R. and Ramsey, B. W. (2018) 'Azithromycin for Early Pseudomonas Infection in Cystic Fibrosis. The OPTIMIZE Randomized Trial', American Journal of Respiratory & Critical Care Medicine, 198(9), pp. 1177-1187.
92. Energy balance in cystic fibrosis when stable and during a respiratory exacerbation	Mc Closkey, M., Redmond, A. O. B., Mc Cabe, C., Pyper, S., Westerterp, K. R. and Elborn, S. J. (2004) 'Energy balance in cystic fibrosis when stable and during a respiratory exacerbation', Clinical nutrition (Edinburgh, Scotland), 23(6), pp. 1405-12.
93. Long-term multicentre randomised controlled study of high frequency chest wall oscillation versus positive expiratory pressure mask in cystic fibrosis	McIlwaine, M. P., Alarie, N., Davidson, G. F., Lands, L. C., Ratjen, F., Milner, R., Owen, B. and Agnew, J. L. (2013) 'Long-term multicentre randomised controlled study of high frequency chest wall oscillation versus positive expiratory pressure mask in cystic fibrosis', Thorax, 68(8), pp. 746-751.

94. Pilot study of inhaled dry powder mannitol in young people with CF hospitalised with pulmonary exacerbation	Middleton, A., Robinson, P., McKay, K. and Selvadurai, H. (2012) 'Pilot study of inhaled dry powder mannitol in young people with CF hospitalised with pulmonary exacerbation', Pediatric pulmonology, 47(SUPPL. 35), pp. 355-356.
95. Elexacaftor-Tezacaftor-Ivacaftor for Cystic Fibrosis with a Single Phe508del Allele	Middleton, P. G., Mall, M. A., Drevinek, 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. and Rowe, S. M. (2019) 'Elexacaftor-Tezacaftor-Ivacaftor for Cystic Fibrosis with a Single Phe508del Allele', New England Journal of Medicine, 381(19), pp. 1809-1819.
96. Objective Measurement of Adherence to Out-Patient Airway Clearance Therapy by High-Frequency Chest Wall Compression in Cystic Fibrosis	Mikesell, C. L., Kempainen, R. R., Laguna, T. A., Menk, J. S., Wey, A. R., Gaillard, P. R. and Regelmann, W. E. (2017) 'Objective Measurement of Adherence to Out-Patient Airway Clearance Therapy by High-Frequency Chest Wall Compression in Cystic Fibrosis', Respiratory Care, 62(7), pp. 920-927.
97. Effects of aerobic interval training on glucose tolerance in children and adolescents with cystic fibrosis: a randomized trial protocol	Monteiro, K. S., Azevedo, M. d. P., Jales, L. M., da Silva, F. E. P., Arrais, R. F. and de Mendonça, K. M. P. P. (2019) 'Effects of aerobic interval training on glucose tolerance in children and adolescents with cystic fibrosis: a randomized trial protocol', Trials, 20(1), pp. 1-9.
98. One-year glargine treatment can improve the course of lung disease in children and adolescents with cystic fibrosis and early glucose derangements	Mozzillo, E., Franzese, A., Valerio, G., Sepe, A., De Simone, I., Mazzarella, G., Ferri, P. and Raia, V. (2009) 'One-year glargine treatment can improve the course of lung disease in children and adolescents with cystic fibrosis and early glucose derangements', Pediatric Diabetes, 10(3), pp. 162-167.
99. Validation of a Spanish version of the Leicester Cough Questionnaire in cystic fibrosis	Munoz, G., de Gracia, J., Giron, R., Olveira, C., Alvarez, A., Buxo, M., Birring, S. S. and Vendrell, M. (2021) 'Validation of a Spanish version of the Leicester Cough Questionnaire in cystic fibrosis', Chronic respiratory disease, 18, pp. 14799731211036903.
100. 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)	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. and 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), pp. 902-910.
101. Resting Energy Expenditure: Evolution During Antibiotic Treatment for Pulmonary Exacerbation in Cystic Fibrosis	Naon, H., Hack, S., Shelton, M. T., Gotthoffer, R. C. and Gozal, D. (1993) 'Resting energy expenditure. Evolution during antibiotic treatment for pulmonary exacerbation in cystic fibrosis', CHEST, 103(6), pp. 1819-1825.
102. A prospective randomised controlled mixed-methods pilot study of home monitoring in adults with cystic fibrosis	Nash, E. F., Choyce, J., Carrolan, V., Justice, E., Shaw, K. L., Sitch, A., Mistry, H. and Whitehouse, J. L. (2022) 'A prospective randomised controlled mixed-methods pilot study of home monitoring in adults with cystic fibrosis', Therapeutic advances in respiratory disease, 16, pp. 17534666211070133.
103. Lung T1 mapping magnetic resonance imaging in the assessment of pulmonary disease in children with cystic fibrosis: a pilot study	Neemuchwala, F., Ghadimi Mahani, M., Pang, Y., Lee, E., Johnson, T. D., Galbán, C. J., Fortuna, A. B., Sanchez-Jacob, R., Flask, C. A. and Nasr, S. Z. (2020) 'Lung T1 mapping magnetic resonance imaging in the assessment of pulmonary disease in children with cystic fibrosis: a pilot study', Pediatric Radiology, 50(7), pp. 923-934.
104. Exhaled breath condensate pH and ammonia in cystic fibrosis and response to treatment of acute pulmonary exacerbations	Newport, S., Amin, N. and Dozor, A. J. (2009) 'Exhaled breath condensate pH and ammonia in cystic fibrosis and response to treatment of acute pulmonary exacerbations', Pediatric pulmonology, 44(9), pp. 866-72.
105. Relationship between pulmonary hyperinflation and dyspnoea severity during acute exacerbations of cystic fibrosis	Nicholson, T. T., Barry, P. J., Waterhouse, D. F., Nolan, G. M., McKone, E. F. and Gallagher, C. G. (2017) 'Relationship between pulmonary hyperinflation and dyspnoea severity during acute exacerbations of cystic fibrosis', Respirology (Carlton, Vic.), 22(1), pp. 141-148.

106. Exhaled breath condensate pH and exhaled nitric oxide in allergic asthma and in cystic fibrosis	Ojoo, J. C., Mulrennan, S. A., Kastelik, J. A., Morice, A. H. and Redington, A. E. (2005) 'Exhaled breath condensate pH and exhaled nitric oxide in allergic asthma and in cystic fibrosis', Thorax, 60(1), pp. 22-6.
107. Exhaled molecular profiles in the assessment of cystic fibrosis and primary ciliary dyskinesia	Paff, T., van der Schee, M. P., Daniels, J. M. A., Pals, G., Postmus, P. E., Sterk, P. J. and Haarman, E. G. (2013) 'Exhaled molecular profiles in the assessment of cystic fibrosis and primary ciliary dyskinesia', Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society, 12(5), pp. 454-60.
108. Airways in cystic fibrosis are acidified: Detection by exhaled breath condensate	Tate, S., MacGregor, G., Davis, M., Innes, J. A. and Greening, A. P. (2002) 'Airways in cystic fibrosis are acidified: detection by exhaled breath condensate', Thorax, 57(11), pp. 926-9.
109. Exhaled volatile organic compounds detect pulmonary exacerbations early in children with cystic fibrosis: results of a 1 year observational pilot study	van Horck, M., Smolinska, A., Wesseling, G., de Winter-de Groot, K., de Vreede, I., Winkens, B., Jobsis, Q., Dallinga, J., Dompeling, E. and van Schooten, F.-J. (2021) 'Exhaled volatile organic compounds detect pulmonary exacerbations early in children with cystic fibrosis: results of a 1 year observational pilot study', Journal of breath research, 15(2), pp. 026012.
110. Continuous glucose monitoring indices predict poor FEV1 recovery following cystic fibrosis pulmonary exacerbations	Pallin, M., Kumar, S., Daley, C., Dawadi, S., Leong, P., Carr, E. and Soldatos, G. (2021) 'Continuous glucose monitoring indices predict poor FEV1 recovery following cystic fibrosis pulmonary exacerbations', Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society, 20(5), pp. 785-791.
111. Comparison of active cycle of breathing and high-frequency oscillation jacket in children with cystic fibrosis	Phillips, G. E., Pike, S. E., Jaffe, A. and Bush, A. (2004) 'Comparison of active cycle of breathing and high-frequency oscillation jacket in children with cystic fibrosis', Pediatric pulmonology, 37(1), pp. 71-5.
112. A two-year randomized, placebo-controlled trial of dornase alfa in young patients with cystic fibrosis with mild lung function abnormalities	Quan, J. M., Tiddens, H. A., Sy, J. P., McKenzie, S. G., Montgomery, M. D., Robinson, P. J., Wohl, M. E. and Konstan, M. W. (2001) 'A two-year randomized, placebo-controlled trial of dornase alfa in young patients with cystic fibrosis with mild lung function abnormalities', The Journal of pediatrics, 139(6), pp. 813-20.
113. Determination of the Minimal Clinically Important Difference Scores for the Cystic Fibrosis Questionnaire-Revised Respiratory Symptom Scale in Two Populations of Patients With Cystic Fibrosis and Chronic Pseudomonas aeruginosa Airway Infection	Quittner, A. L., Modi, A. C., Wainwright, C., Otto, K., Kirihara, J., Montgomery, A. B., Quittner, A. L., Modi, A. C., Wainwright, C., Otto, K., Kirihara, J. and Montgomery, A. B. (2009) 'Determination of the minimal clinically important difference scores for the Cystic Fibrosis Questionnaire-Revised respiratory symptom scale in two populations of patients with cystic fibrosis and chronic Pseudomonas aeruginosa airway infection', CHEST, 135(6), pp. 1610-1618.
114. A CFTR Potentiator in Patients with Cystic Fibrosis and the G551D Mutation	Ramsey, B. W., Davies, J., McElvaney, N. G., Tullis, E., Bell, S. C., Devínek, 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. and Ramsey, B. W. (2011) 'A CFTR potentiator in patients with cystic fibrosis and the G551D mutation', New England Journal of Medicine, 365(18), pp. 1663-1672.
115. Hyperpolarised 129Xe magnetic resonance imaging to monitor treatment response in children with cystic fibrosis	Rayment, J. H., Couch, M. J., McDonald, N., Kanhere, N., Manson, D., Santyr, G. and Ratjen, F. (2019) 'Hyperpolarised 129Xe magnetic resonance imaging to monitor treatment response in children with cystic fibrosis', The European respiratory journal, 53(5).
116. Lung clearance index to monitor treatment response in pulmonary exacerbations in preschool children with cystic fibrosis	Rayment, J. H., Stanojevic, S., Davis, S. D., Retsch-Bogart, G. and Ratjen, F. (2018) 'Lung clearance index to monitor treatment response in pulmonary exacerbations in preschool children with cystic fibrosis', Thorax, 73(5), pp. 451-458.
117. Energy balance during acute respiratory exacerbations in children with cystic fibrosis	Reilly, J. J., Ralston, J. M., Paton, J. Y., Edwards, C. A., Weaver, L. T., Wilkinson, J. and Evans, T. J. (1999) 'Energy balance during acute respiratory exacerbations in children with cystic fibrosis', The European respiratory journal, 13(4), pp. 804-9.

118. Comparison between magnetic resonance imaging and computed tomography of the lung in patients with cystic fibrosis with regard to clinical, laboratory, and pulmonary functional parameters	Renz, D. M., Scholz, O., Bottcher, J., Maurer, M. H., Denecke, T., Schwarz, C., Pfeil, A., Streitparth, F., Huppertz, A., Mehl, A., Poellinger, A., Staab, D., Hamm, B. and Mentzel, H.-J. (2015) 'Comparison between magnetic resonance imaging and computed tomography of the lung in patients with cystic fibrosis with regard to clinical, laboratory, and pulmonary functional parameters', Investigative radiology, 50(10), pp. 733-42.
119. Clarithromycin therapy for patients with cystic fibrosis: a randomized controlled trial	Robinson, P., Schechter, M. S., Sly, P. D., Winfield, K., Smith, J., Brennan, S., Shinkai, M., Henke, M. O. and Rubin, B. K. (2012) 'Clarithromycin therapy for patients with cystic fibrosis: a randomized controlled trial', Pediatric pulmonology, 47(6), pp. 551-7.
120. Using index of ventilation to assess response to treatment for acute pulmonary exacerbation in children with cystic fibrosis	Robinson, P. D., Cooper, P., Van Asperen, P., Fitzgerald, D. and Selvadurai, H. (2009) 'Using index of ventilation to assess response to treatment for acute pulmonary exacerbation in children with cystic fibrosis', Pediatric pulmonology, 44(8), pp. 733-42.
121. Dornase alfa in early cystic fibrosis lung disease	Robinson, P. J. (2002) 'Dornase alfa in early cystic fibrosis lung disease', Pediatric pulmonology, 34(3), pp. 237-41.
122. Defining a pulmonary exacerbation in cystic fibrosis	Rosenfeld, M., Emerson, J., Williams-Warren, J., Pepe, M., Smith, A., Montgomery, A. B. and Ramsey, B. (2001) 'Defining a pulmonary exacerbation in cystic fibrosis', Journal of Pediatrics, 139(3), pp. 359-365.
123. Inhaled hypertonic saline in infants and children younger than 6 years with cystic fibrosis: the ISIS randomized controlled trial.	Rosenfeld, M., Ratjen, F., Brumback, L., Daniel, S., Rowbotham, R., McNamara, S., Johnson, R., Kronmal, R., Davis, S. D., Rosenfeld, M., Ratjen, F., Brumback, L., Daniel, S., Rowbotham, R., McNamara, S., Johnson, R., Kronmal, R. and Davis, S. D. (2012) 'Inhaled hypertonic saline in infants and children younger than 6 years with cystic fibrosis: the ISIS randomized controlled trial', JAMA: Journal of the American Medical Association, 307(21), pp. 2269-2277.
124. Effects of an Antioxidant-enriched Multivitamin in Cystic Fibrosis. A Randomized, Controlled, Multicenter Clinical Trial	Sagel, S. D., Khan, U., Jain, R., Graff, G., Daines, C. L., Dunitz, J. M., Borowitz, D., Orenstein, D. M., Abdulhamid, I., Noe, J. and et al. (2018) 'Effects of an Antioxidant-enriched Multivitamin in Cystic Fibrosis. A Randomized, Controlled, Multicenter Clinical Trial', American journal of respiratory and critical care medicine, 198(5), pp. 639-647.
125. Effect of azithromycin on pulmonary function in patients with cystic fibrosis uninfected with Pseudomonas aeruginosa: a randomized controlled trial	Saiman, L., Anstead, M., Mayer-Hamblett, N., Lands, L. C., Kloster, M., Hocevar-Trnka, J., Goss, C. H., Rose, L. M., Burns, J. L., Marshall, B. C., Ratjen, F., Saiman, L., Anstead, M., Mayer-Hamblett, N., Lands, L. C., Kloster, M., Hocevar-Trnka, J., Goss, C. H., Rose, L. M. and Burns, J. L. (2010) 'Effect of azithromycin on pulmonary function in patients with cystic fibrosis uninfected with Pseudomonas aeruginosa: a randomized controlled trial', JAMA: Journal of the American Medical Association, 303(17), pp. 1707-1715.
126. Azithromycin in Patients With Cystic Fibrosis Chronically Infected With Pseudomonas aeruginosa	Saiman, L., Marshall, B. C., Mayer-Hamblett, N., Burns, J. L., Quittner, A. L., Cibene, D. A., Coquillette, S., Fieberg, A. Y., Accurso, F. J., Campbell, P. W., III, Saiman, L., Marshall, B. C., Mayer-Hamblett, N., Burns, J. L., Quittner, A. L., Cibene, D. A., Coquillette, S., Fieberg, A. Y., Accurso, F. J. and Campbell, P. W., 3rd (2003) 'Azithromycin in patients with cystic fibrosis chronically infected with Pseudomonas aeruginosa: a randomized controlled trial', JAMA: Journal of the American Medical Association, 290(13), pp. 1749-1756.
127. Evaluation of children with cystic fibrosis by impulse oscillometry when stable and at exacerbation	Sakarya, A., Uyan, Z. S., Baydemir, C., Anik, Y., Erdem, E., Gokdemir, Y., Karadag, B., Karakoc, F. and Ersu, R. (2016) 'Evaluation of children with cystic fibrosis by impulse oscillometry when stable and at exacerbation', Pediatric pulmonology, 51(11), pp. 1151-1158.
128. Standardized treatment of pulmonary exacerbations (STOP) study: Clinical presentations of pulmonary exacerbations	Sanders, D. B., Goss, C. H., Van Devanter, D. R., Heltse, S. L., Thompson, V. and Flume, P. (2015) 'Standardized treatment of pulmonary exacerbations (STOP) study: Clinical presentations of pulmonary exacerbations', Journal of Cystic Fibrosis, 14(SUPPL. 1), pp. S106.

