Tentative hope: An exploration of the impact of Cystic Fibrosis transmembrane conductance regulator modulators on people with Cystic Fibrosis and their families.

Hannah Edwards

Primary Supervisor: Dr Amy Carroll

Secondary Supervisors: Dr Gail Clare and Dr Louise Morgan

Doctorate in Clinical Psychology

University of East Anglia

Faculty of Medicine and Health Sciences

Submission Date: 2nd April 2024

Thesis Word Count: 24,531

Candidate Registration Number: 100373540

Thesis Portfolio Abstract

Background. Cystic Fibrosis (CF) is a rare, life-limiting genetic condition, which impacts the functioning of multiple organ systems (Bierlaagh et al., 2021). People with CF (pwCF) experience a range of difficulties, which affect their physical and psychological health (Ernst et al., 2010), as well as that of their families (Daly et al., 2022).

Cystic Fibrosis transmembrane conductance regulator (CFTR) modulator therapies are a new and highly anticipated treatment for CF (Bierlaagh et al., 2021). They have been found to significantly improve the physical health of pwCF and are hoped to improve life-expectancy (Balfour-Lynn & King, 2022). There is, however, little known about the psychological experience of starting these potentially lifechanging medications, for either pwCF or their families. Indeed, early research has intimated possible negative psychological experiences (Talwalkar et al., 2017). It is therefore important to understand the nature of the relationship between CFTR modulators and the psychological experiences of pwCF and their families.

Aims. This thesis aims to understand the impact of CFTR modulators on the psychological wellbeing of pwCF and to gain insight into the experiences of parents whose children have started CFTR modulators.

Methods. A systematic review was conducted on the impact of CFTR modulators on the psychological wellbeing of pwCF. Ten papers were identified and reviewed using narrative synthesis. Interpretative Phenomenological Analysis (IPA) was used to explore parental experiences.

Results. In the systematic review, CFTR modulators were observed to have a slight positive impact on the quality of life of pwCF, but not on levels of anxiety and depression. Several themes emerged in the qualitative paper, illustrating parents' complex feelings towards the medication and the factors that influenced this including hope, uncertainty, and adjustment.

Conclusion. PwCF and their families have a complex psychological relationship to starting CFTR modulators influenced by nonphysical factors such as hope and uncertainty.

Table of Contents

Acknowledgements

This research has been completed in partial contribution for the Clinical Psychology Doctorate Course at the University of East Anglia.

I would first like to thank Dr Amy Carroll, Dr Gail Clare and Dr Louise Morgan for their support, guidance, and patience, whilst I have been completing this project. Your kindness and encouragement throughout this journey have been remarkable and I am incredibly grateful for all you have done.

I would also like to thank Jack Johnson and the other members of the Paediatric Cystic Fibrosis teams who supported recruitment for this project. Your hard work and passion for your patients was amazing to witness and the impact of this illustrated throughout the experiences of the participants I interviewed.

I would like to thank my family and friends, both those here and no longer with us, all of whom have offered their unending support, time, and word findings skills to allow me to create this portfolio. Thank you for your compassion and patience. I would particularly like to thank my friends Kate Roberts, who first introduced me to the world of Cystic Fibrosis and Emma Heathcote, who acted as a second coder for my Systematic Review. Thank you for joining me on this journey.

Lastly, I would like to thank all the families who took part in this research. I have learnt so much from what you have shared, and it has been a real privilege to hear your stories.

Chapter One: Thesis Portfolio Introduction

This Thesis Portfolio aims to explore the impact of a new treatment for Cystic Fibrosis (CF), Cystic Fibrosis transmembrane conductance regulator (CFTR) modulator therapies, from a psychological perspective. Using a narrative systematic approach, current understanding of the impact of CFTR modulators on the psychological wellbeing of people with CF will be reviewed. The empirical paper will then employ a qualitative approach to explore the experiences of parents of children with CF once their child has started CFTR modulators.

The following chapter will provide a general introduction to both CF and CFTR modulators. To begin with, an overview of the CF is presented along with an introduction to its impact, the progression of the condition, as well as an introduction to the socio-political context of CFTR modulators. This introductory chapter aims to set the context for the systematic review and empirical paper that will follow in chapters two and four.

Cystic Fibrosis

CF is a rare genetic condition that affects approximately 11,148 people in the United Kingdom (UK) (Natio et al., 2023). CF is a recessive condition, caused by a person inheriting two faulty copies of the CFTR gene (Lopes-Pacheco, 2020). The CFTR gene is responsible for encoding a protein, which regulates the movement of salt and water molecules into and out of the cells that line many of the body's key organ systems (Lopes-Pacheco, 2020). In people with CF (pwCF), this protein is ineffective, leading to thick and sticky mucus developing along the lining of these organs, such as the pancreas, liver and digestive system (Chen et al., 2021; McBennett et al., 2022). CF most significantly affects the lungs, with the sticky mucus trapping bacteria, making pwCF more vulnerable to chest infections. It also causes inflammation, which gradually damages the lungs (Turcios, 2020). Over time, pwCF's lung functioning decreases, eventually leading to respiratory failure, which is the most common cause of death for pwCF (McBennett et al., 2022). Respiratory failure is known to be a distressing process for both the person with CF and their families and carers (Dellon et al., 2010).

Historically, pwCF had a very short life expectancy, with most not being expected to live beyond early childhood (McBennett et al., 2022). This has changed significantly since it was first identified in 1938, with vast developments in CF treatment (McBennett et al., 2022). This has included the creation of antibiotics which fight infection and airway clearance techniques which attempt to dislodge the mucus in the lungs improving lung function (Jaques et al., 2020). Traditionally, treatment has only been able to focus on managing CF symptomatology and a cure for the condition has yet to be found (Bierlaagh et al., 2021). Nevertheless, the vast improvements in CF

treatment have meant that the median life expectancy of people born with CF in 2022 has increased to 56.1 years (Bierlaagh et al., 2021; Natio et al., 2023).

Living with Cystic Fibrosis

Although the developments in CF treatment have led to significant increases in life expectancy, pwCF are still affected by a variety of physical symptoms associated with the condition (McBennett et al., 2022). These may include frequent coughing, shortness of breath, fatigue, sleep disturbances, pain and difficulties gaining and maintaining weight (Sawicki et al., 2008).

The daily treatment to support the management of CF symptoms is burdensome. PwCF are estimated to complete one and a half hours of treatments each day (Cameron et al., 2022). These can include physiotherapy, inhalation therapies, various oral medications, self-monitoring of symptoms, as well as the time and effort needed to integrate this into daily life (Altabee et al., 2022; Davies et al., 2020). PwCF also attend regular hospital appointments for monitoring (Cystic Fibrosis [CF]Trust, 2011) and may be admitted for periods of time if their lung function becomes poor (Ernst et al., 2010). The high treatment burden in CF is associated with poorer treatment adherence, which is often a source of concern for clinicians (Sawicki et al., 2013). Poor treatment adherence has been associated with a greater risk of hospitalisation, worsening lung health and quicker disease progression (Goodfellow et al., 2015).

CF also has social implications for those who live with the condition (Ernst et al., 2010; Pfeffer et al., 2003). Owing to the physical impact of the medication and its high treatment burden, pwCF may not be able to engage in the same activities as their peers (Gulledge et al., 2021). PwCF report high social isolation, which is exacerbated by not being able to socialise with other pwCF due to the high risk of cross infection (Gulledge et al., 2021). Adolescents with CF, in particular, find the social impact of CF difficult and are less likely to engage in their treatments due to not wanting to stand out and be different (Oliver et al., 2014).

Psychological Wellbeing and Cystic Fibrosis

As indicated above, living with CF is associated with significant physical, functional and social challenges, all facets of a person's quality of life (QoL). QoL is a multidimensional construct, composed of a person's physical, psychological, social and functional experiences (Megari, 2013). QoL is considered an important outcome in healthcare research, representing how an individual perceives their life is being impacted by a condition or a treatment (Kaplan, 2003). QoL measures are valuable tools, which offer a more person-centred perspective and are increasingly becoming key outcomes in clinical trials (Abbott et al., 2011). In general, CF is seen to have a negative impact on the QoL of pwCF (Parekh et al., 2015). A number of factors have been associated with this, including

lung function and social support, however, a person's psychological wellbeing, such as their experiences of anxiety and depression have been found to be some of the strongest predictors of poor QoL in pwCF (Ancel et al., 2022).

Recent global systematic reviews and meta-analyses have reported that pwCF are approximately five times more likely than the general population to experience anxiety and depression (Guta et al., 2021; Lord et al., 2023). This has been of particular concern, due to the impact of anxiety and depression on pwCF's QoL. Anxiety and depression have also been associated with reduced physical health outcomes such as poorer lung functioning and poorer treatment adherence, which in turn impacts physical health outcomes (Guta et al., 2021; Knudsen et al., 2016). As a result, CF is one of the few physical health conditions in the UK in which the National Institute of Health Care and Excellence (NICE) recommends that a clinical psychologist is a core part of the multidisciplinary team ([NICE], 2017). Clinical psychologists are responsible for identifying the psychological needs of pwCF and offering interventions to support those experiencing psychological distress such as anxiety, depression, poor QoL, adherence difficulties and difficulties adjusting to the condition (Conway et al., 2014; Oxley & Webb, 2005).

Advances in Cystic Fibrosis Treatment

In 2012, a new type of CF treatment was approved in the United States (US). The medication known as Ivacaftor, later Kalydeco in the UK, was the first of a new type of medication known collectively as CFTR modulators (CF Trust, n.d.). These are oral medications, which are designed to correct the ineffective CFTR proteins, which cause the sticky mucus in pwCF and are the first to treat this underlying cause (Lopes-Pacheco, 2020). CFTR modulators cannot undo the damage that has already been caused by CF, however, they work to prevent further damage and reduce the cumulative disease burden (Edmondson et al., 2021). Research into Ivacaftor demonstrated improved lung function, weight gain and respiratory QoL (Guimbellot et al., 2021) representing a significant advance in treatment effectiveness for pwCF (Allen et al., 2023), however the treatment has significantly higher financial cost at £182,625 per year (England, 2015). When deciding to fund treatment, the NHS makes decisions based upon the QoL and length of life a person will gain due to the intervention. These are known as quality-adjusted life years (QALYs). An intervention is considered cost effective if the treatment costs £20,000 per QALY gained (NICE, 2013). Ivacaftor was estimated to cost between £335,000 and £1.274 million per QALY (England, 2015), which far exceeds the £20,000. The NHS underwent negotiations with manufacturers of Ivacaftor in order to acquire a discount which would be better aligned with current NHS guidelines around the cost of medication (England, 2015). This was successful, although the medications were still considerably more

expensive than £20,000 per QALY, it was accepted and the medication was made available in England for people six years and above with a specific CFTR gene mutation (CF Trust, n.d.).

CFTR modulators are highly specialised and not all pwCF can benefit from all CFTR modulators (Lopes-Pacheco, 2020). Over the past 12 years, however, further research has been conducted into improving this and increasing the number of CFTR modulators available to pwCF both into developing more CFTR modulator therapies and testing their effectiveness in people with a wider range of CFTR variants (Bentley et al., 2022). A further three CFTR modulators have since been developed: lumacaftor/ivacaftor (Orkambi), tezacaftor/ivacaftor (Symkevi) and elexacaftor/texacaftor/ivacaftor (Kaftrio), with Orkambi and Symkevi being made available in England towards the end of 2019 (Jacqui, 2023). In 2020, following years of campaigning by pwCF, their families and supporters, the final modulator, Kaftrio, was made available on the NHS (CF Trust, n.d). Kaftrio is particularly important as it can be taken by approximately 90% of pwCF (Jacqui, 2023). Kaftrio was originally approved in people over the age of 12, however, this age has since been lowered (Bentley et al., 2022). As of 2022, 7950 pwCF have commenced modulators in the UK (Natio et al., 2023).