129. Standardized Treatment of Pulmonary Exacerbations (STOP) study: Observations at the initiation of intravenous antibiotics for cystic fibrosis pulmonary exacerbations	Sanders, D. B., Solomon, G. M., Beckett, V. V., West, N. E., Daines, C. L., Heltshe, S. L., VanDevanter, D. R., Spahr, J. E., Gibson, R. L., Nick, J. A., Marshall, B. C., Flume, P. A. and Goss, C. H. (2017) 'Standardized Treatment of Pulmonary Exacerbations (STOP) study: Observations at the initiation of intravenous antibiotics for cystic fibrosis pulmonary exacerbations', Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society, 16(5), pp. 592-599.
130. 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	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. and 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), pp. 675-683.
131. Patients with cystic fibrosis and normoglycemia exhibit diabetic glucose tolerance during pulmonary exacerbation	Sc, N. N. M., Shoseyov, D., Kerem, E. and Zangen, D. H. (2010) 'Patients with cystic fibrosis and normoglycemia exhibit diabetic glucose tolerance during pulmonary exacerbation', Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society, 9(3), pp. 199-204.
132. "Thrust out of normality"-How adults living with cystic fibrosis experience pulmonary exacerbations: A qualitative study	Schmid-Mohler, G., Caress, A.-L., Spirig, R., Benden, C. and Yorke, J. (2019) '"Thrust out of normality"-How adults living with cystic fibrosis experience pulmonary exacerbations: A qualitative study', Journal of clinical nursing, 28(1-2), pp. 190-200.
133. MRI of cystic fibrosis lung manifestations: sequence evaluation and clinical outcome analysis	Scholz, O., Denecke, T., Böttcher, J., Schwarz, C., Mentzel, H. J., Streitparth, F., Maurer, M. H., Pfeil, A., Huppertz, A., Mehl, A., Staab, D., Hamm, B. and Renz, D. M. (2017) 'MRI of cystic fibrosis lung manifestations: sequence evaluation and clinical outcome analysis', Clinical Radiology, 72(9), pp. 754-763.
134. Clinical impact of levofloxacin inhalation solution in cystic fibrosis patients in a real-world setting.	Schwarz, C., Grehn, C., Temming, S., Holz, F. and Eschenhagen, P.N., 2021. Clinical impact of levofloxacin inhalation solution in cystic fibrosis patients in a real-world setting. Journal of Cystic Fibrosis, 20(6), pp.1035-1039.
135. Factors associated with a shorter time until the next pulmonary exacerbation in adult patients with cystic fibrosis	Sequeiros, I. M. and Jarad, N. (2012) 'Factors associated with a shorter time until the next pulmonary exacerbation in adult patients with cystic fibrosis', Chronic respiratory disease, 9(1), pp. 9-16.
136. Extending the course of intravenous antibiotics in adult patients with cystic fibrosis with acute pulmonary exacerbations	Sequeiros, I. M. and Jarad, N. A. (2012) 'Extending the course of intravenous antibiotics in adult patients with cystic fibrosis with acute pulmonary exacerbations', Chronic respiratory disease, 9(4), pp. 213-20.
137. Growth hormone as a nutritional adjunct in cystic fibrosis: results of a pilot study	Sackey, A. H., Taylor, C. J., Barraclough, M., Wales, J. K. H. and Pickering, M. (1995) 'Growth hormone as a nutritional adjunct in cystic fibrosis: Results of a pilot study', Journal of Human Nutrition and Dietetics, 8(3), pp. 185-191.
138. High-resolution CT in the acute exacerbation of cystic fibrosis: evaluation of acute findings, reversibility of those findings, and clinical correlation	Shah, R. M., Sexauer, W., Ostrum, B. J., Fiel, S. B. and Friedman, A. C. (1997) 'High-resolution CT in the acute exacerbation of cystic fibrosis: evaluation of acute findings, reversibility of those findings, and clinical correlation', AJR. American journal of roentgenology, 169(2), pp. 375-80.
139. A Short extension to multiple breath washout provides additional signal of distal airway disease in people with CF: A pilot study.	Short, C., Semple, T., Saunders, C., Hughes, D., Irving, S., Gardener, L., Rosenthal, M., Robinson, P. D. and Davies, J. C. (2022) 'A Short extension to multiple breath washout provides additional signal of distal airway disease in people with CF: A pilot study', Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society, 21(1), pp. 146-154.
140. Use of Dynamic Chest Radiography to Assess Treatment of Pulmonary Exacerbations in Cystic Fibrosis	FitzMaurice, T. S., McCann, C., Nazareth, D. S., McNamara, P. S. and Walshaw, M. J. (2022) 'Use of Dynamic Chest Radiography to Assess Treatment of Pulmonary Exacerbations in Cystic Fibrosis', Radiology, 303(3), pp. 675-681.

141. Randomized controlled study of aerosolized hypertonic xylitol versus hypertonic saline in hospitalized patients with pulmonary exacerbation of cystic fibrosis.	Singh, S., Hornick, D., Fedler, J., Launspach, J. L., Teresi, M. E., Santacroce, T. R., Cavanaugh, J. E., Horan, R., Nelson, G., Starner, T. D., Zabner, J. and Durairaj, L. (2020) 'Randomized controlled study of aerosolized hypertonic xylitol versus hypertonic saline in hospitalized patients with pulmonary exacerbation of cystic fibrosis', Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society, 19(1), pp. 108-113.
142. Objective measurement of cough during pulmonary exacerbations in adults with cystic fibrosis	Smith, J. A., Owen, E. C., Jones, A. M., Dodd, M. E., Webb, A. K. and Woodcock, A. (2006) 'Objective measurement of cough during pulmonary exacerbations in adults with cystic fibrosis', Thorax, 61(5), pp. 425-9.
143. Once versus three-times daily regimens of tobramycin treatment for pulmonary exacerbations of cystic fibrosis—the TOPIC study: a randomised controlled trial	Smyth, A., Tan, K. H. V., Hyman-Taylor, P., Mulheran, M., Lewis, S., Stableforth, D. and Knox, A. (2005) 'Once versus three-times daily regimens of tobramycin treatment for pulmonary exacerbations of cystic fibrosis - The TOPIC study: A randomised controlled trial', Lancet, 365(9459), pp. 573-578.
144. 110 Real-world outcomes in cystic fibrosis telehealth clinical care during the COVID-19 pandemic	Somerville, L., List, R., Compton, M., Bruschwein, H., Jennings, D., Murray, R., Starheim, E., Webb, K., Kalmanek, J., Gettle, L. and Albon, D. (2021) '110 Real-world outcomes in cystic fibrosis telehealth clinical care during the COVID-19 pandemic', Journal of Cystic Fibrosis, 20(Supplement 2), pp. S55-S56.
145. Does the lung clearance index track with disease progression in early childhood?	Sonneveld, N., Stanojevic, S., Jensen, R., Subbarao, P. and Ratjen, F. (2015) 'Does the lung clearance index track with disease progression in early childhood?', European Respiratory Journal, 46(SUPPL. 59).
146. Magnetic Resonance Imaging Detects Progression of Lung Disease and Impact of Newborn Screening in Preschool Children with Cystic Fibrosis	Stahl, M., Steinke, E., Graeber, S. Y., Joachim, C., Seitz, C., Kauczor, H.-U., Eichinger, M., Hämmerling, S., Sommerburg, O., Wielpüz, M. O., Mall, M. A. and Wielpütz, M. O. (2021) 'Magnetic Resonance Imaging Detects Progression of Lung Disease and Impact of Newborn Screening in Preschool Children with Cystic Fibrosis', American Journal of Respiratory & Critical Care Medicine, 204(8), pp. 943-953.
147. Preventive Inhalation of Hypertonic Saline in Infants with Cystic Fibrosis (PRESIS). A Randomized, Double-Blind, Controlled Study	Preventive Inhalation of Hypertonic Saline in Infants with Cystic Fibrosis (PRESIS). A Randomized, Double-Blind, Controlled Study
148. Acute pulmonary exacerbation is not associated with increased energy expenditure in children with cystic fibrosis	Stallings, V. A., Fung, E. B., Hofley, P. M. and Scanlin, T. F. (1998) 'Acute pulmonary exacerbation is not associated with increased energy expenditure in children with cystic fibrosis', The Journal of pediatrics, 132(3 Pt 1), pp. 493-9.
149. A phase 3, open-label, randomized trial to evaluate the safety and efficacy of levofloxacin inhalation solution (APT-1026) versus tobramycin inhalation solution in stable cystic fibrosis patients	Stuart Elborn, J., Geller, D. E., Conrad, D., Aaron, S. D., Smyth, A. R., Fischer, R., Kerem, E., Bell, S. C., Loutit, J. S., Dudley, M. N., Morgan, E. E., VanDevanter, D. R. and Flume, P. A. (2015) 'A phase 3, open-label, randomized trial to evaluate the safety and efficacy of levofloxacin inhalation solution (APT-1026) versus tobramycin inhalation solution in stable cystic fibrosis patients', Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society, 14(4), pp. 507-14.
150. Comparison of hypertonic saline and alternate-day or daily recombinant human deoxyribonuclease in children with cystic fibrosis: A randomised trial	Suri, R., Metcalfe, C., Lees, B., Grieve, R., Flather, M., Normand, C., Thompson, S., Bush, A. and Wallis, C. (2001) 'Comparison of hypertonic saline and alternate-day or daily recombinant human deoxyribonuclease in children with cystic fibrosis: a randomised trial', Lancet (London, England), 358(9290), pp. 1316-21.
151. Assessing the usefulness of outcomes measured in a cystic fibrosis treatment trial	Suri, R., Metcalfe, C., Wallis, C. and Bush, A. (2007) 'Assessing the usefulness of outcomes measured in a cystic fibrosis treatment trial', Respiratory medicine, 101(2), pp. 254-60.

152. Vitamin D for the Immune System in Cystic Fibrosis (DISC): a double-blind, multicenter, randomized, placebo-controlled clinical trial	Tangpricha, V., Lukemire, J., Chen, Y., Binongo, J. N. G., Judd, S. E., Michalski, E. S., Lee, M. J., Walker, S., Ziegler, T. R., Tirouvanziam, R., Zughaier, S. M., Chesdachai, S., Hermes, W. A., Chmiel, J. F., Grossmann, R. E., Gaggar, A., Joseph, P. M. and Alvarez, J. A. (2019) 'Vitamin D for the Immune System in Cystic Fibrosis (DISC): a double-blind, multicenter, randomized, placebo-controlled clinical trial', American Journal of Clinical Nutrition, 109(3), pp. 544-553.
153. Validating chest MRI to detect and monitor cystic fibrosis lung disease in a pediatric cohort	Tepper, L. A., Ciet, P., Caudri, D., Quittner, A. L., Utens, E. M. W. J. and Tiddens, H. A. W. M. (2016) 'Validating chest MRI to detect and monitor cystic fibrosis lung disease in a pediatric cohort', Pediatric pulmonology, 51(1), pp. 34-41.
154. Impact of bronchiectasis and trapped air on quality of life and exacerbations in cystic fibrosis	Tepper, L. A., Utens, E. M. W. J., Caudri, D., Bos, A. C., Gonzalez-Graniel, K., Duivenvoorden, H. J., van der Wiel, E. C. W., Quittner, A. L. and Tiddens, H. A. W. M. (2013) 'Impact of bronchiectasis and trapped air on quality of life and exacerbations in cystic fibrosis', The European respiratory journal, 42(2), pp. 371-9.
155. A multi-centre, randomized, controlled trial on coaching and telemonitoring in patients with cystic fibrosis: conneCT CF	Thee, S., Stahl, M., Fischer, R., Sutharsan, S., Ballmann, M., Müller, A., Lorenz, D., Urbanski-Rini, D., Püschner, F., Amelung, V. E., Fuchs, C. and Mall, M. A. (2021) 'A multi-centre, randomized, controlled trial on coaching and telemonitoring in patients with cystic fibrosis: conneCT CF', BMC Pulmonary Medicine, 21(1), pp. 1-11.
156. Comparative efficacy and safety of 4 randomized regimens to treat early Pseudomonas aeruginosa infection in children with cystic fibrosis	Treggiari, M. M., Retsch-Bogart, G., Mayer-Hamblett, N., Khan, U., Kulich, M., Kronmal, R., Williams, J., Hiatt, P., Gibson, R. L., Spencer, T., Orenstein, D., Chatfield, B. A., Froh, D. K., Burns, J. L., Rosenfeld, M. and Ramsey, B. W. (2011) 'Comparative efficacy and safety of 4 randomized regimens to treat early Pseudomonas aeruginosa infection in children with cystic fibrosis', Archives of pediatrics & adolescent medicine, 165(9), pp. 847-56.
157. Early anti-pseudomonal acquisition in young patients with cystic fibrosis: Rationale and design of the EPIC clinical trial and observational study	Treggiari, M. M., Rosenfeld, M., Mayer-Hamblett, N., Retsch-Bogart, G., Gibson, R. L., Williams, J., Emerson, J., Kronmal, R. A. and Ramsey, B. W. (2009) 'Early anti-pseudomonal acquisition in young patients with cystic fibrosis: rationale and design of the EPIC clinical trial and observational study'', Contemporary clinical trials, 30(3), pp. 256-68.
158. Probiotics in cystic fibrosis patients: A double blind crossover placebo controlled study: Pilot study from the ESPGHAN Working Group on Pancreas/CF	Van Biervliet, S., Hauser, B., Verhulst, S., Stepman, H., Delanghe, J., Warzee, J.-P., Pot, B., Vandewiele, T. and Wilschanski, M. (2018) 'Probiotics in cystic fibrosis patients: A double blind crossover placebo controlled study: Pilot study from the ESPGHAN Working Group on Pancreas/CF', Clinical nutrition ESPEN, 27, pp. 59-65.
159. Factors associated with changes in health-related quality of life in children with cystic fibrosis during 1-year follow-up.	Horck, M., Winkens, B., Wesseling, G., Winter-de Groot, K., Vreede, I., Jöbsis, Q., Dompeling, E., van Horck, M., de Winter-de Groot, K., de Vreede, I. and Jöbsis, Q. (2017) 'Factors associated with changes in health-related quality of life in children with cystic fibrosis during 1-year follow-up', European Journal of Pediatrics, 176(8), pp. 1047-1054.
160. Early detection of pulmonary exacerbations in children with Cystic Fibrosis by electronic home monitoring of symptoms and lung function	van Horck, M., Winkens, B., Wesseling, G., van Vliet, D., van de Kant, K., Vaassen, S., de Winter-de Groot, K., de Vreede, I., Jobsis, Q. and Dompeling, E. (2017) 'Early detection of pulmonary exacerbations in children with Cystic Fibrosis by electronic home monitoring of symptoms and lung function', Scientific reports, 7(1), pp. 12350.
161. Lung clearance index predicts pulmonary exacerbations in young patients with cystic fibrosis	Vermeulen, F., Proesmans, M., Boon, M., Havermans, T. and De Boeck, K. (2014) 'Lung clearance index predicts pulmonary exacerbations in young patients with cystic fibrosis', Thorax, 69(1), pp. 39-45.
162. Withdrawal of dornase alfa increases ventilation inhomogeneity in children with cystic fibrosis	Voldby, C., Green, K., Philipsen, L., Sandvik, R.M., Skov, M., Buchvald, F., Pressler, T. and Nielsen, K.G., 2021. Withdrawal of dornase alfa increases ventilation inhomogeneity in children with cystic fibrosis. Journal of Cystic Fibrosis, 20(6), pp.949-956.

163. The effects of the addition of a new airway clearance device to chest physiotherapy in children with cystic fibrosis pulmonary exacerbations	Walicka-Serzysko, K., Postek, M., Jeneralska, N., Cichocka, A., Milczewska, J. and Sands, D., 2021. The effects of the addition of a new airway clearance device to chest physiotherapy in children with cystic fibrosis pulmonary exacerbations. Journal of Mother and Child, 24(3), pp.16-24.
164. Efficacy of lumacaftor/ivacaftor in patients with mild lung disease	Wang J. (2017) 'Efficacy of lumacaftor/ivacaftor in patients with mild lung disease', Pediatric pulmonology., 52(Supplement 47), .
165. Airway clearance by exercising in mild cystic fibrosis (ACE-CF): A feasibility study	Ward, N., Stiller, K., Rowe, H., Morrow, S., Morton, J., Greville, H. and Holland, A.E., 2018. Airway clearance by exercising in mild cystic fibrosis (ACE-CF): a feasibility study. Respiratory medicine, 142, pp.23-28.
166. Time course and recovery of arterial blood gases during exacerbations in adults with Cystic Fibrosis	Waterhouse, D. F., mclaughlin, A. M. And Gallagher, C. G. (2009) 'Time course and recovery of arterial blood gases during exacerbations in adults with Cystic Fibrosis', Journal of Cystic Fibrosis, 8(1), pp. 9-13.
167. Lung clearance index during hospital admission in school-age children with cystic fibrosis	Welsh, L., Nesci, C., Tran, H., Tomai, M. And Ranganathan, S. (2014) 'Lung clearance index during hospital admission in school-age children with cystic fibrosis', Journal of Cystic Fibrosis, 13(6), pp. 687-691.
168. Glucose Tolerance during Pulmonary Exacerbations in Children with Cystic Fibrosis	Widger, J., Oliver, M.R., O'Connell, M., Cameron, F.J., Ranganathan, S. and Robinson, P.J., 2012. Glucose tolerance during pulmonary exacerbations in children with cystic fibrosis.
169. Acute respiratory infection in patients with cystic fibrosis with mild pulmonary impairment: comparison of two physiotherapy regimens	Williams, M.T., Parsons, D.W., Frick, R.A., Ellis, E.R., Martin, A.J., Giles, S.E. and Grant, E.R., 2001. Acute respiratory infection in patients with cystic fibrosis with mild pulmonary impairment: comparison of two physiotherapy regimens. Australian journal of physiotherapy, 47(4), pp.227-236.
170. Aerosolized recombinant human DNase in hospitalized cystic fibrosis patients with acute pulmonary exacerbations	Wilmott, R.W., Amin, R.S., Colin, A.A., devault, A., Dozor, A.J., Eigen, H., Johnson, C., Lester, L.A., mccoy, K., mckean, L.P. and Moss, R., 1996. Aerosolized recombinant human dnase in hospitalized cystic fibrosis patients with acute pulmonary exacerbations. American journal of respiratory and critical care medicine, 153(6), pp.1914-1917.
171. Effect of long term treatment with azithromycin on disease parameters in cystic fibrosis: a randomised trial	Wolter, J., Seeney, S., Bell, S., Bowler, S., Masel, P. and McCormack, J., 2002. Effect of long term treatment with azithromycin on disease parameters in cystic fibrosis: a randomised trial. Thorax, 57(3), pp.212-216.
172. A smartphone application for reporting symptoms in adults with cystic fibrosis improves the detection of exacerbations: Results of a randomised controlled trial	Wood, J., Jenkins, S., Putrino, D., Mulrennan, S., Morey, S., Cecins, N., Bear, N. and Hill, K., 2020. A smartphone application for reporting symptoms in adults with cystic fibrosis improves the detection of exacerbations: Results of a randomised controlled trial. Journal of Cystic Fibrosis, 19(2), pp.271-276.
173. The impact of treatment of pulmonary exacerbations on the health-related quality of life of patients with cystic fibrosis: does hospitalization make a difference?	Yi, M. S., Tsevat, J., Wilmott, R. W., Kotagal, U. R. And Britto, M. T. (2004) 'The impact of treatment of pulmonary exacerbations on the health-related quality of life of patients with cystic fibrosis: does hospitalization make a difference?', Journal of Pediatrics, 144(6), pp. 711-718.
174. Clinical predictors of cystic fibrosis chronic rhinosinusitis severity	Zemke, A.C., Nouraie, S.M., Moore, J., Gaston, J.R., Rowan, N.R., Pilewski, J.M., Bomberger, J.M. and Lee, S.E., 2019, July. Clinical predictors of cystic fibrosis chronic rhinosinusitis severity. In International forum of allergy & rhinology (Vol. 9, No. 7, pp. 759-765).
175. Twice vs three-times daily antibiotics in the treatment of pulmonary exacerbations of cystic fibrosis	Adeboyeku, D., Jones, A.L. and Hodson, M.E., 2011. Twice vs three-times daily antibiotics in the treatment of pulmonary exacerbations of cystic fibrosis. Journal of Cystic Fibrosis, 10(1), pp.25-30.
176. Increase in exhaled carbon monoxide during exacerbations of cystic fibrosis	Antuni, J.D., Kharitonov, S.A., Hughes, D., Hodson, M.E. and Barnes, P.J., 2000. Increase in exhaled carbon monoxide during exacerbations of cystic fibrosis. Thorax, 55(2), pp.138-142.

177. Long term azithromycin in children with cystic fibrosis: A randomised, placebo-controlled crossover trial	Equi, A., Balfour-Lynn, I.M., Bush, A. and Rosenthal, M., 2002. Long term azithromycin in children with cystic fibrosis: a randomised, placebo-controlled crossover trial. The Lancet, 360(9338), pp.978-984.
178. 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	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
179. Efficacy and safety of lumacaftor and ivacaftor in patients aged 6–11 years with cystic fibrosis homozygous for F508del-CFTR: a randomised, placebo-controlled phase 3 trial	Ratjen, F., Hug, C., Marigowda, G., Tian, S., Huang, X., Stanojevic, S., Milla, C. E., Robinson, P. D., Waltz, D., Davies, J. C., Rosenfeld, M., Starner, T., Retsch-Bogart, G., Chmiel, J., Orenstein, D., Milla, C., Rubenstein, R., Walker, S., Cornell, A., Asfour, F., Black, P., Colombo, J., Froh, D., McColley, S., Ruiz, F., Quintero, D., Casey, A., Mueller, G., Flume, P., Livingston, F., Rock, M., O'Sullivan, B., Schmidt, H., Lahiri, T., McNamara, J., Chidekel, A., Sass, L., Keens, T., Schaeffer, D., Solomon, M., Chilvers, M., Lands, L., Junge, S., Griese, M., Staab, D., Pressler, T., van Koningsburggen-Rietschel, S., Naehrlich, L., Reid, A., Balfour-Lynn, I., Urquhart, D., Lee, T., Munck, A., Gaudelus, I. S., De Boeck, C., Reix, P., Malfroot, A., Bui, S., Selvadurai, H., Robinson, P., Wainwright, C., Clements, B., Hilton, J. and Hjelte, L. (2017) 'Efficacy and safety of lumacaftor and ivacaftor in patients aged 6–11 years with cystic fibrosis homozygous for F508del-CFTR: a randomised, placebo-controlled phase 3 trial', The Lancet Respiratory Medicine, 5(7), pp. 557-567.
180. Long-term safety and efficacy of lumacaftor-ivacaftor therapy in children aged 6-11 years with cystic fibrosis homozygous for the F508del-CFTR mutation: a phase 3, open-label, extension study	Chilvers, M. A., Davies, J. C., Milla, C., Tian, S., Han, Z., Cornell, A. G., Owen, C. A. and Ratjen, F. (2021) 'Long-term safety and efficacy of lumacaftor-ivacaftor therapy in children aged 6-11 years with cystic fibrosis homozygous for the F508del-CFTR mutation: a phase 3, open-label, extension study', The Lancet. Respiratory medicine, 9(7), pp. 721-732.
181. Tezacaftor–Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del	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. and Elborn, J. S. (2017) 'Tezacaftor-Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del', The New England journal of medicine, 377(21), pp. 2013-2023.
182. Evolution of pulmonary function during an acute exacerbation in hospitalized patients with cystic fibrosis	Gozal, D., Bailey, S. L. and Keens, T. G. (1993) 'Evolution of pulmonary function during an acute exacerbation in hospitalized patients with cystic fibrosis', Pediatric Pulmonology, 16(6), pp. 347-53.
183. Long-term amikacin liposome inhalation suspension in cystic fibrosis patients with chronic P. aeruginosa infection	Bilton, D., Fajac, I., Pressler, T., Clancy, J. P., Sands, D., Minic, P., Cipolli, M., Galeva, I., Sole, A., Quittner, A. L., Jumadilova, Z., Ciesielska, M. and Konstan, M. W. (2021) 'Long-term amikacin liposome inhalation suspension in cystic fibrosis patients with chronic P. aeruginosa infection', Journal of Cystic Fibrosis, 20(6), pp. 1010-1017.
184. Impact of exacerbations of cystic fibrosis on muscle strength	Burtin, C., Van Remoortel, H., Vrijsen, B., Langer, D., Colpaert, K., Gosselink, R., Decramer, M., Dupont, L. and Troosters, T. (2013) 'Impact of exacerbations of cystic fibrosis on muscle strength', Respiratory Research, 14(1).
185. Long term effects of azithromycin in patients with cystic fibrosis: A double blind, placebo controlled trial	Clement, A., Tamalet, A., Leroux, E., Ravilly, S., Fauroux, B. and Jais, J. P. (2006) 'Long term effects of azithromycin in patients with cystic fibrosis: A double blind, placebo controlled trial', Thorax, 61(10), pp. 895-902.
186. Longitudinal trends in health-related quality of life in adults with cystic fibrosis	Dill, E. J., Dawson, R., Sellers, D. E., Robinson, W. M. and Sawicki, G. S. (2013) 'Longitudinal trends in health-related quality of life in adults with cystic fibrosis', Chest, 144(3), pp. 981-989.
187. Safety and efficacy of prolonged levofloxacin inhalation solution (APT-1026) treatment for cystic fibrosis and chronic Pseudomonas aeruginosa airway infection	Elborn, J. S., Flume, P. A., Cohen, F., Loutit, J. and VanDevanter, D. R. (2016) 'Safety and efficacy of prolonged levofloxacin inhalation solution (APT-1026) treatment for cystic fibrosis and chronic Pseudomonas aeruginosa airway infection', Journal of Cystic Fibrosis, 15(5), pp. 634-640.

188. Carbohydrate metabolism impairment in children and adolescents with cystic fibrosis	Escudero Garcia, J., Martin Rivada, A., Uribe Posada, A., Sanz Santiago, V., Argente, J. and Martos-Moreno, G. A. (2022) 'Carbohydrate metabolism impairment in children and adolescents with cystic fibrosis', Endocrinologia, Diabetes y Nutricion, 69(8), pp. 576-583.
189. Ozone is associated with an increased risk of respiratory exacerbations in patients with cystic fibrosis	Farhat, S. C. L., Almeida, M. B., Silva-Filho, L. V. R. F., Farhat, J., Rodrigues, J. C. and Braga, A. L. F. (2013) 'Ozone is associated with an increased risk of respiratory exacerbations in patients with cystic fibrosis', Chest, 144(4), pp. 1186-1192.
190. Intravenous colistin sulphomethate in acute respiratory exacerbations in adult patients with cystic fibrosis	Conway, S. P., Pond, M. N., Watson, A., Etherington, C., Robey, H. L. and Goldman, M. H. (1997) 'Intravenous colistin sulphomethate in acute respiratory exacerbations in adult patients with cystic fibrosis', Thorax, 52(11), pp. 987-93.
191. The Differential Clinical Impact of Human Coronavirus Species in Children With Cystic Fibrosis	Da Silva Filho, L. V. R. F., Zerbinati, R. M., Tateno, A. F., Boas, L. V., De Almeida, M. B., Levi, J. E., Drexler, J. F., Drosten, C. and Pannuti, C. S. (2012) 'The differential clinical impact of human coronavirus species in children with cystic fibrosis', Journal of Infectious Diseases, 206(3), pp. 384-388.
192. Impact of routine spirometry in the frequency of acute pulmonary exacerbation diagnosis in cystic fibrosis	De Aquino Mota, C. S. B., Da Silva Filho, L. V. R. F. and Rodrigues, J. C. (2016) 'Impact of routine spirometry in the frequency of acute pulmonary exacerbation diagnosis in cystic fibrosis', Pediatric Pulmonology, 51(Supplement 42), pp. S50.
193. Sinonasal quality-of-life declines in cystic fibrosis patients with pulmonary exacerbations	Safi, C., DiMango, E., Keating, C., Zhou, Z. and Gudis, D. A. (2020) 'Sinonasal quality-of-life declines in cystic fibrosis patients with pulmonary exacerbations', International forum of allergy & rhinology, 10(2), pp. 194-198.
194. Increasing Vitamin D Serum Levels Is Associated With Reduced Pulmonary Exacerbations in Patients With Cystic Fibrosis	Abu-Fraiha, Y., Elyashar-Earon, H., Shoseyov, D., Cohen-Cymberknoh, M., Armoni, S., Kerem, E. and Wilschanski, M. (2019) 'Increasing Vitamin D Serum Levels Is Associated With Reduced Pulmonary Exacerbations in Patients With Cystic Fibrosis', Journal of Pediatric Gastroenterology and Nutrition, 68(1), pp. 110-115.
195. Procalcitonin predicts the severity of cystic fibrosis pulmonary exacerbations and readmissions in adult patients: a prospective cohort study	Bailey, K. L., Murphy, P. J., Lineberry, O. K., Haack, M. R., Dickinson, J. D. and Kalil, A. C. (2020) 'Procalcitonin predicts the severity of cystic fibrosis pulmonary exacerbations and readmissions in adult patients: a prospective cohort study', Journal of investigative medicine : the official publication of the American Federation for Clinical Research, 68(4), pp. 856-863.
196. Increased physical activity post-exacerbation is associated with decreased systemic inflammation in cystic fibrosis – An observational study	Burton, K., Morris, N. R., Reid, D., Smith, D. and Kuys, S. (2020) Increased physical activity post-exacerbation is associated with decreased systemic inflammation in cystic fibrosis – An observational study, Philadelphia, Pennsylvania: Taylor & Francis Ltd (0959-3985. Available at: https://search.ebscohost.com/login.aspx?direct=true&db=cin20&AN=146906644&site=ehost-live.
197. Divergent dynamics of inflammatory mediators and multiplex PCRs during airway infection in cystic fibrosis patients and healthy controls: Serial upper airway sampling by nasal lavage	Erdmann, N., Schilling, T., Hentschel, J., Lehmann, T., von Bismarck, P., Ankermann, T., Duckstein, F., Baier, M., Zagoya, C. and Mainz, J. G. (2022) 'Divergent dynamics of inflammatory mediators and multiplex PCRs during airway infection in cystic fibrosis patients and healthy controls: Serial upper airway sampling by nasal lavage', Frontiers in Immunology, 13, pp. 947359.
198. Role of respiratory viruses in pulmonary exacerbations in children with cystic fibrosis	Asner, S., Waters, V., Solomon, M., Yau, Y., Richardson, S. E., Grasemann, H., Gharabaghi, F. and Tran, D. (2012) 'Role of respiratory viruses in pulmonary exacerbations in children with cystic fibrosis', Journal of Cystic Fibrosis, 11(5), pp. 433-439.
199. Inhaled aztreonam lysine for chronic airway Pseudomonas aeruginosa in cystic fibrosis	McCoy, K. S., Quittner, A. L., Oermann, C. M., Gibson, R. L., Retsch-Bogart, G. Z. and Montgomery, A. B. (2008) 'Inhaled aztreonam lysine for chronic airway Pseudomonas aeruginosa in cystic fibrosis', American Journal of Respiratory and Critical Care Medicine, 178(9), pp. 921-8.