The development of CFTR modulators has been a source of great hope and excitement in the CF community (Bierlaagh et al., 2021). They are the first CF treatment designed to target the cause of CF (Harvey et al., 2022) and it is hoped that they will limit the progression of the condition and in doing so, significantly improve life expectancy (Balfour-Lynn & King, 2022). However, research into the impact of CFTR modulators is in its infancy. Thus far, research has only been able to ascertain the short-term impact of CFTR modulators, such as its impact over weeks or a couple of years (Li et al., 2022). Research has also primarily focused on physical health outcomes such as lung function, weight gain and respiratory QoL (Habib et al., 2019). Much research is currently underway and more needed in the pursuit to understand the potential impact of CFTR modulators more fully (Allen et al., 2023).

On the 3rd of November 2023, NICE published a preliminary review on the availability of CFTR modulator therapies (CF Trust, 2024). NICE stated that although Orkambi, Symkevi and Kaftrio are clinically effective for pwCF, they cannot continue to recommend that the NHS offers it at the current price. After much anxiety in the CF community in the UK, they confirmed that anyone who had already commenced CFTR treatment would continue to be able to do so, however, they intended to stop making Orkambi, Symkevi and Kaftrio available as a new treatment to those who have not yet started them. The treatments, whose prices have been kept a secret, have been reported to be well above the £20,000 per QALY that is considered acceptable by the NHS

(Brendbekken & Bhopal, 2024) . The decision by NICE to halt the roll out of CFTR medication has quite understandably caused much distress and concern in the CF community (Snowdon, 2023). At the time of writing, NICE has agreed to pause their appraisal of the medications and continue discussions with the pharmaceutical company that provides CFTR modulator therapies on conditions such as price (CF Trust, 2024).

Despite the known impact of CF on the psychological wellbeing of pwCF and the potential impact of CFTR modulators on the lives of pwCF, comparatively little research has explored this connection. This thesis, therefore, aims to contribute to this growing area of research, highlighting the importance of psychological wellbeing as an outcome in our understanding of the treatment of physical illness. This research feels particularly pertinent, considering NICE's appraisal of the medication and hopes to offer a different perspective on the value of the medication.

Outline of Thesis Portfolio

This thesis aims to contribute to current understanding of the psychological impact of CFTR modulators. In the next chapter, a systematic review will synthesise current research into the impact of CFTR modulators on the psychological wellbeing of people with CF. The empirical paper presented in chapter four aims to explore the experiences of parents whose children have commenced CFTR modulators. The final chapter will reflect on the body of work as a whole and critically discuss its strengths, limitations, and clinical implications. It will also consider potential future research.

Chapter Two: Systematic Review

The impact of the new Cystic Fibrosis transmembrane regulator modulator therapies on the psychological wellbeing of people with Cystic Fibrosis: A Systematic Review

Hannah Edwards, Dr Gail Clare, Dr Louise Morgan and Dr Amy Carroll,

Department of Clinical Psychology and Psychological Therapies, University of East Anglia, UK.

Cambridge and Peterborough NHS Foundation Trust

The Queen Elizabeth Hospital King's Lynn NHS Foundation Trust

Norfolk and Norwich University Hospitals NHS Foundation Trust

Prepared for: The Journal of Cystic Fibrosis (author guidelines in Appendix K)

Word Count excluding abstract, titles, tables and references: 5091

Word Count: including titles, tables/figures: 7466

Any queries regarding this review should be directed to Hannah Edwards, Norwich Medical School, University of East Anglia, Norwich, Norfolk, NR4 7TJ, UK

Email: h.edwards3@uea.ac.uk

Abstract

Background: Cystic Fibrosis transmembrane conductance regulator (CFTR) modulator therapies are an important new treatment for Cystic Fibrosis (CF) (Lopes-Pacheco, 2020) and have been reported to have a significant impact on the physical health of people with CF (Gramegna et al., 2020). There have been concerns, however, that CFTR modulators are having a negative impact on the psychological wellbeing of some people with CF including the development of anxiety and depression (Talwalkar et al., 2017). This is particularly concerning as people with CF are already known to be at increased risk of struggling with their psychological wellbeing (Ancel et al., 2022). A broader understanding of the impact of CFTR modulators on psychological wellbeing is needed.

Aims of Review: This review aims to explore current research into the impact of CFTR modulators on psychological wellbeing.

Methods: Medline Ultimate, CINAHL Ultimate and Scopus were searched for papers exploring the impact of CFTR modulators on quality of life, anxiety and depression in people with CF. A narrative synthesis was conducted on both quantitative and qualitative studies.

Results: Ten studies were identified and critically appraised. There was some evidence of improvement in overall quality of life during approximately the first 12 months of taking CFTR medication. No changes were observed in levels of anxiety and depression across the studies appraised.

Conclusion: Despite improvements in physical health after commencing CFTR modulator therapy, people with CF do not experience a similar level of improvement in their psychological wellbeing, Further research is needed to better understand the long-term implications of CFTR modulators as well as its relationship with psychological wellbeing.

Introduction

Cystic Fibrosis (CF) is a complex, life limiting genetic condition, which affects multiple organ systems (Saluzzo et al., 2022). CF can impact a person's social, emotional and occupational functioning, and is known to have an overall negative impact on people with CF (pwCF)'s psychological wellbeing (Ancel et al., 2022). A large multi-national study exploring the prevalence of anxiety and depression in pwCF reported that 28.4% of pwCF met the threshold for an anxiety disorder and 27.2% for depression (Guta et al., 2021). This is approximately five times the rate of the general population, which report 4% and 5% respectively (World Health Organisation, 2023a; World Health Organsation, 2023). Identifying the psychological needs of pwCF has therefore become a priority, (Alexandra et al., 2016).

Cystic Fibrosis transmembrane conductance regulator (CFTR) modulator therapies are a family of new and highly anticipated oral medications designed for the treatment of CF (Lopes-Pacheco, 2020). Unlike traditional treatment for CF, which focuses on managing CF symptomatology, CFTR modulators target the cause of CF (Edmondson et al., 2021). They have been observed to significantly improve physical health outcomes for pwCF, particularly with regards to lung function (Bower et al., 2023). CFTR modulators have been heralded as an important shift in CF treatment and are expected to have a significant impact on life expectancy, however, the long term-effects are yet to be known (Bardin et al., 2021). Further research is needed to understand the wider implications of the medication.