200. Evaluation of Copeptin during Pulmonary Exacerbation in Cystic Fibrosis	Wojsyk-Banaszak, I., Sobkowiak, P., Jonczyk-Potoczna, K., Narozna, B., Langwinski, W., Szczepanik, M., Kycler, Z., Breborowicz, A. and Szczepankiewicz, A. (2019) 'Evaluation of Copeptin during Pulmonary Exacerbation in Cystic Fibrosis', Mediators of Inflammation, 2019, pp. 1939740.
201. Adult cystic fibrosis exacerbations and new strains of Pseudomonas aeruginosa	Aaron, S. D., Ramotar, K., Ferris, W., Vandemheen, K., Saginur, R., Tullis, E., Haase, D., Kottachchi, D., St. Denis, M. and Chan, F. (2004) 'Adult cystic fibrosis exacerbations and new strains of Pseudomonas aeruginosa', American Journal of Respiratory & Critical Care Medicine, 169(7), pp. 811-815.
202. Effect of Bronchoalveolar Lavage–Directed Therapy on Pseudomonas aeruginosa Infection and Structural Lung Injury in Children With Cystic Fibrosis	Wainwright, C. E., Vidmar, S., Armstrong, D. S., Byrnes, C. A., Carlin, J. B., Cheney, J., Cooper, P. J., Grimwood, K., Moodie, M., Robertson, C. F. and Tiddens, H. A. (2011) 'Effect of bronchoalveolar lavage-directed therapy on Pseudomonas aeruginosa infection and structural lung injury in children with cystic fibrosis: a randomized trial', JAMA, 306(2), pp. 163-71.
203. Pulmonary function, inflammation, exercise capacity and quality of life in cystic fibrosis	Bradley, J., McAlister, O. and Elborn, S. (2001) 'Pulmonary function, inflammation, exercise capacity and quality of life in cystic fibrosis', The european respiratory journal, 17(4), pp. 712-5.
204. Health values of adolescents with cystic fibrosis	Yi, M. S., Britto, M. T., Wilmott, R. W., Kotagal, U. R., Eckman, M. H., Nielson, D. W., Kociela, V. L. and Tsevat, J. (2003) 'Health values of adolescents with cystic fibrosis', The Journal of Pediatrics, 142(2), pp. 133-40.
205. Real-time, once-daily monitoring of symptoms and FEV in cystic fibrosis patients--a feasibility study using a novel device	Sarfaraz, S., Sund, Z. and Jarad, N. (2010) 'Real-time, once-daily monitoring of symptoms and FEV in cystic fibrosis patients--a feasibility study using a novel device', The clinical respiratory journal, 4(2), pp. 74-82.
206. Is HBA1C a useful marker for pulmonary exacerbations in patients with CF but no known diabetes?	Srivastava, S. A., Burgess, J. C., Bilton, D., Hodson, M. E., Gyi, K. M. And Baker, E. H. (2010) 'Is HBA1C a useful marker for pulmonary exacerbations in patients with CF but no known diabetes?', Pediatric Pulmonology, 45(SUPPL. 33), pp. 375.
207. Physical activity levels of patients with cystic fibrosis hospitalised with an acute respiratory exacerbation	Ward, N., White, D., Rowe, H., Stiller, K. and Sullivan, T. (2013) 'Physical activity levels of patients with cystic fibrosis hospitalised with an acute respiratory exacerbation', Respiratory Medicine, 107(7), pp. 1014-20.
208. The lung clearance index can detect acute respiratory events in school-age children with cystic fibrosis	Perrem, L., Klingel, M., Stanojevic, S., Isaac, S. M., Jensen, R., Sanders, D. B., Solomon, M., Grasemann, H., Waters, V. J., Sweezey, N., Davis, S. D. And Ratjen, F. (2019) 'The lung clearance index can detect acute respiratory events in school-age children with cystic fibrosis', Pediatric Pulmonology, 54(Supplement 2), pp. 361.
209. Once-daily tobramycin in the treatment of adult patients with cystic fibrosis A.	Whitehead, A., Conway, S. P., Etherington, C., Caldwell, N. A., Setchfield, N. and Bogle, S. (2002) 'Once-daily tobramycin in the treatment of adult patients with cystic fibrosis', European Respiratory Journal, 19(2), pp. 303-309.
210. Symptom duration and the lung clearance index in children with cystic fibrosis and pulmonary exacerbations	Perrem, L., Stanojevic, S., Klingel, M., Isaac, S., Jensen, R., Solomon, M., Grasemann, H., Waters, V., Sweezey, N., Davis, S. And Ratjen, F. (2019) 'Symptom duration and the lung clearance index in children with cystic fibrosis and pulmonary exacerbations', European Respiratory Journal, 54(Supplement 63).
211. Replacement of hospital clinic appointments with telehealth appointments delivered directly to the home for people with cystic fibrosis (CF)	Actrn (2020) 'Replacement of hospital clinic appointments with telehealth appointments delivered directly to the home for people with cystic fibrosis (CF)', https://trialsearch.who.int/Trial2.aspx?Trialid=ACTRN12620000311954.
212. The Lung Clearance Index detects incomplete lung function recovery with acute respiratory events in school-age children with cystic fibrosis	Perrem, L., Stanojevic, S., Shaw, M., Jensen, R., Guido, J., Solomon, M., Grasemann, H., Sweezey, N., Davies, S., Sanders, D. B., mcdonald, N., Isaac, S., Jara, S., Clem, C. And Ratjen, F. (2020) 'The Lung Clearance Index detects incomplete lung function recovery with acute respiratory events in school-age children with cystic fibrosis', European Respiratory Journal, 56(Supplement 64).

213. Iron Deficiency in Cystic Fibrosis: A Cross-Sectional Single-Centre Study in a Referral Adult Centre	Lobbes, H., Durupt, S., Mainbourg, S., Pereira, B., Nove-Josserand, R., Durieu, I. and Reynaud, Q. (2022) 'Iron Deficiency in Cystic Fibrosis: A Cross-Sectional Single-Centre Study in a Referral Adult Centre', Nutrients, 14(3).
214. Impact of vitamin D status on CF and non-CF bronchiectasis outcomes	Ali, H. A., Deraz, T. E., Mohamed, D. A. and Mahmoud, M. Z. (2022) 'Impact of vitamin D status on CF and non-CF bronchiectasis outcomes', Egyptian Pediatric Association Gazette, 70(1), pp. 3.
215. Effect of azithromycin maintenance treatment on infectious exacerbations among patients with non-cystic fibrosis bronchiectasis: the BAT randomized controlled trial	Altenburg, J., de Graaff, C. S., Stienstra, Y., Sloos, J. H., van Haren, E. H. J., Koppers, R. J. H., van der Werf, T. S. and Boersma, W. G. (2013) 'Effect of azithromycin maintenance treatment on infectious exacerbations among patients with non-cystic fibrosis bronchiectasis: the BAT randomized controlled trial', JAMA, 309(12), pp. 1251-9.
216. The efficacy and safety of meropenem and tobramycin vs ceftazidime and tobramycin in the treatment of acute pulmonary exacerbations in patients with cystic fibrosis	Blumer, J. L., Saiman, L., Konstan, M. W. and Melnick, D. (2005) 'The efficacy and safety of meropenem and tobramycin vs ceftazidime and tobramycin in the treatment of acute pulmonary exacerbations in patients with cystic fibrosis', Chest, 128(4), pp. 2336-2346.
217. Lessons from a French collaborative case–control study in cystic fibrosis patients during the 2009 A/H1N1 influenza pandemy	Bucher, J., Boelle, P. Y., Hubert, D., Lebourgeois, M., Stremler, N., Durieu, I., Bremont, F., Deneuville, E., Delaisi, B., Corvol, H., Bassinet, L., Grenet, D., Remus, N., Vodoff, M. V., Boussaud, V., Troussier, F., Leruez-Ville, M., Treluyer, J. M., Launay, O. and Sermet-Gaudelus, I. (2016) 'Lessons from a French collaborative case-control study in cystic fibrosis patients during the 2009 A/H1N1 influenza pandemy', BMC Infectious Diseases, 16(1), pp. 55.
218. Safety and efficacy of lenabasum in a phase 2 randomized, placebo-controlled trial in adults with cystic fibrosis	Chmiel, J. F., Flume, P., Downey, D. G., Dozor, A. J., Colombo, C., Mazurek, H., Sapiejka, E., Rachel, M., Constantine, S., Conley, B., Dgetluck, N., Dinh, Q., White, B. and Elborn, J. S. (2021) 'Safety and efficacy of lenabasum in a phase 2 randomized, placebo-controlled trial in adults with cystic fibrosis', Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society, 20(1), pp. 78-85.
219. Safety and tolerability of bolus intravenous colistin in acute respiratory exacerbations in adults with cystic fibrosis	Conway, S. P., Etherington, C., Munday, J., Goldman, M. H., Strong, J. J., Wootton, M., Conway, S. P., Etherington, C., Munday, J., Goldman, M. H., Strong, J. J. and Wootton, M. (2000) 'Safety and tolerability of bolus intravenous colistin in acute respiratory exacerbations in adults with cystic fibrosis', Annals of Pharmacotherapy, 34(11), pp. 1238-1242.
220. Oral cysteamine as an adjunct treatment in cystic fibrosis pulmonary exacerbations: An exploratory randomized clinical trial.	Devereux, G., Wrolstad, D., Bourke, S. J., Daines, C. L., Doe, S., Dougherty, R., Franco, R., Innes, A., Kopp, B. T., Lascano, J., Layish, D., MacGregor, G., Murray, L., Peckham, D., Lucidi, V., Lovie, E., Robertson, J., Fraser-Pitt, D. J. and O'Neil, D. A. (2020) 'Oral cysteamine as an adjunct treatment in cystic fibrosis pulmonary exacerbations: An exploratory randomized clinical trial', PLoS ONE, 15(12), pp. e0242945.
221. Oral corticosteroid therapy in cystic fibrosis patients hospitalized for pulmonary exacerbation: a pilot study	Dovey, M., Aitken, M. L., Emerson, J., McNamara, S., Waltz, D. A. and Gibson, R. L. (2007) 'Oral corticosteroid therapy in cystic fibrosis patients hospitalized for pulmonary exacerbation: a pilot study', Chest, 132(4), pp. 1212-8.
222. The effect of the weather on pulmonary exacerbations and viral infections among adults with cystic fibrosis	Flight, W. G., Bright-Thomas, R. J., Sarran, C., Mutton, K. J., Morris, J., Webb, A. K. and Jones, A. M. (2014) 'The effect of the weather on pulmonary exacerbations and viral infections among adults with cystic fibrosis', International Journal of Biometeorology, 58(9), pp. 1845-51.
223. Incidence and clinical impact of respiratory viruses in adults with cystic fibrosis	Flight, W. G., Bright-Thomas, R. J., Tilston, P., Mutton, K. J., Guiver, M., Morris, J., Webb, A. K. and Jones, A. M. (2014) 'Incidence and clinical impact of respiratory viruses in adults with cystic fibrosis', Thorax, 69(3), pp. 247-53.
224. Iron supplementation does not worsen respiratory health or alter the sputum microbiome in cystic fibrosis	Gifford, A. H., Alexandru, D. M., Li, Z., Dorman, D. B., Moulton, L. A., Price, K. E., Hampton, T. H., Sogin, M. L., Zuckerman, J. B., Parker, H. W., Stanton, B. A. and O'Toole, G. A. (2014) 'Iron supplementation does not worsen respiratory health or alter the sputum microbiome in cystic fibrosis', Journal of Cystic Fibrosis, 13(3), pp. 311-318.

225. Increased prevalence of Pneumocystis jirovecii colonisation in acute pulmonary exacerbations of cystic fibrosis	Green, H. D., Bright-Thomas, R. J., Mutton, K. J., Guiver, M. and Jones, A. M. (2016) 'Increased prevalence of Pneumocystis jirovecii colonisation in acute pulmonary exacerbations of cystic fibrosis', Journal of Infection, 73(1), pp. 1-7.
226. Relationship of pulmonary outcomes, microbiology, and serum antibiotic concentrations in cystic fibrosis patients	Hahn, A., Jensen, C., Fanous, H., Chaney, H., Sami, I., Perez, G. F., Louie, S., Koumbourlis, A. C., Bost, J. E. and van den Anker, J. N. (2018) 'Relationship of pulmonary outcomes, microbiology, and serum antibiotic concentrations in cystic fibrosis patients', Journal of Pediatric Pharmacology and Therapeutics, 23(5), pp. 379-389.
227. The presence of Aspergillus fumigatus is associated with worse respiratory quality of life in cystic fibrosis	Hong, G., Alby, K., Ng, S. C. W., Fleck, V., Kubrak, C., Rubenstein, R. C., Dorgan, D. J., Kawut, S. M. and Hadjiliadis, D. (2020) 'The presence of Aspergillus fumigatus is associated with worse respiratory quality of life in cystic fibrosis', Journal of Cystic Fibrosis, 19(1), pp. 125-130.
228. Continuous versus intermittent infusions of ceftazidime for treating exacerbation of cystic fibrosis	Hubert, D., Le Roux, E., Lavrut, T., Wallaert, B., Scheid, P., Manach, D., Grenet, D., Sermet-Gaudelus, I., Ramel, S., Cracowski, C., Sardet, A., Wizla, N., Deneuville, E. and Garraffo, R. (2009) 'Continuous versus intermittent infusions of ceftazidime for treating exacerbation of cystic fibrosis', Antimicrobial Agents and Chemotherapy, 53(9), pp. 3650-3656.
229. Factors Associated with Worse Lung Function in Cystic Fibrosis Patients with Persistent Staphylococcus aureus.	Junge, S., Gorlich, D., den Reijer, M., Wiedemann, B., Tummler, B., Ellemunter, H., Dubbers, A., Kuster, P., Ballmann, M., Koerner-Rettberg, C., Grose-Onnebrink, J., Heuer, E., Sextro, W., Mainz, J. G., Hammermann, J., Riethmuller, J., Graepler-Mainka, U., Staab, D., Wollschlager, B., Szczepanski, R., Schuster, A., Tegtmeyer, F.-K., Sutharsan, S., Wald, A., Nofer, J.-R., van Wamel, W., Becker, K., Peters, G. and Kahl, B. C. (2016) 'Factors Associated with Worse Lung Function in Cystic Fibrosis Patients with Persistent Staphylococcus aureus', PLoS ONE, 11(11), pp. e0166220.
230. The renoprotective effect of concomitant fosfomycin in the treatment of pulmonary exacerbations in cystic fibrosis	Al-Aloul, M., Nazareth, D. and Walshaw, M. (2019) 'The renoprotective effect of concomitant fosfomycin in the treatment of pulmonary exacerbations in cystic fibrosis', Clinical Kidney Journal, 12(5), pp. 652-658.
231. Adverse alterations in bone metabolism are associated with lung infection in adults with cystic fibrosis	Aris, R. M., Stephens, A. R., Ontjes, D. A., Blackwood, A. D., Lark, R. K., Hensler, M. B., Neuringer, I. P. and Lester, G. E. (2000) 'Adverse alterations in bone metabolism are associated with lung infection in adults with cystic fibrosis', American Journal of Respiratory and Critical Care Medicine, 162(5), pp. 1674-1678.
232. Association Between Cystic Fibrosis Severity Markers and CFTR Genotypes in Turkish Children	Başaran, A. E., Başaran, A., Kocacik Uygun, D. F., Yılmaz, E., Moballegh, A., Öz, L., Alper, Ö. and Bingöl, A. (2021) 'Association Between Cystic Fibrosis Severity Markers and CFTR Genotypes in Turkish Children', Turkish Thoracic Journal / Turk Toraks Dergisi, 22(6), pp. 426-431.
233. Metabolic and inflammatory responses to pulmonary exacerbation in adults with cystic fibrosis	Bell, S. C., Bowerman, A. M., Nixon, L. E., Macdonald, I. A., Elborn, J. S. and Shale, D. J. (2000) 'Metabolic and inflammatory responses to pulmonary exacerbation in adults with cystic fibrosis', European Journal of Clinical Investigation, 30(6), pp. 553-9.
234. Lactate in cystic fibrosis sputum	Bensel, T., Stotz, M., Borneff-Lipp, M., Wollschlager, B., Wienke, A., Taccetti, G., Campana, S., Meyer, K. C., Jensen, P. O., Lechner, U., Ulrich, M., Doring, G. and Worlitzsch, D. (2011) 'Lactate in cystic fibrosis sputum', Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society, 10(1), pp. 37-44.
235. Application of quantitative PCR to the diagnosis and monitoring of Pseudomonas aeruginosa colonization in 5-18-year-old cystic fibrosis patients	Billard-Pomares, T., Herwegh, S., Wizla-Derambure, N., Turck, D., Courcol, R. and Husson, M.-O. (2011) 'Application of quantitative PCR to the diagnosis and monitoring of Pseudomonas aeruginosa colonization in 5-18-year-old cystic fibrosis patients', Journal of Medical Microbiology, 60(Pt 2), pp. 157-161.