Cystic Fibrosis transmembrane conductance regulator modulator therapies and psychological wellbeing

Despite the effectiveness of CFTR modulators on managing physical symptomatology, there have been concerns that it may be having a negative impact on pwCF's psychological wellbeing (VanElzakker et al., 2023).

Several case studies have reported concerns of pwCF either developing or experiencing increased levels of anxiety and depression after commencing one of the CFTR modulators. For example, Talwalkar et al. (2017) observed three patients experiencing increased rates of anxiety and depression after starting lumacaftor/ivacaftor. In each of these cases the patients had a history of mental health difficulties, however, these had stabilised prior to starting the medication. Similarly, Arslan et al. (2023) described two cases where adolescents attempted suicide after developing depression after commencing elexcaftor/tezacaftor/ivacaftor (ETI). In these cases, neither had reported depression prior to starting the medication, and although there were several external factors that may have had an influence, reduction in ETI was associated with better mental health.

Researchers have begun to hypothesise why some people with pwCF experience poorer mental health after starting CFTR modulators. Theories have included the emotional impact of starting a life changing medication and what this means for their future or the impact of negative side effects from the medication (Talwalkar et al., 2017). It has also been suggested that CFTR modulators may be having a direct impact on the nervous system (VanElzakker et al., 2023). These case studies, however, reflect only a small portion of the CF population and although they are concerning, they are not evidence of CFTR modulators having a more general impact on pwCF's psychological wellbeing. They do suggest, however, a greater understanding of the impact of CFTR modulators on psychological wellbeing is needed. Such understanding would allow clinicians to better support pwCF during this period.

Purpose of this review

This review aims to systematically explore current research into the impact of CFTR modulators on the psychological wellbeing of pwCF. For the purposes of this review, psychological wellbeing will be defined as the therapies' impact on quality of life (QoL), anxiety and depression. QoL is considered an important marker of the effectiveness of CF treatment and is often incorporated into research trials (Abbott & Hart, 2005). This has been investigated in clinical trials for CFTR modulators; however, trials have tended to only report the respiratory domain (Habib et al., 2019) of what is intended to be a bio-psycho-social and multi-domain concept, reflecting people's perspectives of their physical, social, emotional and practical functioning (Abbott & Gee, 2003). This review intends to explore the impact of CFTR modulators on QoL across multiple domains.

Anxiety and depression will also be explored, due to the concerns around the negative impact of CFTR modulator therapies centring these (e.g. (Talwalkar et al., 2017; VanElzakker et al., 2023) and the prevalence of these common mental health problems for pwCF (Lord et al., 2023). Anxiety and depression have also been associated with poorer QoL and poorer treatment adherence in studies predating CFTR modulators. It is therefore important to understand the relationship between CFTR modulators and anxiety and depression (Lord et al., 2023).

Review Aim

The aim of this review is to explore the following question: W*hat is the impact of CFTR modulator therapies on the psychological wellbeing of pwCF*? The review will incorporate both qualitative and quantitative results, to gain a diverse overview of the area. Case studies, however, will be excluded, with this review prioritising understanding the experiences of pwCF more broadly.

Methods

This systematic review and subsequent amendments were prospectively registered with PROSPERO (CRD42023404594).

Search Strategy

Medline Ultimate, CINAHL Ultimate and Scopus online databases were systematically searched between the 1st January 2012 and the 5th November 2023. This search period was chosen as CFTR modulators were first approved for general use in January 2012 by United States (US) Federal Drug Administration (FDA) (Lopes-Pacheco, 2020). Due to CFTR modulators being a relatively new medication and an emerging field of study MeSH terms were not employed to ensure the search strategy was broad and flexible, including terms that were yet to be indexed. An example of the search strategy can be found in appendix A.

Inclusion and Exclusion Criteria

Inclusion Criteria for the review were as follows: experimental, observational, or qualitative studies where the paper was published in English, participants had a diagnosis of CF, had commenced at least one CFTR modulator therapy, with a primary measure of anxiety, depression or QoL.

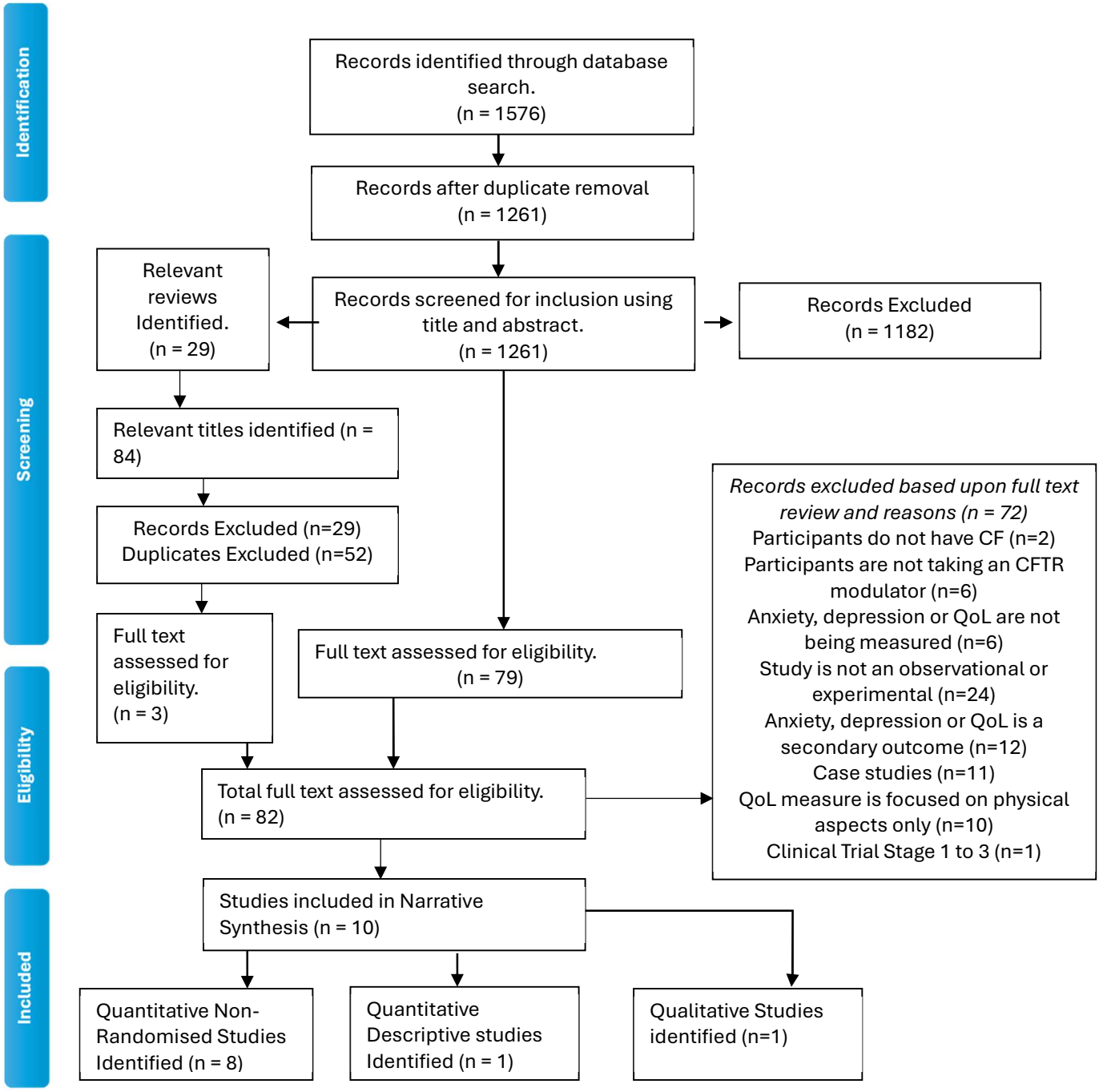
Exclusion Criteria were as follows: case studies or reviews, although when reviews were identified, their reference lists were checked for potentially appropriate papers, which once noted, were included for title and abstract review; clinical trials from phase one to three, studies where anxiety, depression or QoL were a secondary outcome and studies where QoL measures only reported physical domains or did not focus on impact of CF. This is because several studies used QoL measures such as the Sino-Nasal Outcome Test-22 QoL scale, which is primarily designed to measure the impact of rhinitis on QoL. Although pwCF can struggle with rhinitis, this measure would not illustrate the CF related QoL.

Selection of Studies

Database searches identified 1576 potential papers. Searches were completed using the CADIMA systematic review software and after duplicates were removed 1261 papers were identified for title and abstract screening. 82 papers which met the inclusion or exclusion criteria or where it was unclear whether they met the criteria were fully screened. To ensure reliability, 20% of the full texts were screened for inclusion and exclusion criteria by a second independent coder. Very few disagreements were noted, all of which were discussed and resolved. The PRISMA diagram in figure 1. illustrates the process in more detail.

Figure 1.

A PRISMA diagram, representing the process of identification of papers for this Systematic Review.



Data Extraction and Management

The following data were extracted from each included study: type of modulator taken, number of participants, age range, ethnicity, study country, study type, study methodology, measure type and relevant outcomes (quantitative and qualitative).

Data of interest were tabulated according to core study characteristics, QoL measures, anxiety measures and depression measures. Due to the heterogeneity of study design, a meta-analysis could not be performed. A full table of study characteristics can be found in appendix C.

Quality Assessment

All papers were assessed for quality by the primary researcher using the Quality assessment with Diverse Studies (QuADS) critical appraisal tool (Harrison et al., 2021). The QuADS is a quality appraisal tool, which has been developed with healthcare research in mind (Harrison et al., 2021). The QuADS comprises 13 criteria, each of which are rated on a four-point scale, where 0 means the criterion has not been reported upon and 3 means the criterion has been reported upon more comprehensively. The full criteria are in appendix B. The QuADS has demonstrated substantial inter-rater reliability (k=0.66) and good face and content validity (Harrison et al., 2021).

The QuADS does not use categories such as high, medium and low to classify a study's methodological quality, deeming this to be arbitrary and therefore a less helpful way to categorise a study. Instead, the tool invites you to calculate an overall score for each study and then discuss criterion more broadly in appraisal (Harrison et al., 2021).

To ensure reliability, 25% of the papers were randomly selected and assessed by a second reviewer. The second reviewer was blinded to the decisions of the original researcher and any disagreements were discussed.

Results

Appraisal of Study Characteristics

Ten studies were identified to meet the inclusion and exclusion criteria set for this review. A summary of characteristics is reported in table 1.1.

Each study focused on a single type of modulator, with most looking at the impact of ETI. No included study looked at tezacaftor/ivacaftor. This is noteworthy as ETI was only made available for use in 2020 (Jacqui, 2023), but appears to have received the most attention with regards to research into psychological wellbeing. One explanation for this is that ETI is the most widely used modulator, compatible with approximately 90% of pwCF (Jacqui, 2023) and likely to have the most impact on

pwCF. Nevertheless, the previous modulators have been available to pwCF for a much longer period, and it is surprising that such little research into their impact on psychological wellbeing has taken place. In fact, the earliest paper identified in this study was published in 2019, reflecting the tendency of CF research to focus on physical health outcomes over mental health outcomes (Alexandra et al., 2016). Considering that CF is a physical health condition, prioritising physical health outcomes is understandable, however they only represent one part of pwCF's lived experience of the condition.

A total of 485 pwCF who had commenced a modulator therapy were included in this review, with a further 222 controls. Overall, approximately 43.74% of participants were female. Ethnicity was only reported in two studies, and nearly all participants were identified as white. These proportions are typical of what is observed in the CF community (Natio et al., 2023). There was little variance in the average age of participants across the studies but greater variance within them.