236. Impact of Anaerobic Antibacterial Spectrum on Cystic Fibrosis Airway Microbiome Diversity and Pulmonary Function	Bozzella, M. J., Chaney, H., Sami, I., Koumbourlis, A., Bost, J. E., Zemanick, E. T., Freishtat, R. J., Crandall, K. A. and Hahn, A. (2021) 'Impact of Anaerobic Antibacterial Spectrum on Cystic Fibrosis Airway Microbiome Diversity and Pulmonary Function', Pediatric Infectious Disease Journal, 40(11), pp. 962-968.
237. Effect of cystic fibrosis exacerbations on neutrophil function	Brockbank, S., Downey, D., Elborn, J. S. and Ennis, M. (2005) 'Effect of cystic fibrosis exacerbations on neutrophil function', International Immunopharmacology, 5(3), pp. 601-608.
238. Respiratory viruses in children with cystic fibrosis: Viral detection and clinical findings	Burns, J. L., Emerson, J., Kuypers, J., Campbell, A. P., Gibson, R. L., McNamara, S., Worrell, K. and Englund, J. A. (2012) 'Respiratory viruses in children with cystic fibrosis: Viral detection and clinical findings', Influenza and other Respiratory Viruses, 6(3), pp. 218-223.
239. Serum bactericidal test as a prognostic indicator in acute pulmonary exacerbations of cystic fibrosis.	Cahen, P., Le Bourgeois, M., Delacourt, C., Coustere, C., Nicaise, P., de Blic, J., Veron, M., Scheinmann, P. and Gaillard, J. L. (1993) 'Serum bactericidal test as a prognostic indicator in acute pulmonary exacerbations of cystic fibrosis', Pediatrics, 91(2), pp. 451-5.
240. G-CSF and GM-CSF Modify Neutrophil Functions at Concentrations found in Cystic Fibrosis	Castellani, S., D'Oria, S., Diana, A., Polizzi, A. M., Di Gioia, S., Mariggiò, M. A., Guerra, L., Favia, M., Vinella, A., Leonetti, G., De Venuto, D., Gallo, C., Montemurro, P. and Conese, M. (2019) 'G-CSF and GM-CSF Modify Neutrophil Functions at Concentrations found in Cystic Fibrosis', Scientific Reports, 9(1).
241. Acute effects of viral respiratory tract infections on sputum bacterial density during CF pulmonary exacerbations	Chin, M., De Zoysa, M., Slinger, R., Gaudet, E., Vandemheen, K. L., Chan, F., Hyde, L., Mah, T.-F., Ferris, W., Mallick, R. and Aaron, S. D. (2015) 'Acute effects of viral respiratory tract infections on sputum bacterial density during CF pulmonary exacerbations', Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society, 14(4), pp. 482-9.
242. Acute pulmonary exacerbation and lung function decline in patients with cystic fibrosis: High-mobility group box 1 (HMGB1) between inflammation and infection	Chirico, V., Lacquaniti, A., Leonardi, S., Grasso, L., Rotolo, N., Romano, C., Di Dio, G., Lionetti, E., David, A., Arrigo, T., Salpietro, C. and La Rosa, M. (2015) 'Acute pulmonary exacerbation and lung function decline in patients with cystic fibrosis: High-mobility group box 1 (HMGB1) between inflammation and infection', Clinical Microbiology and Infection, 21(4), pp. 368.e1-368.e9.
243. Lipoxin A4 and interleukin-8 levels in cystic fibrosis sputum after antibiotherapy	Chiron, R., Grumbach, Y. Y., Quynh, N. V. T., Verriere, V. and Urbach, V. (2008) 'Lipoxin A4 and interleukin-8 levels in cystic fibrosis sputum after antibiotherapy', Journal of Cystic Fibrosis, 7(6), pp. 463-468.
244. Sputum Candida albicans presages FEV_1 decline and hospital-treated exacerbations in cystic fibrosis	Chotirmall, S. H., O'Donoghue, E., Bennett, K., Gunaratnam, C., O'Neill, S. J., McElvaney, N. G., Chotirmall, S. H., O'Donoghue, E., Bennett, K., Gunaratnam, C., O'Neill, S. J. and McElvaney, N. G. (2010) 'Sputum Candida albicans presages FEV_1 decline and hospital-treated exacerbations in cystic fibrosis', Chest, 138(5), pp. 1186-1195.
245. Clinical and microbiological profile of chronic Burkholderia cepacia complex infections in a cystic fibrosis reference hospital in Brazil	da Costa Capizzani, C. P., Cacador, N. C., Torres, L. A. G. M. M., Tonani, L., Vandamme, P. and da Costa Darini, A. L. (2017) 'Clinical and microbiological profile of chronic Burkholderia cepacia complex infections in a cystic fibrosis reference hospital in Brazil', European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology, 36(11), pp. 2263-2271.
246. Combination antibiotic susceptibility of biofilm-grown Burkholderia cepacia and Pseudomonas aeruginosa isolated from patients with pulmonary exacerbations of cystic fibrosis	Dales, L., Ferris, W., Vandemheen, K. and Aaron, S. D. (2009) 'Combination antibiotic susceptibility of biofilm-grown Burkholderia cepacia and Pseudomonas aeruginosa isolated from patients with pulmonary exacerbations of cystic fibrosis', European Journal of Clinical Microbiology and Infectious Diseases, 28(10), pp. 1275-1279.
247. Rhinovirus C and respiratory exacerbations in children with cystic fibrosis	de Almeida, M. B., Zerbinati, R. M., Tateno, A. F., Oliveira, C. M., Romão, R. M., Rodrigues, J. C., Pannuti, C. S. and da Silva Filho, L. V. F. (2010) 'Rhinovirus C and respiratory exacerbations in children with cystic fibrosis', Emerging Infectious Diseases, 16(6), pp. 996-999.

248. Circulating adhesion molecules in cystic fibrosis	De Rose, V., Oliva, A., Messore, B., Grosso, B., Mollar, C. and Pozzi, E. (1998) 'Circulating adhesion molecules in cystic fibrosis', American Journal of Respiratory and Critical Care Medicine, 157(4 Pt 1), pp. 1234-9.
249. Human neutrophil lipocalin, a highly specific marker for acute exacerbation in cystic fibrosis	Eichler, I., Nilsson, M., Rath, R., Enander, I., Venge, P. and Koller, D. Y. (1999) 'Human neutrophil lipocalin, a highly specific marker for acute exacerbation in cystic fibrosis', The european respiratory journal, 14(5), pp. 1145-9.
250. Inflammation in children with cystic fibrosis: contribution of bacterial production of long-chain fatty acids	Felton, E., Burrell, A., Chaney, H., Sami, I., Koumbourlis, A. C., Freishtat, R. J., Crandall, K. A. and Hahn, A. (2021) 'Inflammation in children with cystic fibrosis: contribution of bacterial production of long-chain fatty acids', Pediatric Research, 90(1), pp. 99-108.
251. sTREM-1 is elevated in cystic fibrosis and correlates with proteases	Forrester, D. L., Barr, H. L., Fogarty, A. and Knox, A. (2017) 'sTREM-1 is elevated in cystic fibrosis and correlates with proteases', Pediatric Pulmonology, 52(4), pp. 467-471.
252. Comparison of methods to test antibiotic combinations against heterogeneous populations of multiresistant Pseudomonas aeruginosa from patients with acute infective exacerbations in cystic fibrosis	Foweraker, J. E., Laughton, C. R., Brown, D. F. and Bilton, D. (2009) 'Comparison of methods to test antibiotic combinations against heterogeneous populations of multiresistant Pseudomonas aeruginosa from patients with acute infective exacerbations in cystic fibrosis', Antimicrobial Agents and Chemotherapy, 53(11), pp. 4809-4815.
253. Alpha 1-antitrypsin deficiency alleles in cystic fibrosis lung disease	Frangolias, D. D., Ruan, J., Wilcox, P. J., Davidson, A. G. F., Wong, L. T. K., Berthiaume, Y., Hennessey, R., Freitag, A., Pedder, L., Corey, M., Sweezey, N., Zielenski, J., Tullis, E. and Sandford, A. J. (2003) 'Alpha 1-antitrypsin deficiency alleles in cystic fibrosis lung disease', American Journal of Respiratory Cell and Molecular Biology, 29(3 Pt 1), pp. 390-6.
254. Correlation between activity of Beta-Lactam agents in vitro and bacteriological outcome in acute pulmonary exacerbations of cystic fibrosis	Gaillard, J. L., Cahen, P., Delacourt, C., Silly, C., Le Bourgeois, M., Coustere, C., De Blic, J., Lenoir, G. and Scheinmann, P. (1995) 'Correlation between activity of Beta-Lactam agents in vitro and bacteriological outcome in acute pulmonary exacerbations of cystic fibrosis', European Journal of Clinical Microbiology and Infectious Diseases, 14(4), pp. 291-296.
255. The Respiratory Microbiome in Cystic Fibrosis: Compartment Patterns and Clinical Relationships in Early Stage Disease	Garcia-Nunez, M., Garcia-Gonzalez, M., Pomares, X., Monton, C., Millares, L., Quero, S., Prina, E., Asensio, O., Bosque, M., Capilla, S., Cuevas, O. and Monso, E. (2020) 'The Respiratory Microbiome in Cystic Fibrosis: Compartment Patterns and Clinical Relationships in Early Stage Disease', Frontiers in Microbiology, 11, pp. 1463.
256. Iron homeostasis during cystic fibrosis pulmonary exacerbation	Gifford, A. H., Moulton, L. A., Dorman, D. B., Olbina, G., Westerman, M., Parker, H. W., Stanton, B. A. and O'Toole, G. A. (2012) 'Iron homeostasis during cystic fibrosis pulmonary exacerbation', Clinical and Translational Science, 5(4), pp. 368-373.
257. Complex molecular epidemiology of methicillin-resistant Staphylococcus aureus isolates from children with cystic fibrosis in the era of epidemic community-associated methicillin-resistant S aureus	Glikman, D., Siegel, J. D., David, M. Z., Okoro, N. M., Boyle-Vavra, S., Dowell, M. L. and Daum, R. S. (2008) 'Complex molecular epidemiology of methicillin-resistant Staphylococcus aureus isolates from children with cystic fibrosis in the era of epidemic community-associated methicillin-resistant S aureus', Chest, 133(6), pp. 1381-1387.
258. Changes in microbiome diversity following beta-lactam antibiotic treatment are associated with therapeutic versus subtherapeutic antibiotic exposure in cystic fibrosis	Hahn, A., Fanous, H., Jensen, C., Chaney, H., Sami, I., Perez, G. F., Koumbourlis, A. C., Louie, S., Bost, J. E., van den Anker, J. N., Freishtat, R. J., Zemanick, E. T. and Crandall, K. A. (2019) 'Changes in microbiome diversity following beta-lactam antibiotic treatment are associated with therapeutic versus subtherapeutic antibiotic exposure in cystic fibrosis', Scientific Reports, 9(1), pp. 2534.
259. Local and systemic alterations of the l-arginine/nitric oxide pathway in sputum, blood, and urine of pediatric cystic fibrosis patients and effects of antibiotic treatment	Hanusch, B., Brinkmann, F., Mayorandan, S., Chobanyan-Jürgens, K., Wiemers, A., Jansen, K., Ballmann, M., Schmidt-Choudhury, A., Bollenbach, A., Derichs, N., Tsikas, D. and Lücke, T. (2020) 'Local and systemic alterations of the l-arginine/nitric oxide pathway in sputum, blood, and urine of pediatric cystic fibrosis patients and effects of antibiotic treatment', Journal of Clinical Medicine, 9(12), pp. 1-19.

260. MUC5AC and MUC5B mucins increase in cystic fibrosis airway secretions during pulmonary exacerbation	Henke, M. O., John, G., Germann, M., Lindemann, H. and Rubin, B. K. (2007) 'MUC5AC and MUC5B mucins increase in cystic fibrosis airway secretions during pulmonary exacerbation', American Journal of Respiratory & Critical Care Medicine, 175(8), pp. 816-821.
261. Incidence of viral respiratory pathogens causing exacerbations in adult cystic fibrosis patients	Hoek, R. A. S., Paats, M. S., Pas, S. D., Bakker, M., Hoogsteden, H. C., Boucher, C. A. B. and Van Der Eerden, M. M. (2013) 'Incidence of viral respiratory pathogens causing exacerbations in adult cystic fibrosis patients', Scandinavian Journal of Infectious Diseases, 45(1), pp. 65-69.
262. Proteinase 3 mRNA expression is induced in monocytes but not in neutrophils of patients with cystic fibrosis	Just, J., Moog-Lutz, C., Houzel-Charavel, A., Canteloup, S., Grimfeld, A., Witko-Sarsat, V. and Cayre, Y. E. (1999) 'Proteinase 3 mRNA expression is induced in monocytes but not in neutrophils of patients with cystic fibrosis', FEBS Letters, 457(3), pp. 437-440.
263. Long-term daily high and low doses of azithromycin in children with cystic fibrosis: a randomized controlled trial	Kabra, S. K., Pawaiya, R., Lodha, R., Kapil, A., Kabra, M., Vani, A. S., Agarwal, G. and Shastri, S. S. (2010) 'Long-term daily high and low doses of azithromycin in children with cystic fibrosis: a randomized controlled trial', Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society, 9(1), pp. 17-23.
264. The use of soluble transferin receptor to assess iron deficiency in adults with cystic fibrosis	Khalid, S., McGrowder, D., Kemp, M. and Johnson, P. (2007) 'The use of soluble transferin receptor to assess iron deficiency in adults with cystic fibrosis', Clinica Chimica Acta, 378(1-2), pp. 194-200.
265. Pharmacokinetics of telavancin in adult patients with cystic fibrosis during acute pulmonary exacerbation	Kidd, J. M., Sakon, C. M., Oleksiuk, L. M., Cies, J. J., Pettit, R. S., Nicolau, D. P. and Kuti, J. L. (2020) 'Pharmacokinetics of telavancin in adult patients with cystic fibrosis during acute pulmonary exacerbation', Antimicrobial Agents and Chemotherapy, 64(1).
266. High rhinovirus burden in lower airways of children with cystic fibrosis	Kieninger, E., Singer, F., Tapparel, C., Alves, M. P., Latzin, P., Tan, H. L., Bossley, C., Casaulta, C., Bush, A., Davies, J. C., Kaiser, L. and Regamey, N. (2013) 'High rhinovirus burden in lower airways of children with cystic fibrosis', Chest, 143(3), pp. 782-790.
267. Relationship between disease severity and inflammatory markers in cystic fibrosis	Koller, D. Y., Gotz, M., Wojnarowski, C. and Eichler, I. (1996) 'Relationship between disease severity and inflammatory markers in cystic fibrosis', Archives of Disease in Childhood, 75(6), pp. 498-501.
268. Lower airway microbiota and decreasing lung function in young Brazilian cystic fibrosis patients with pulmonary Staphylococcus and Pseudomonas infection	Kussek, P., Mesa, D., Vasconcelos, T. M., Rodrigues, L. S., Krul, D., Ibanez, H., Faoro, H., Palmeiro, J. K. and Costa, L. M. D. (2022) 'Lower airway microbiota and decreasing lung function in young Brazilian cystic fibrosis patients with pulmonary Staphylococcus and Pseudomonas infection', PLoS ONE, 17(8 August).
269. Longitudinal study of oxidative status in 312 cystic fibrosis patients in stable state and during bronchial exacerbation	Lagrange-Puget, M., Durieu, I., Ecochard, R., Abbas-Chorfa, F., Drai, J., Steghens, J.-P., Pacheco, Y., Vital-Durand, D. and Bellon, G. (2004) 'Longitudinal study of oxidative status in 312 cystic fibrosis patients in stable state and during bronchial exacerbation', Pediatric Pulmonology, 38(1), pp. 43-9.
270. Microbiome networks and change-point analysis reveal key community changes associated with cystic fibrosis pulmonary exacerbations	Layeghifard, M., Li, H., Wang, P. W., Donaldson, S. L., Coburn, B., Clark, S. T., Caballero, J. D., Zhang, Y., Tullis, D. E., Yau, Y. C. W., Waters, V., Hwang, D. M. and Guttman, D. S. (2019) 'Microbiome networks and change-point analysis reveal key community changes associated with cystic fibrosis pulmonary exacerbations', npj Biofilms and Microbiomes, 5(1), pp. 4.
271. Prospective multicenter randomized patient recruitment and sample collection to enable future measurements of sputum biomarkers of inflammation in an observational study of cystic fibrosis	Liou, T. G., Adler, F. R., Argel, N., Asfour, F., Brown, P. S., Chatfield, B. A., Daines, C. L., Durham, D., Francis, J. A., Glover, B., Heynekamp, T., Hoidal, J. R., Jensen, J. L., Keogh, R., Kopecky, C. M., Lechtzin, N., Li, Y., Lysinger, J., Molina, O., Nakamura, C., Packer, K. A., Poch, K. R., Quittner, A. L., Radford, P., Redway, A. J., Sagel, S. D., Sprandel, S., Taylor-Cousar, J. L., Vroom, J. B., Yoshikawa, R., Clancy, J. P., Elborn, J. S., Olivier, K. N. and Cox, D. R. (2019) 'Prospective multicenter randomized patient recruitment and sample collection to enable future measurements of sputum biomarkers of inflammation in an observational study of cystic fibrosis', BMC Medical Research Methodology, 19(1), pp. 88.