The studies were completed in a range of different western countries, with the United States (US) being most represented. Approximately half of the studies were completed on patients under a compassionate use programme, in which patients were given early access to the medication due to their lung function dropping to below 40%, at which they are considered to be at high risk of death (Zolin et al., 2018). These patients would have been very unwell prior to commencing the modulator therapy, which is negatively associated with psychological wellbeing (Quittner et al., 2014).

Six studies recruited sample sizes of less than 50 participants. This is not unexpected as many of the studies only offered the medication on compassionate grounds, reducing the available population in what is already a relatively rare condition (Natio et al., 2023). It does mean, however, that many of these studies are likely to be underpowered and therefore less able to detect change even if it was present (Serdar et al., 2021).

In most studies that explored ETI, a proportion of participants had already taken a different form of CFTR modulator. Although the proportion of these was often reported in the research, this was never factored into analysis. In these instances, it is difficult to distinguish between ETI's impact on psychological wellbeing and the impact of previous modulators.

The studies employed a wide range of research designs. Seven studies used a quasi-experimental design, collecting data before and after participants started a modulator. Most included multiple follow up points. An advantage of this design is being able to measure direct change after the CFTR modulator is commenced, as well as its longer-term effects. However, it is difficult to establish whether change is directly attributable to the medication and very few of the

studies controlled for extraneous variables. Additionally, two studies used retrospective chart reviews, where data quality is less controllable and may therefore be influencing results.

Two studies used control groups, a design which can account for the impact of extraneous variables, however, Migliorisi et al., (2022) only collected psychological wellbeing outcomes for the experimental group, meaning the comparison could not occur.

Table 1.1

A summary of study characteristics

Author and Year	Modulator Assessed	Country	Patient Characteristics					Study Characteristics	
			Number of Participants	Age	Gender	Ethnicity	Length of time on Modulators	Type	Design
Aspinall et al., (2022)	Elexacaftor/ tezcaftor/ ivacaftor	United Kingdom	12	Mean = 28.1 SD = 6.4	83% female 17% male	Not reported	6 months to over 1 year	Qualitative	Qualitative Content Analysis
McCoy et al., (2022)[a]	Elexacaftor/ tezcaftor/ ivacaftor	United States	18	mean = 33.8 years, range = 15 to 49	44% female, 56% male	Not reported	2 years	Quantitative	Retrospective Chart Review
Carrasco Hernández et al., (2023)[a]	Elexacaftor/ tezcaftor/ ivacaftor	Spain	114	mean = 30.2 SD = 9.6	48.2% female, 51.8% male	Not reported	24 months	Quantitative	Observational pre-post study
Allgood et al., (2023)	Elexacaftor/ tezcaftor/ ivacaftor	United States	22	median = 35.3 (IQR 11.1)	40.9% female,	100% white	14 weeks	Quantitative	Prospective observational study

					59.1% male				
Piehler et al., (2023)	Elexacaftor/ tezcaftor/ ivacaftor	Germany	70	median = 27.9 (IQR 22.5 - 34.1)	51.4% female, 48.6% male	Not reported	8 to 16 weeks	Quantitative	Prospective observational study
DiMango et al (2021)	Elexacaftor/ tezcaftor/ ivacaftor	United States	43	mean = 34.0 (30.5 - 37.5)	67% female 33% male	Not reported	3 months	Quantitative	Prospective cohort study
Zhang et al., (2022)[a]	Elexacaftor/ tezcaftor/ ivacaftor	United States	100	mean = 35.3 (11.3)	48% female 52% male	96% white, 4% black, biracial or multiracial	unclear	Quantitative	Retrospective chart review
Eijofor et al., (2020)[a]	Lumacaftor/ivacaftor	Denmark	21	Median = 33.0 (23,40)	46% female, 54% male	Not reported	median 68.7 (58.1, 77.7) weeks	Quantitative	Follow up

Migliorisi et al., (2022)[a]	Elexacaftor/ tezcaftor/ ivacaftor	Italy	26 (13 control)	Median =29.5, IQR 22.25, 39.00	50% female, 50% male	Not reported	12 months	Quantitative	Retrospective case control study
Bell et al., (2019)	Ivacaftor	France, United Kingdom, Germany Australia and Ireland	209 (137 control)	Mean = 24.3 (SD 12.1)	44% female, 56% male	Not reported	Mean = 21.8 (SD = 15.1) months	Quantitative	Cross-sectional study (control group)

[a] Indicates studies in which access to CFTR modulators had been granted as part of a Compassionate Use Programme.

Summary of Quality Appraisal

All studies were critically appraised using the QuADs. Each of the scores was discussed with a second independent reviewer and an inter-rater reliability score of 86.11% was achieved. This score is considered acceptable for health care research (McHugh, 2012) and indicates that the primary researcher's appraisal is acceptable.

Using the QuADs, a total score of 39 points is available, with a higher score indicating criteria were reported upon comprehensively and felt to be appropriate by the reviewer. The total QuADs score for each study included in the review has been presented as a percentage in table 1.2 below. The scores ranged from 46.15% (Migliorisi et al., 2022) to 79.78% (Bell et al., 2019). Although the QuADS states that the categorisation of studies into levels of quality such as high, low and medium are arbitrary, it does categorise its scores and invites the rater to make a judgement as to the appropriateness of the study design. With this in mind, it would suggest studies that higher scores on the QuADS indicate a study demonstrating higher levels of methodological and evidential quality.

Overall, the studies were consistently found to have a clear theoretical focus and research aims. They nearly all described their samples and methodology clearly, allowing for detailed scrutiny and replication. The studies used relatively appropriate analytic methods, although many of the quantitative studies did not include potential confounding variables in their analysis, despite data being collected that could allow for this. One explanation for this could be that relatively small sample sizes meant this was not possible, but this was not clearly stated within the papers themselves.

The studies were consistently poorer at justifying their decision making. Very few explained why they made both made decisions around the tools they used or their analytic method and although in the reviewer's opinion they were appropriate to the review aims, understanding the rationale behind the decisions would improve clarity.

Table 1.2

A summary of quality appraisal scores.

Author and Year	Total Score (%)
Aspinall et al., (2022)	56.41
McCoy et al., (2022)	53.85
Carrasco Hernández et al., (2023)	53.85
Allgood et al., (2023)	64.10

Piehler et al., (2023)	71.79
DiMango et al (2021)	51.28
Zhang et al., (2022)	64.10
Eijofor et al., (2020)	66.67
Migliorisi et al., (2022)	46.15
Bell et al., (2019)	79.48

Summary and Appraisal of Quality-of-Life Outcomes

Eight studies explored the impact of modulators on QoL. Seven employed quantitative measures and one a qualitative design. All seven quantitative studies used the Cystic Fibrosis Questionnaire-Revised (CFQ-R), a multi-domain measure that has been specifically developed to measure health-related QoL in adolescents and adults with CF. The measure has been demonstrated to have good reliability and validity (Quittner et al., 2012), is a widely used tool and has been approved for use in clinical trials (Ancel et al., 2022).

Bell et al., (2019) used the EQ-5D-5L in addition to the CFQ-R. The EQ-5D-5L is the newest version of the EQ-5D, a widely used generic measure of health-related QoL. The EQ-5D is recommended for use in the appraisal of health technology by the National Institute for Health and Care Excellence (NICE) (Acaster et al., 2015). The EQ-5D-5L has been reported to have excellent validity and reliability in a variety of different health conditions (Feng et al., 2021), but has yet to be formally validated in CF. Previous versions of the EQ-5D, have, however, been used successfully in pwCF (Feng et al., 2021).

Despite the studies in this review using generally the same high-quality psychometrics, the heterogeneity of study designs mean that an overall measure of effect cannot be reported. More broadly, the studies indicate that participants' QoL improved slightly after commencing modulators. The only exception was reported by Carrasco Hernández et al., (2023), where there were initial improvements in all domains up until the 12 month follow up point, after which these scores plateaued or declined. This was despite the physical elements of the medication, such as improvements in lung function continuing beyond this time. One reason for this could be that Carrasco Hernández et al., (2023)'s study recorded participants who had been on the study for one of the longest time periods, and the possibility that after a period of time following initiation, pwCF become used to the impact of the medication. However, McCoy et al., (2022) also report change over a similar two-year period but the same decline is not observed. McCoy et al., (2022) and

Carrasco Hernández et al., (2023) do not differ considerably with regards to their methodological quality. Nevertheless, Carrasco Hernández et al., (2023) is, a much larger study, with over 100 participants, meaning that it is less likely to be affected by individual experiences and have greater statistical power making it better able to detect the impact of the medication (Serdar et al., 2021). The changes observed in nearly all other studies would fit within Carrasco Hernández et al., (2023) initial 12 months period of improvement.

The general improvement in domains did not appear to differ widely between the modulator types, with both Eijofor et al., (2020) and Bell et al., (2019) reporting similar improvements. They were, however, the only study exploring that specific type of medication so a more generalised pattern could not be observed. Bell et al., (2019) study, however, is a large study including participants from several different countries which implies that this is a stronger pattern. The study also has the strongest quality, emphasising its value.

Improvements in QoL were observed across nearly all domains in both the CFQ-R and the EQ-5D-5L, however, the extent of the improvement varied between the domains in the CFQ-R. Generally, the emotional domain in the CFQ-R improved the least, with an average change score between -13.8 to 13.4 and physical functioning generally improved the most, with an average change score of 8.6 to 50, followed closely by respiratory functioning. The latter domains represent more of the physical health related aspects of QoL and corroborate physical improvements in pwCF after commencing CFTR modulator treatment. The former more closely relates to measures of anxiety and depression (e.g. Piehler et al., 2023)and is similar to findings observed in the anxiety and depression outcomes described later in this review.

Improvements in QoL were also observed in the qualitative study, corroborating many of the results in the CFQ-R. For instance, many reported reduced coughing, reduced breathlessness, more energy and ability to complete tasks more easily. These are similar to what is reported in the respiratory, vitality and physical and or role functioning domains. Some, however, also reported poorer QoL due to negative side effects from the medication, including brain fog and weight gain. The latter provides useful context to participants' QoL: it may help to explain some of the variance in the studies with some participants potentially experiencing greater side effects than others. It would be interesting to explore the relationship between side effects and QoL scores.

Table 1.3

A summary of outcomes from studies which conducted the Cystic Fibrosis Questionnaire-Revised (CFQ-R)

Change in CFQ-R scores between baseline and final time point														
Author and Year	Overall	Physical Functioning	Role Functioning	Vitality	Emotional Functioning	Social Functioning	School Functioning	Body Image	Eating Problems	Treatment Burden	Health Perceptions	Weight	Respiratory Symptoms	Digestive Symptoms
McCoy et al., (2022)[a]	n/a	50*	25	29.17*	13.34	16.66*	n/a	22.23	22.22	16.67*	38.89*	100	38.89*	5.56
Carrasco Hernández et al., (2023)	n/a	8.6 (-8.1 - 25.4)	-4.4 (-21.9-13.0)	-0.1 (-15.9 - 15.7)	-12.8 (-29.1 - 3.5)	n/a	n/a	n/a	-16.1* (-34.7 - 2.4)	2.0 (-12.2 - 16.1)	n/a	n/a	5.8 (-10.7 - 22.3)	-20.8* (-37.5 - 4.1)
Piehler et al., (2023)	n/a	12.5 (4.2–29.2)*	8.3 (0.0–16.7)*	8.3 (0.0–25.0)*	0.0 (−6.7 to 6.7)	5.6 (−5.6–16.7)*		11.1 (0.0–11.1)*	0.0 (0.0–0.0)	11.1 (0.0–16.7)*	11.1 (0.0–22.2)*	0.0 (0.0–33.3)	22.2 (11.1–44.4)*	0.0 (−19.4 to 11.1)
DiMango et al (2021)[a]	n/a	13.3*	10*	12.5*	2.7	6.7*	n/a	2.3	10*	11.2*	15.5	16.7*	22.7	1.1
Eijofor et al., (2020)[a]	150.9*	23.8*	5.7	19.1*	5.3	10.6*	n/a	12.2*	18.7*	5.3	22.18*	26*	5.9	13.5*
Migliorisi et al., (2022[b]	53.18	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a

Comparison of CFQ-R scores between modulator group and control														
Bell et al., (2019)	n/a	74.6 vs 66.6*	77.0 vs 73.5	63.5 vs 55.9*	78.8 vs 75.0	70.2 vs 68.6	83.1 vs 82.7	74.9 vs 67.8	91.1 vs 84.2*	65.3 vs 54.8*	67.6 vs 58.6*	80.7 vs 64.2*	75.4 vs 62.5	85.5 vs 78.0*

a. Indicates studies in which the change scores have been estimated based upon pre and post scores reported in the study manuscript.

b. Indicates studies in which an average of change scores has been estimated based upon pre and post scores reported in the study manuscript.