272. Efficacy of once-daily tobramycin monotherapy for acute pulmonary exacerbations of cystic fibrosis: a preliminary study	Master, V., Roberts, G. W., Coulthard, K. P., Baghurst, P. A., Martin, A., Roberts, M. E., Onishko, C. R., Martin, A. J., Linke, R. J., Holmes, M., Jarvinen, A., Kennedy, D., Colebatch, K. A., Hansman, D. and Parsons, D. W. (2001) 'Efficacy of once-daily tobramycin monotherapy for acute pulmonary exacerbations of cystic fibrosis: a preliminary study', Pediatric Pulmonology, 31(5), pp. 367-76.
273. Serum vascular endothelial growth factor is elevated in cystic fibrosis and decreases with treatment of acute pulmonary exacerbation	McColley, S. A., Stellmach, V., Boas, S. R., Jain, M. and Crawford, S. E. (2000) 'Serum vascular endothelial growth factor is elevated in cystic fibrosis and decreases with treatment of acute pulmonary exacerbation', American Journal of Respiratory and Critical Care Medicine, 161(6), pp. 1877-1880.
274. Breath isoprene during acute respiratory exacerbation in cystic fibrosis	McGrath, L. T., Patrick, R., Mallon, P., Dowey, L., Silke, B., Norwood, W. and Elborn, S. (2000) 'Breath isoprene during acute respiratory exacerbation in cystic fibrosis', The european respiratory journal, 16(6), pp. 1065-9.
275. miR-224-5p and miR-545-5p Levels Relate to Exacerbations and Lung Function in a Pilot Study of X-Linked MicroRNA Expression in Cystic Fibrosis Monocytes	McKiernan, P. J., Molloy, K. P., Glasgow, A. M. A., McElvaney, N. G. and Greene, C. M. (2021) 'miR-224-5p and miR-545-5p Levels Relate to Exacerbations and Lung Function in a Pilot Study of X-Linked MicroRNA Expression in Cystic Fibrosis Monocytes', Frontiers in Genetics, 12.
276. High peripheral blood th17 percent associated with poor lung function in cystic fibrosis	Mulcahy, E. M., Hudson, J. B., Beggs, S. A., Reid, D. W., Roddam, L. F. and Cooley, M. A. (2015) 'High peripheral blood th17 percent associated with poor lung function in cystic fibrosis', PLoS ONE, 10(3), pp. e0120912.
277. Refining the Application of Microbial Lipids as Tracers of Staphylococcus aureus Growth Rates in Cystic Fibrosis Sputum	Neubauer, C., Kasi, A. S., Grahl, N., Sessions, A. L., Kopf, S. H., Kato, R., Hogan, D. A. and Newman, D. K. (2018) 'Refining the Application of Microbial Lipids as Tracers of Staphylococcus aureus Growth Rates in Cystic Fibrosis Sputum', Journal of Bacteriology, 200(24).
278. Circulating immunoreactive interleukin-6 in cystic fibrosis	Nixon, L. S., Yung, B., Bell, S. C., Elborn, J. S. and Shale, D. J. (1998) 'Circulating immunoreactive interleukin-6 in cystic fibrosis', American Journal of Respiratory and Critical Care Medicine, 157(6 PART I), pp. 1764-1769.
279. Posaconazole therapy in children with cystic fibrosis and Aspergillus-related lung disease	Patel, D., Popple, S., Claydon, A., Modha, D. E. and Gaillard, E. A. (2020) 'Posaconazole therapy in children with cystic fibrosis and Aspergillus-related lung disease', Medical Mycology, 58(1), pp. 11-21.
280. Population pharmacokinetics of meropenem administered as a prolonged infusion in children with cystic fibrosis	Pettit, R. S., Neu, N., Cies, J. J., Lapin, C., Muhlebach, M. S., Novak, K. J., Nguyen, S. T., Saiman, L., Nicolau, D. P. and Kuti, J. L. (2016) 'Population pharmacokinetics of meropenem administered as a prolonged infusion in children with cystic fibrosis', Journal of Antimicrobial Chemotherapy, 71(1), pp. 189-195.
281. Clinical manifestations of exacerbations of cystic fibrosis associated with nonbacterial infections	Pribble, C. G., Black, P. G., Bosso, J. A. and Turner, R. B. (1990) 'Clinical manifestations of exacerbations of cystic fibrosis associated with nonbacterial infections', The Journal of Pediatrics, 117(2 Pt 1), pp. 200-4.
282. Inflammatory markers in cystic fibrosis patients with lung Pseudomonas aeruginosa infection	Pukhalsky, A. L., Kapranov, N. I., Kalashnikova, E. A., Shmarina, G. V., Shabalova, L. A., Kokarovtseva, S. N., Pukhalskaya, D. A., Kashirskaja, N. J. and Simonova, O. I. (1999) 'Inflammatory markers in cystic fibrosis patients with lung Pseudomonas aeruginosa infection', Mediators of Inflammation, 8(3), pp. 159-167.
283. High-Resolution longitudinal dynamics of the cystic fibrosis sputum microbiome and metabolome through antibiotic therapy	Raghuvanshi, R., Vasco, K., Vazquez-Baeza, Y., Jiang, L., Morton, J. T., Li, D., Gonzalez, A., DeRight Goldasich, L., Humphrey, G., Ackermann, G., Swafford, A. D., Conrad, D., Knight, R., Dorrestein, P. C. and Quinn, R. A. (2020) 'High-Resolution longitudinal dynamics of the cystic fibrosis sputum microbiome and metabolome through antibiotic therapy', mSystems, 5(3), pp. e00292-20.
284. Changes in airway inflammation during pulmonary exacerbations in patients with cystic fibrosis and primary ciliary dyskinesia	Ratjen, F., Waters, V., Klingel, M., McDonald, N., Dell, S., Leahy, T. R., Yau, Y. and Grasemann, H. (2016) 'Changes in airway inflammation during pulmonary exacerbations in patients with cystic fibrosis and primary ciliary dyskinesia', The european respiratory journal, 47(3), pp. 829-36.

285. Measurement of serum calprotectin in stable patients predicts exacerbation and lung function decline in cystic fibrosis	Reid, P. A., McAllister, D. A., Boyd, A. C., Innes, J. A., Porteous, D., Greening, A. P. and Gray, R. D. (2015) 'Measurement of serum calprotectin in stable patients predicts exacerbation and lung function decline in cystic fibrosis', American Journal of Respiratory & Critical Care Medicine, 191(2), pp. 233-236.
286. Serum matrix metalloproteinases in adult CF patients: Relation to pulmonary exacerbation	Roderfeld, M., Rath, T., Schulz, R., Seeger, W., Tschuschner, A., Graf, J. and Roeb, E. (2009) 'Serum matrix metalloproteinases in adult CF patients: Relation to pulmonary exacerbation', Journal of Cystic Fibrosis, 8(5), pp. 338-347.
287. Whole Blood Gene Expression Profiling Predicts Severe Morbidity and Mortality in Cystic Fibrosis: A 5-Year Follow-Up Study	Saavedra, M. T., Quon, B. S., Faino, A., Caceres, S. M., Poch, K. R., Sanders, L. A., Malcolm, K. C., Nichols, D. P., Sagel, S. D., Taylor-Cousar, J. L., Leach, S. M., Strand, M. and Nick, J. A. (2018) 'Whole Blood Gene Expression Profiling Predicts Severe Morbidity and Mortality in Cystic Fibrosis: A 5-Year Follow-Up Study', Annals of the American Thoracic Society, 15(5), pp. 589-598.
288. Association of Serum TGF-beta1 Levels with Different Clinical Phenotypes of Cystic Fibrosis Exacerbation	Sagwal, S., Chauhan, A., Kaur, J., Prasad, R., Singh, M. and Singh, M. (2020) 'Association of Serum TGF-beta1 Levels with Different Clinical Phenotypes of Cystic Fibrosis Exacerbation', Lung, 198(2), pp. 377-383.
289. Macrorheology of cystic fibrosis, chronic obstructive pulmonary disease & normal sputum	Serisier, D. J., Carroll, M. P., Shute, J. K. and Young, S. A. (2009) 'Macrorheology of cystic fibrosis, chronic obstructive pulmonary disease & normal sputum', Respiratory Research, 10, pp. 63.
290. Comparison of a beta-lactam alone versus beta-lactam and an aminoglycoside for pulmonary exacerbation in cystic fibrosis	Smith, A. L., Doershuk, C., Goldmann, D., Gore, E., Hilman, B., Marks, M., Moss, R., Ramsey, B., Redding, G., Rubio, T., Williams-Warren, J., Wilmott, R., Wilson, H. D. and Yogev, R. (1999) 'Comparison of a beta-lactam alone versus beta-lactam and an aminoglycoside for pulmonary exacerbation in cystic fibrosis', The Journal of Pediatrics, 134(4), pp. 413-21.
291. Infection with Burkholderia cepacia complex bacteria and pulmonary exacerbations of cystic fibrosis	St. Denis, M., Ramotar, K., Vandemheen, K., Tullis, E., Ferris, W., Chan, F., Lee, C., Slinger, R. and Aaron, S. D. (2007) 'Infection with Burkholderia cepacia complex bacteria and pulmonary exacerbations of cystic fibrosis', Chest, 131(4), pp. 1188-1196.
292. Increased sputum amino acid concentrations and auxotrophy of Pseudomonas aeruginosa in severe cystic fibrosis lung disease	Thomas, S. R., Ray, A., Hodson, M. E. and Pitt, T. L. (2000) 'Increased sputum amino acid concentrations and auxotrophy of Pseudomonas aeruginosa in severe cystic fibrosis lung disease', Thorax, 55(9), pp. 795-7.
293. Controlled trial of cycled antibiotic prophylaxis to prevent initial Pseudomonas aeruginosa infection in children with cystic fibrosis	Tramper-Stranders, G. A., Wolfs, T. F. W., van Haren Noman, S., van Aalderen, W. M. C., Nagelkerke, A. F., Nuijsink, M., Kimpen, J. L. L. and van der Ent, C. K. (2010) 'Controlled trial of cycled antibiotic prophylaxis to prevent initial Pseudomonas aeruginosa infection in children with cystic fibrosis', Thorax, 65(10), pp. 915-20.
294. Efficacy, tolerance, and pharmacokinetics of once daily tobramycin for pseudomonas exacerbations in cystic fibrosis	Vic, P., Ategbo, S., Turck, D., Husson, M. O., Launay, V., Loeuille, G. A., Sardet, A., Deschildre, A., Druon, D. and Arrouet-Lagande, C. (1998) 'Efficacy, tolerance, and pharmacokinetics of once daily tobramycin for pseudomonas exacerbations in cystic fibrosis', Archives of Disease in Childhood, 78(6), pp. 536-539.
295. IL-8 and pH values in exhaled condensate after antibiotics in cystic fibrosis children	Bodini, A., D'Orazio, C., Peroni, D. G., Corradi, M., Zerman, L., Folesani, G., Assael, B. M., Boner, A. L. and Piacentini, G. L. (2007) 'IL-8 and pH values in exhaled condensate after antibiotics in cystic fibrosis children', International Journal of Immunopathology and Pharmacology, 20(3), pp. 467-472.
296. A randomized placebo-controlled study on high-dose oral algal docosahexaenoic acid supplementation in children with cystic fibrosis	Alicandro, G., Faelli, N., Gagliardini, R., Santini, B., Magazzu, G., Biffi, A., Rise, P., Galli, C., Tirelli, A. S., Loi, S., Valmarana, L., Cirilli, N., Palmas, T., Vieni, G., Bianchi, M. L., Agostoni, C. and Colombo, C. (2013) 'A randomized placebo-controlled study on high-dose oral algal docosahexaenoic acid supplementation in children with cystic fibrosis', Prostaglandins, leukotrienes, and essential fatty acids, 88(2), pp. 163-9.

297. Plasma Ceramides and Sphingomyelins of Pediatric Patients Increase in Primary Ciliary Dyskinesia but Decrease in Cystic Fibrosis	Bal Topçu, D., Tugcu, G., Ozcan, F., Aslan, M., Yalcinkaya, A., Polat, S. E., Hizal, M., Yalcin, E. E., Ersoz, D. D., Ozcelik, U., Kiper, N., Lay, I. and Oztas, Y. (2020) 'Plasma Ceramides and Sphingomyelins of Pediatric Patients Increase in Primary Ciliary Dyskinesia but Decrease in Cystic Fibrosis', Lipids, 55(3), pp. 213-223.
298. Genetic Variation Near chrXq22-q23 Is Linked to Emotional Functioning in Cystic Fibrosis	Barbato, E., Daly, B., Douglas, S., Kerr, M., Litman, P. and Darrah, R. (2020) 'Genetic Variation Near chrXq22-q23 Is Linked to Emotional Functioning in Cystic Fibrosis', Biological Research for Nursing, 22(3), pp. 319-325.
299. Aetiological agents for pulmonary exacerbations in children with cystic fibrosis: An observational study from a tertiary care centre in northern India	Arvind, B., Medigeshi, G. R., Kapil, A., Xess, I., Singh, U., Lodha, R. and Kabra, S. K. (2020) 'Aetiological agents for pulmonary exacerbations in children with cystic fibrosis: An observational study from a tertiary care centre in northern India', The Indian journal of medical research, 151(1), pp. 65-70.
300. Oral ciprofloxacin vs. intravenous ceftazidime plus tobramycin in pediatric cystic fibrosis patients: comparison of antipseudomonas efficacy and assessment of safety with ultrasonography and magnetic resonance imaging. Cystic Fibrosis Study Group	Richard, D. A., Nousia-Arvanitakis, S., Sollich, V., Hampel, B. J., Sommerauer, B. and Schaad, U. B. (1997) 'Oral ciprofloxacin vs. intravenous ceftazidime plus tobramycin in pediatric cystic fibrosis patients: comparison of antipseudomonas efficacy and assessment of safety with ultrasonography and magnetic resonance imaging. Cystic Fibrosis Study Group', The Pediatric infectious disease journal, 16(6), pp. 572-8.
301. Comparison of nebulized and intravenous terbutaline during exacerbations of pulmonary infection in patients with cystic fibrosis	Finnegan, M. J., Hughes, D. V. and Hodson, M. E. (1992) 'Comparison of nebulized and intravenous terbutaline during exacerbations of pulmonary infection in patients with cystic fibrosis', The European respiratory journal, 5(9), pp. 1089-91.
302. Complement effectors, C5a and C3a, in cystic fibrosis lung fluid correlate with disease severity	Hair, P. S., Sass, L. A., Vazifedan, T., Shah, T. A., Krishna, N. K. and Cunnion, K. M. (2017) 'Complement effectors, C5a and C3a, in cystic fibrosis lung fluid correlate with disease severity', PloS one, 12(3), pp. e0173257.
303. Does Circadian Rhythm Affect the Pharmacokinetics of Once-Daily Tobramycin in Adults With Cystic Fibrosis?	van Maarseveen, E. M., van der Meer, R., Neef, C., Heijerman, H. G. M. and Touw, D. J. (2020) 'Does Circadian Rhythm Affect the Pharmacokinetics of Once-Daily Tobramycin in Adults With Cystic Fibrosis?', Therapeutic drug monitoring, 42(4), pp. 595-599.
304. Investigation of respiratory rate in patients with cystic fibrosis using a minimal-impact biomotion system	Straßburg, S., Linker, C.-M., Brato, S., Schöbel, C., Taube, C., Götze, J., Stehling, F., Sutharsan, S., Welsner, M. and Weinreich, G. (2022) 'Investigation of respiratory rate in patients with cystic fibrosis using a minimal-impact biomotion system', BMC Pulmonary Medicine, 22(1), pp. 1-6.
305. Pharmacokinetics of Vancomycin in Adult Cystic Fibrosis Patients	Pleasants, R. A., Michalets, E. L., Williams, D. M., Samuelson, W. M., Rehm, J. R. and Knowles, M. R. (1996) 'Pharmacokinetics of vancomycin in adult cystic fibrosis patients', Antimicrobial agents and chemotherapy, 40(1), pp. 186-90.
306. Population pharmacokinetics and use of Monte Carlo simulation to evaluate currently recommended dosing regimens of ciprofloxacin in adult patients with cystic fibrosis	Montgomery, M.J., Beringer, P.M., Aminimanizani, A., Louie, S.G., Shapiro, B.J., Jelliffe, R. and Gill, M.A., 2001. Population pharmacokinetics and use of Monte Carlo simulation to evaluate currently recommended dosing regimens of ciprofloxacin in adult patients with cystic fibrosis. Antimicrobial agents and chemotherapy, 45(12), pp.3468-3473.
307. A randomised controlled trial of hypertonic saline inhalation to enhance airway clearance physiotherapy in adults hospitalised with Cystic Fibrosis (CF)	Dentice, R., Elkins, M. and Bye, P., 2015. A randomised controlled trial of hypertonic saline inhalation to enhance airway clearance physiotherapy in adults hospitalised with Cystic Fibrosis (CF). Physiotherapy, 101, p.e356.
308. Relationship between exacerbation frequency and clinical outcomes in patients with cystic fibrosis	de Boer, K., Vandemheen, K.L., Tullis, E., Doucette, S., Fergusson, D., Freitag, A., Paterson, N., Jackson, M., Lougheed, M.D., Kumar, V. and Aaron, S.D., 2011. Relationship Between Exacerbation Frequency And Clinical Outcomes In Patients With Cystic Fibrosis. A23. ADULT CYSTIC FIBROSIS: ADVANCES IN TREATMENT AND UNDERSTANDING OF MECHANISMS OF DISEASE, pp.A1113-A1113.

309. Identification of neutrophil activation markers as novel surrogate markers of CF lung disease	Rath, T., Zwaschka, L., Hage, L., Kugler, M., Menendez, K., Naehrlich, L., Schulz, R., Roderfeld, M. and Roeb, E. (2014) 'Identification of neutrophil activation markers as novel surrogate markers of CF lung disease', PLoS ONE [Electronic Resource], 9(12), p. e115847.
310. Associations between Gut Microbial Colonization in Early Life and Respiratory Outcomes in Cystic Fibrosis	Hoen, A.G., Li, J., Moulton, L.A., O'Toole, G.A., Housman, M.L., Koestler, D.C., Guill, M.F., Moore, J.H., Hibberd, P.L., Morrison, H.G., Sogin, M.L., Karagas, M.R. and Madan, J.C. (2015) 'Associations between Gut Microbial Colonization in Early Life and Respiratory Outcomes in Cystic Fibrosis', Journal of Pediatrics, 167(1), pp. 138-147.e3.
311. Increased plasma fatty acid concentrations after respiratory exacerbations are associated with elevated oxidative stress in cystic fibrosis patients	Wood, L. G., Fitzgerald, D. A., Gibson, P. G., Cooper, D. M. and Garg, M. L. (2002) 'Increased plasma fatty acid concentrations after respiratory exacerbations are associated with elevated oxidative stress in cystic fibrosis patients', American Journal of Clinical Nutrition, 75(4), pp. 668-675.
312. Testing two different doses of tiotropium Respimat® in cystic fibrosis: Phase 2 randomized trial results	Bradley, J. M., Koker, P., Deng, Q., Moroni-Zentgraf, P., Ratjen, F., Geller, D. E. and Stuart Elborn, J. (2014) 'Testing two different doses of tiotropium Respimat® in cystic fibrosis: Phase 2 randomized trial results', PloS one, 9(9).
313. Plasma biomarkers and cystic brosis fibrosis lung disease	Cantin, A. M., Bilodeau, G., Larivee, P. and Richter, M. V. (2012) 'Plasma biomarkers and cystic brosis fibrosis lung disease', Clinical and Investigative Medicine, 35(4), pp. E173-E181.
314. Acute Pulmonary Exacerbation Phenotypes in Patients with Cystic Fibrosis	Carter, S. C., Franciosi, A. N., O'Shea, K. M., O'Carroll, O. M., Sharma, A., Bell, A., Keogan, B., O'Reilly, P., Coughlan, S., Law, S. M., Gray, R. D., Hisert, K. B., Singh, P. K., Cooke, G., Grogan, B., De Gascun, C. F., Gallagher, C. G., Nicholson, T. T., Quon, B. S. and McKone, E. F. (2022) 'Acute Pulmonary Exacerbation Phenotypes in Patients with Cystic Fibrosis', Annals of the American Thoracic Society, 19(11), pp. 1818-1826.
315. A short-term comparison of two methods of sputum expectoration in cystic fibrosis	Chatham, K., Ionescu, A. A., Nixon, L. S. and Shale, D. J. (2004) 'A short-term comparison of two methods of sputum expectoration in cystic fibrosis', The European respiratory journal, 23(3), pp. 435-9.
316. Aspergillus/allergic bronchopulmonary aspergillosis in an Irish cystic fibrosis population: a diagnostically challenging entity	Chotirmall, S. H., Branagan, P., Gunaratnam, C. and McElvaney, N. G. (2008) 'Aspergillus/allergic bronchopulmonary aspergillosis in an Irish cystic fibrosis population: a diagnostically challenging entity', Respiratory Care, 53(8), pp. 1035-41.
317. Duration of effect of intravenous antibiotics on spirometry and sputum cytokines in children with cystic fibrosis	Cunningham, S., McColm, J. R., Mallinson, A., Boyd, I. and Marshall, T. G. (2003) 'Duration of effect of intravenous antibiotics on spirometry and sputum cytokines in children with cystic fibrosis', Pediatric pulmonology, 36(1), pp. 43-8.
318. Efficacy and safety of ivacaftor in patients with cystic fibrosis and a non-G551D gating mutation	De Boeck, K., Munck, A., Walker, S., Faro, A., Hiatt, P., Gilmartin, G. and Higgins, M. (2014) 'Efficacy and safety of ivacaftor in patients with cystic fibrosis and a non-G551D gating mutation', Journal of Cystic Fibrosis, 13(6), pp. 674-680.
319. Lactobacillus reuteri ATCC55730 in cystic fibrosis	Di Nardo, G., Oliva, S., Menichella, A., Pistelli, R., De Biase, R. V., Patriarchi, F., Cucchiara, S. and Stronati, L. (2014) 'Lactobacillus reuteri ATCC55730 in cystic fibrosis', Journal of pediatric gastroenterology and nutrition, 58(1), pp. 81-6.
320. Long-term clarithromycin in cystic fibrosis: effects on inflammatory markers in BAL and clinical status	Dogru, D., Dalgic, F., Kiper, N., Ozcelik, U., Yalcin, E., Aslan, A. T., Gurcan, N., Saricaoglu, F., Gur, D., Karayazgan, Y. and Firat, P. (2009) 'Long-term clarithromycin in cystic fibrosis: effects on inflammatory markers in BAL and clinical status', The Turkish journal of pediatrics, 51(5), pp. 416-23.
321. Vitamin A status in acute exacerbations of cystic fibrosis	Duggan, C., Colin, A. A., Agil, A., Higgins, L. and Rifai, N. (1996) 'Vitamin A status in acute exacerbations of cystic fibrosis', American Journal of Clinical Nutrition, 64(4), pp. 635-639.

322. Comparison of hospital and home intravenous antibiotic therapy in adults with cystic fibrosis	Esmond, G., Butler, M. and McCormack, A. M. (2006) 'Comparison of hospital and home intravenous antibiotic therapy in adults with cystic fibrosis', Journal of Clinical Nursing (Wiley-Blackwell), 15(1), pp. 52-60.
323. The Adult Cystic Fibrosis Airway Microbiota Is Stable over Time and Infection Type, and Highly Resilient to Antibiotic Treatment of Exacerbations	Fodor, A. A., Klem, E. R., Gilpin, D. F., Elborn, J. S., Boucher, R. C., Tunney, M. M. and Wolfgang, M. C. (2012) 'The adult cystic fibrosis airway microbiota is stable over time and infection type, and highly resilient to antibiotic treatment of exacerbations', PloS one, 7(9), pp. e45001.
324. Role of C-reactive protein as a biomarker for prediction of the severity of pulmonary exacerbations in patients with cystic fibrosis	Girón-Moreno, R. M., Justicia, J. L., Yamamoto, S., Valenzuela, C., Cisneros, C., Gómez-Punter, R. M., Fernandes-Vasconcelos, G. and Ancochea, J. (2014) 'Role of C-reactive protein as a biomarker for prediction of the severity of pulmonary exacerbations in patients with cystic fibrosis', BMC Pulmonary Medicine, 14(1), pp. 150-150.
325. Sputum and serum calprotectin are useful biomarkers during CF exacerbation	Gray, R. D., Imrie, M., Boyd, A. C., Porteous, D., Innes, J. A. and Greening, A. P. (2010) 'Sputum and serum calprotectin are useful biomarkers during CF exacerbation', Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society, 9(3), pp. 193-8.
326. Importance of beta-lactam pharmacokinetics and pharmacodynamics on the recovery of microbial diversity in the airway of persons with cystic fibrosis	Hahn, A., Burrell, A., Chaney, H., Sami, I., Koumbourlis, A. C., Freishtat, R. J., Zemanick, E. T., Louie, S. and Crandall, K. A. (2021) 'Importance of beta-lactam pharmacokinetics and pharmacodynamics on the recovery of microbial diversity in the airway of persons with cystic fibrosis', Journal of investigative medicine : the official publication of the American Federation for Clinical Research, 69(7), pp. 1350-1359.
327. One-minute sit-to-stand test is practical to assess and follow the muscle weakness in cystic fibrosis	Hardy, S., Berardis, S., Aubriot, A. S., Reychler, G. and Gohy, S. (2022) 'One-minute sit-to-stand test is practical to assess and follow the muscle weakness in cystic fibrosis', Respiratory Research, 23(1).
328. Plasma TGF-beta1 in pediatric cystic fibrosis: potential biomarker of lung disease and response to therapy	Harris, W. T., Muhlebach, M. S., Oster, R. A., Knowles, M. R., Clancy, J. P. and Noah, T. L. (2011) 'Plasma TGF-beta1 in pediatric cystic fibrosis: potential biomarker of lung disease and response to therapy', Pediatric pulmonology, 46(7), pp. 688-95.
329. Outcomes and Treatment of Chronic Methicillin-Resistant Staphylococcus aureus Differs by Staphylococcal Cassette Chromosome mec (SCCmec) Type in Children With Cystic Fibrosis	Heltshe, S. L., Saiman, L., Popowitch, E. B., Miller, M. B., Kloster, M., Thompson, V., Ferkol, T. W., Hoover, W. C., Schechter, M. S. and Muhlebach, M. S. (2015) 'Outcomes and Treatment of Chronic Methicillin-Resistant Staphylococcus aureus Differs by Staphylococcal Cassette Chromosome mec (SCCmec) Type in Children With Cystic Fibrosis', Journal of the Pediatric Infectious Diseases Society, 4(3), pp. 225-31.
330. Cystic fibrosis: inflammatory response to infection with Burkholderia cepacia and Pseudomonas aeruginosa	Hendry, J., Elborn, J. S., Nixon, L., Shale, D. J. and Webb, A. K. (1999) 'Cystic fibrosis: inflammatory response to infection with Burkholderia cepacia and Pseudomonas aeruginosa', The European respiratory journal, 14(2), pp. 435-8.
331. Longitudinal monitoring of pediatric cystic fibrosis lung disease using nitrite in exhaled breath condensate	Horak, F., Jr., Moeller, A., Singer, F., Straub, D., Holler, B., Helbich, T. H., Schneider, B., Eichler, I., Wildhaber, J. H. and Hall, G. L. (2007) 'Longitudinal monitoring of pediatric cystic fibrosis lung disease using nitrite in exhaled breath condensate', Pediatric pulmonology, 42(12), pp. 1198-206.
332. Bone density, body composition, and inflammatory status in cystic fibrosis	Ionescu, A. A., Nixon, L. S., Evans, W. D., Stone, M. D., Lewis-Jenkins, V., Chatham, K. and Shale, D. J. (2000) 'Bone density, body composition, and inflammatory status in cystic fibrosis', American journal of respiratory and critical care medicine, 162(3 Pt 1), pp. 789-94.
333. Oral azithromycin and response to pulmonary exacerbations treated with intravenous tobramycin in children with cystic fibrosis	Klingel, M., Stanojevic, S., Tullis, E., Ratjen, F. and Waters, V. (2019) 'Oral Azithromycin and Response to Pulmonary Exacerbations Treated with Intravenous Tobramycin in Children with Cystic Fibrosis', Annals of the American Thoracic Society, 16(7), pp. 861-867.
334. Sputum desmosine during hospital admission for pulmonary exacerbation in cystic fibrosis	Laguna, T. A., Wagner, B. D., Luckey, H. K., Mann, S. A., Sagel, S. D., Regelmann, W., Accurso, F. J., Laguna, T. A., Wagner, B. D., Luckey, H. K., Mann, S. A., Sagel, S. D., Regelmann, W. and Accurso, F. J. (2009) 'Sputum desmosine during hospital admission for pulmonary exacerbation in cystic fibrosis', CHEST, 136(6), pp. 1561-1568.

335. Urinary desmosine: a biomarker of structural lung injury during CF pulmonary exacerbation	Laguna, T. A., Wagner, B. D., Starcher, B., Luckey Tarro, H. K., Mann, S. A., Sagel, S. D. and Accurso, F. J. (2012) 'Urinary desmosine: a biomarker of structural lung injury during CF pulmonary exacerbation', Pediatric pulmonology, 47(9), pp. 856-63.
336. Sputum club cell protein concentration is associated with pulmonary exacerbation in cystic fibrosis	Laguna, T. A., Williams, C. B., Brandy, K. R., Welchlin-Bradford, C., Moen, C. E., Reilly, C. S. and Wendt, C. H. (2015) 'Sputum club cell protein concentration is associated with pulmonary exacerbation in cystic fibrosis', Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society, 14(3), pp. 334-40.
337. Pharmacokinetics of intermittent dosed intravenous vancomycin in adult persons with cystic fibrosis	Lindley, B., Bhakta, Z., Gray, K., Watanabe, A., Leclair, L. and Young, D. C. (2022) 'Pharmacokinetics of intermittent dosed intravenous vancomycin in adult persons with cystic fibrosis', Pediatric pulmonology, 57(11), pp. 2646-2651.
338. Corticosteroid-resistant inflammatory signalling in pseudomonas-infected bronchial cells	Mizutani, M., Berube, J., Ahlgren, H. G., Bernier, J., Matouk, E., Nguyen, D. and Rousseau, S. (2017) 'Corticosteroid-resistant inflammatory signalling in pseudomonas-infected bronchial cells', ERJ Open Research, 3(2), pp. 00144-2016.
339. Increase in interleukin-8 production from circulating neutrophils upon antibiotic therapy in cystic fibrosis patients	Montemurro, P., Mariggio, M. A., Barbuti, G., Cassano, A., Vincenti, A., Serio, G., Guerra, L., Diana, A., Santostasi, T., Polizzi, A., Fumarulo, R., Casavola, V., Manca, A. and Conese, M. (2012) 'Increase in interleukin-8 production from circulating neutrophils upon antibiotic therapy in cystic fibrosis patients', Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society, 11(6), pp. 518-24.
340. Plasma tumour necrosis factor alpha in cystic fibrosis	Norman, D., Elborn, J. S., Cordon, S. M., Rayner, R. J., Wiseman, M. S., Hiller, E. J. and Shale, D. J. (1991) 'Plasma tumour necrosis factor alpha in cystic fibrosis', Thorax, 46(2), pp. 91-5.
341. Cytokines in nasal lavages and plasma and their correlation with clinical parameters in cystic fibrosis	Paats, M.S., Bergen, I.M., Bakker, M., Hoek, R.A., Nietzman-Lammering, K.J., Hoogsteden, H.C., Hendriks, R.W. and van der Eerden, M.M., 2013. Cytokines in nasal lavages and plasma and their correlation with clinical parameters in cystic fibrosis. Journal of Cystic Fibrosis, 12(6), pp.623-629.
342. Method for detection of respiratory viruses in the sputa of patients with cystic fibrosis	Punch, G., Syrmis, M.W., Rose, B.R. et al. Method for detection of respiratory viruses in the sputa of patients with cystic fibrosis. Eur J Clin Microbiol Infect Dis 24, 54–57 (2005). https://doi.org/10.1007/s10096-004-1273-7
343. A novel neutrophil derived inflammatory biomarker of pulmonary exacerbation in cystic fibrosis	Reeves, E. P., Bergin, D. A., Fitzgerald, S., Hayes, E., Keenan, J., Henry, M., Meleady, P., Vega-Carrascal, I., Murray, M. A., Low, T. B., McCarthy, C., O'Brien, E., Clynes, M., Gunaratnam, C. and McElvaney, N. G. (2012) 'A novel neutrophil derived inflammatory biomarker of pulmonary exacerbation in cystic fibrosis', Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society, 11(2), pp. 100-7.
344. Distinct patterns of inflammation in the airway lumen and bronchial mucosa of children with cystic fibrosis	Regamey, N., Tsartsali, L., Hilliard, T. N., Fuchs, O., Tan, H.-L., Zhu, J., Qiu, Y.-S., Alton, E. W. F. W., Jeffery, P. K., Bush, A. and Davies, J. C. (2012) 'Distinct patterns of inflammation in the airway lumen and bronchial mucosa of children with cystic fibrosis', Thorax, 67(2), pp. 164-70.
345. Measurement of parasternal intercostal electromyogram during an infective exacerbation in patients with cystic fibrosis	Reilly, C. C., Jolley, C. J., Elston, C., Moxham, J. and Rafferty, G. F. (2012) 'Measurement of parasternal intercostal electromyogram during an infective exacerbation in patients with cystic fibrosis', The European respiratory journal, 40(4), pp. 977-81.
346. Effects of beta-carotene supplementation for six months on clinical and laboratory parameters in patients with cystic fibrosis	Renner, S., Rath, R., Rust, P., Lehr, S., Frischer, T., Elmadfa, I. and Eichler, I. (2001) 'Effects of beta-carotene supplementation for six months on clinical and laboratory parameters in patients with cystic fibrosis', Thorax, 56(1), pp. 48-52.
347. Spirometer-triggered high-resolution computed tomography and pulmonary function measurements	Robinson, T. E., Leung, A. N., Northway, W. H., Blankenberg, F. G., Bloch, D. A., Oehlert, J. W., Al-Dabbagh, H., Hubli, S. and Moss, R. B. (2001) 'Spirometer-triggered high-resolution computed tomography and

during an acute exacerbation in patients with cystic fibrosis	pulmonary function measurements during an acute exacerbation in patients with cystic fibrosis', Journal of Pediatrics, 138(4), pp. 553-559.
348. Effect of treatment of cystic fibrosis pulmonary exacerbations on systemic inflammation	Sagel, S. D., Thompson, V., Chmiel, J. F., Montgomery, G. S., Nasr, S. Z., Perkett, E., Saavedra, M. T., Slovis, B., Anthony, M. M., Emmett, P. and Heltshe, S. L. (2015) 'Effect of treatment of cystic fibrosis pulmonary exacerbations on systemic inflammation', Annals of the American Thoracic Society, 12(5), pp. 708-717.
349. Zinc supplementation for one year among children with cystic fibrosis does not decrease pulmonary infection	Sharma, G., Lodha, R., Shastri, S., Saini, S., Kapil, A., Singla, M., Mukherjee, A., Jat, K. R., Kabra, M. and Kabra, S. K. (2016) 'Zinc Supplementation for One Year Among Children with Cystic Fibrosis Does Not Decrease Pulmonary Infection', Respiratory Care, 61(1), pp. 78-84.
350. Osteoclastogenesis during infective exacerbations in patients with cystic fibrosis	Shead, E. F., Haworth, C. S., Gunn, E., Bilton, D., Scott, M. A. and Compston, J. E. (2006) 'Osteoclastogenesis during infective exacerbations in patients with cystic fibrosis', American Journal of Respiratory & Critical Care Medicine, 174(3), pp. 306-311.
351. Pyrosequencing reveals transient cystic fibrosis lung microbiome changes with intravenous antibiotics	Smith, D. J., Badrick, A. C., Zakrzewski, M., Krause, L., Bell, S. C., Anderson, G. J. and Reid, D. W. (2014) 'Pyrosequencing reveals transient cystic fibrosis lung microbiome changes with intravenous antibiotics', The European respiratory journal, 44(4), pp. 922-30.
352. Respiratory mycobiome and suggestion of inter-kingdom network during acute pulmonary exacerbation in cystic fibrosis	Soret, P., Vandenborght, L.-E., Francis, F., Coron, N., Enaud, R., Avalos, M., Schaeverbeke, T., Berger, P., Fayon, M., Thiebaut, R. and Delhaes, L. (2020) 'Respiratory mycobiome and suggestion of inter-kingdom network during acute pulmonary exacerbation in cystic fibrosis', Scientific reports, 10(1), pp. 3589.
353. Breath glucose as a marker of pulmonary inflammation in adult patients with cystic fibrosis	Srivastava, S. A., Nguyen, T. T., Burgess, J. C., Bilton, D., Hodson, M. E., Gyi, K. M. and Baker, E. H. (2010) 'Breath glucose as a marker of pulmonary inflammation in adult patients with cystic fibrosis', Pediatric pulmonology, 45(SUPPL. 33), pp. 375.
354. MiRNA Expression Profile in the Airways Is Altered during Pulmonary Exacerbation in Children with Cystic Fibrosis—A Preliminary Report	Stachowiak, Z., Wojsyk-Banaszak, I., Jonczyk-Potoczna, K., Narozna, B., Langwinski, W., Kycler, Z., Sobkowiak, P., Breborowicz, A. and Szczepankiewicz, A. (2020) 'Mirna expression profile in the airways is altered during pulmonary exacerbation in children with cystic fibrosis-A preliminary report', Journal of Clinical Medicine, 9(6), pp. 1-11.
355. Daily home spirometry use in CF patients with an acute exacerbation	Stephen, M. J., Hadjiliadis, D., Hoag, J. B., Holsclaw, D., Fiel, S., Varlotta, L., Zanni, R. L. and Bonsall, C. (2015) 'Daily home spirometry use in CF patients with an acute exacerbation', Pediatric pulmonology, 50(SUPPL. 41), pp. 357-358.
356. Antibiotic perturbation of mixed-strain Pseudomonas aeruginosa infection in patients with cystic fibrosis	Tai, A. S., Sherrard, L. J., Kidd, T. J., Ramsay, K. A., Buckley, C., Syrmis, M., Grimwood, K., Bell, S. C. and Whiley, D. M. (2017) 'Antibiotic perturbation of mixed-strain Pseudomonas aeruginosa infection in patients with cystic fibrosis', BMC Pulmonary Medicine, 17, pp. 1-10.
357. Clinical profile of adult cystic fibrosis patients with frequent epidemic clones of Pseudomonas aeruginosa	Tingpej, P., Elkins, M., Rose, B., Hu, H., Moriarty, C., Manos, J., Barras, B., Bye, P. and Harbour, C. (2010) 'Clinical profile of adult cystic fibrosis patients with frequent epidemic clones of Pseudomonas aeruginosa', Respirology (Carlton, Vic.), 15(6), pp. 923-9.
358. Effects of treatment in the levels of circulating cytokines and growth factors in cystic fibrosis and dialyzed patients by multi-analytical determination with a biochip array platform	Tirelli, A. S., Colombo, C., Torresani, E., Fortunato, F., Biffi, A., Cariani, L., Dacco, V., Carbone, A., Edefonti, A., Paglialonga, F. and Conese, M. (2013) 'Effects of treatment in the levels of circulating cytokines and growth factors in cystic fibrosis and dialyzed patients by multi-analytical determination with a biochip array platform', Cytokine, 62(3), pp. 413-20.
359. Increased Plasma YKL-40 Level and Chitotriosidase Activity in Cystic Fibrosis Patients	Topcu, D. B., Tugcu, G., Er, B., Polat, S. E., Hizal, M., Yalcin, E. E., Ersoz, D. D., Coplu, L., Ozcelik, U., Kiper, N., Lay, I. and Oztas, Y. (2022) 'Increased Plasma YKL-40 Level and Chitotriosidase Activity in Cystic Fibrosis Patients', Inflammation, 45(2), pp. 627-638.

360. Use of culture and molecular analysis to determine the effect of antibiotic treatment on microbial community diversity and abundance during exacerbation in patients with cystic fibrosis	Tunney, M. M., Klem, E. R., Fodor, A. A., Gilpin, D. F., Moriarty, T. F., McGrath, S. J., Muhlebach, M. S., Boucher, R. C., Cardwell, C., Doering, G., Elborn, J. S. and Wolfgang, M. C. (2011) 'Use of culture and molecular analysis to determine the effect of antibiotic treatment on microbial community diversity and abundance during exacerbation in patients with cystic fibrosis', Thorax, 66(7), pp. 579-584.
361. Biomarkers in Exhaled Breath Condensate Are Not Predictive for Pulmonary Exacerbations in Children with Cystic Fibrosis: Results of a One-Year Observational Study.	van Horck, M., Alonso, A., Wesseling, G., de Winter-de Groot, K., van Aalderen, W., Hendriks, H., Winkens, B., Rijkers, G., Jobsis, Q. and Dompeling, E. (2016) 'Biomarkers in Exhaled Breath Condensate Are Not Predictive for Pulmonary Exacerbations in Children with Cystic Fibrosis: Results of a One-Year Observational Study', PloS one, 11(4), pp. e0152156.
362. Pseudomonas hyperimmune globulin passive immunotherapy for pulmonary exacerbations in cystic fibrosis	Van Wye, J. E., Collins, M. S., Baylor, M., Pennington, J. E., Hsu, Y. P., Sampanvejsopa, V. and Moss, R. B. (1990) 'Pseudomonas hyperimmune globulin passive immunotherapy for pulmonary exacerbations in cystic fibrosis', Pediatric pulmonology, 9(1), pp. 7-18.
363. Evidence of an acinar response following treatment for exacerbation in adult patients with cystic fibrosis	Vanderhelst, E., De Meirleir, L., Schuermans, D., Malfroot, A., Vincken, W. and Verbanck, S. (2014) 'Evidence of an Acinar Response following Treatment for Exacerbation in Adult Patients with Cystic Fibrosis', Respiration, 87(6), pp. 492-498.
364. Nutritional impact of antipseudomonas intravenous antibiotic courses in cystic fibrosis	Vic, P., Ategbo, S., Gottrand, F., Launay, V., Loeuille, G. A., Elian, J. C., Druon, D., Farriaux, J. P., Turck, D., Vic, P., Ategbo, S., Gottrand, F., Launay, V., Loeuille, G. A., Elian, J. C., Druon, D., Farriaux, J. P. and Turck, D. (1997) 'Nutritional impact of antipseudomonas intravenous antibiotic courses in cystic fibrosis', Archives of Disease in Childhood, 76(5), pp. 437-440.
365. Lung clearance index-triggered intervention in children with cystic fibrosis – A randomised pilot study	Voldby, C., Green, K., Kongstad, T., Ring, A. M., Sandvik, R. M., Skov, M., Buchvald, F., Pressler, T. and Nielsen, K. G. (2020) 'Lung clearance index-triggered intervention in children with cystic fibrosis – A randomised pilot study', Journal of Cystic Fibrosis, 19(6), pp. 934-941.
366. The role of respiratory viruses in cystic fibrosis.	Wat, D., Gelder, C., Hibbitts, S., Cafferty, F., Bowler, I., Pierrepoint, M., Evans, R. and Doull, I. (2008) 'The role of respiratory viruses in cystic fibrosis', Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society, 7(4), pp. 320-328.
367. Association of Diverse Staphylococcus aureus Populations with Pseudomonas aeruginosa Coinfection and Inflammation in Cystic Fibrosis Airway Infection	Wieneke, M. K., Dach, F., Neumann, C., Gorlich, D., Kaese, L., Thisen, T., Dubbers, A., Kessler, C., Grose-Onnebrink, J., Kuster, P., Schultingkemper, H., Schwartbeck, B., Roth, J., Nofer, J.-R., Treffon, J., Posdorfer, J., Boecken, J. M., Strake, M., Abdo, M., Westhues, S. and Kahl, B. C. (2021) 'Association of Diverse Staphylococcus aureus Populations with Pseudomonas aeruginosa Coinfection and Inflammation in Cystic Fibrosis Airway Infection', mSphere, 6(3), pp. e0035821.
368. Cytokine expression in bronchial biopsies of cystic fibrosis patients with and without acute exacerbation	Wojnarowski, C., Frischer, T., Hofbauer, E., Grabner, C., Mosgoeller, W., Eichler, I. and Ziesche, R. (1999) 'Cytokine expression in bronchial biopsies of cystic fibrosis patients with and without acute exacerbation', The European respiratory journal, 14(5), pp. 1136-44.
369. Are antipseudomonal antibiotics really beneficial in acute respiratory exacerbations of cystic fibrosis?	Wolter, J. M., Bowler, S. D. and McCormack, J. G. (1999) 'Are antipseudomonal antibiotics really beneficial in acute respiratory exacerbations of cystic fibrosis?', Australian and New Zealand journal of medicine, 29(1), pp. 15-21.
370. Home intravenous therapy in cystic fibrosis: a prospective randomized trial examining clinical, quality of life and cost aspects	Wolter, J. M., Bowler, S. D., Nolan, P. J. and McCormack, J. G. (1997) 'Home intravenous therapy in cystic fibrosis: a prospective randomized trial examining clinical, quality of life and cost aspects', The European respiratory journal, 10(4), pp. 896-900.
371. Cytokines and inflammatory mediators do not indicate acute infection in cystic fibrosis	Wolter, J. M., Rodwell, R. L., Bowler, S. D. and McCormack, J. G. (1999) 'Cytokines and inflammatory mediators do not indicate acute infection in cystic fibrosis', Clinical and diagnostic laboratory immunology, 6(2), pp. 260-5.

372. Preliminary method for profiling volatile organic compounds in breath that correlate with pulmonary function and other clinical traits of subjects diagnosed with cystic fibrosis: a pilot study.	Woollam, M., Siegel, A. P., Grocki, P., Saunders, J. L., Sanders, D. B., Agarwal, M. and Davis, M. D. (2022) 'Preliminary method for profiling volatile organic compounds in breath that correlate with pulmonary function and other clinical traits of subjects diagnosed with cystic fibrosis: a pilot study', Journal of breath research, 16(2).
373. Antibiotic-resistant obligate anaerobes during exacerbations of cystic fibrosis patients	Worlitzsch, D., Rintelen, C., Bohm, K., Wollschlager, B., Merkel, N., Borneff-Lipp, M. and Doring, G. (2009) 'Antibiotic-resistant obligate anaerobes during exacerbations of cystic fibrosis patients', Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases, 15(5), pp. 454-60.
374. Doxycycline improves clinical outcomes during cystic fibrosis exacerbations.	Xu, X., Abdalla, T., Bratcher, P. E., Jackson, P. L., Sabbatini, G., Wells, J. M., Lou, X.-Y., Quinn, R., Blalock, J. E., Clancy, J. P. and Gaggar, A. (2017) 'Doxycycline improves clinical outcomes during cystic fibrosis exacerbations', The European respiratory journal, 49(4).
375. Circulating fibrocyte level in children with cystic fibrosis	Yasar, P. A., Kose, M., Erdem, S., Hangul, M., Karaman, Z. F. and Eken, A. (2022) 'Circulating fibrocyte level in children with cystic fibrosis', Pediatrics international : official journal of the Japan Pediatric Society, 64(1), pp. e15058.
376. Comparison of high frequency chest compression and conventional chest physiotherapy in hospitalized patients with cystic fibrosis	Arens, R., Gozal, D., Omlin, K.J., Vega, J., Boyd, K.P., Keens, T.G. and Woo, M.S., 1994. Comparison of high frequency chest compression and conventional chest physiotherapy in hospitalized patients with cystic fibrosis. American journal of respiratory and critical care medicine, 150(4), pp.1154-1157.
377. Neuraminidases produced by cystic fibrosis isolates of Pseudomonas aeruginosa: Gene distribution, enzyme activity and clinical importance	Strateva, T., Abrashev, I., Eneva, R., Petrova, G. and Mitov, I. (2009) 'Neuraminidases produced by cystic fibrosis isolates of Pseudomonas aeruginosa: Gene distribution, enzyme activity and clinical importance', Problems of Infectious and Parasitic Diseases, 37(2), pp. 25-27.