* Indicates a score has been found to be significant to at least $p < .05$

Summary and Appraisal of Anxiety Outcomes

Three of the 10 studies explored the impact of CFTR modulators on anxiety, specifically ETI. A summary of their findings is reported in table 1.4. All studies used the General Anxiety Disorder Scale (GAD-7), a widely used measure of anxiety. The GAD-7 is the recommended measure by the International Committee on Mental Health (ICMH) who publish recommendations for CF, however, as it has not been validated in this population (Verkleij et al., 2018), results must therefore be considered with caution.

Overall, no changes in anxiety were reported after participants commenced ETI. There was very little variation between studies, further supporting this finding. Allgood et al., (2023), the only study in this review to report effect size, observed there to be a small effect (β = -.19) suggesting that any change would have a minimal impact on participants. Interestingly, they reported low baseline scores in anxiety with only two participants meeting threshold for clinical significance, which may have impacted the results, however, Piehler et al., (2023) reported similar rates of anxiety to prevalence studies, with similar results.

Zhang et al., (2022) observed that the ethnicity of their participants had greater bearing on anxiety than ETI, with black, biracial or multiracial participants scoring higher than white participants. Zhang et al., (2022) were the only paper to comment on the role of ethnicity, and this finding suggests that it should be given greater consideration in CF research, particularly with regards to psychological wellbeing. Similarly, Piehler et al., (2023) observed that male participants' scores improved slightly more than female participants, although this was only very slightly (male: -1.0, IQR -3.0 to 0.0; $p<0.05$, female 0.0, IQR -1.0 to 1,0; $p=0.704$). Nevertheless, it suggests that demographic factors may be influencing psychological wellbeing and should be considered further.

Table 1.4

A summary of outcomes from studies exploring the impact of CFTR modulators on anxiety

Author and Year	Measure Used	Outcome Change
Allgood et al., (2023)	GAD-7	-0.19 (-1.25,0.87)
Piehler et al., (2023)	GAD-7	0.0 (IQR -2.0 - 0.0)
Zhang et al., (2022)	GAD-7	-0.2 (0.13)

Summary and Appraisal of Depression Outcomes

Three of the 10 studies explored the impact of ETI on depression. A summary of their findings is reported in table 1.5. A broader range of psychometrics were used. Neither the Patient

Health Questionnaire-9 (PHQ-9), Patient Health Questionnaire-8 (PHQ-8) or the Beck Depression Inventory – Fast Screen (BDI-FS) have been validated for use in the CF population, however, the first two have been recommended for use by the ICMH. The PHQ-9 has been observed to report slightly higher rates of depression than other measures in this population (Lord et al., 2023) and thus must be considered with a critical lens.

As with anxiety, very little change was observed in depression scores after participants commenced ETI. A general trend towards a reduction in depression was observed, however, this is not comparable with change that would be needed for clinically meaningful change (Michael et al., 2012). A similar pattern in the role of ethnicity and gender was also observed.

Table 1. 5

A summary of outcomes from studies exploring the impact of CFTR modulators on depression

Author and Year	Measure Used	Outcome Change
Allgood et al., (2023)	PHQ-8	-0.13 (-1.12,0.86)
Piehler et al., (2023)	PHQ-9	-1.0 (IQR -3.0 to 0.3)*
	BDI-FS	-0.0 (IQR 0.00 to 2.0)*
Zhang et al., (2022)	PHQ-9	-0.08 (0.19)

* Indicates a score has been found to be significant to at least $p < .05$

Although not part of the core analysis of their study, Aspell et al., (2022) also commented on participants' anxiety. In their discussion they explained that participants had reported increased anxiety with regards to the uncertainty of accessing the medication. This was only mentioned briefly in the study and it was therefore difficult to ascertain how strong an influence it may have had, but hints to pwCF experiencing a more complex psychological relationship with CF.

Discussion

This review aimed to explore the impact of CFTR modulators on the psychological wellbeing of pwCF. To do this, psychological wellbeing was operationalised into three commonly measured psychological phenomena common within CF: anxiety, depression and QoL. To this author's knowledge, this systematic review is the first to explore the impact of CFTR modulators on psychological wellbeing. The review was therefore designed to represent a broad view of the research into psychological wellbeing, including both quantitative and qualitative designs.

Ten studies were identified as part of this review. There were a greater number of studies exploring one or more of the aspects of psychological wellbeing defined, as however secondary

outcomes rather than of primary interest. This review privileged studies where the primary focus was psychological wellbeing with the hopes of this providing more detailed data.

With regards to the question, what is the impact of CFTR modulators on the psychological wellbeing of pwCF, this review observed mixed results. Concerning QoL, pwCF's scores generally improved once they commenced a modulator, however, the heterogeneity of the study designs meant that the magnitude of this effect could not be identified. These findings were further corroborated by the findings in the qualitative study. Unfortunately, only one qualitative study met inclusion criteria for this review, however, this suggested that qualitative studies may offer useful insight into pwCF's experiences of the medication. There was some evidence that these improvements were not maintained beyond 12 months, however, this was only observed in one study. Further research is needed into the longer-term implications of the medication.

Improvements in QoL centred primarily on the physical domains, namely physical functioning, and respiratory functioning. Comparatively, participants' emotional functioning improved far less. This is similar to the findings of the studies exploring anxiety and depression, where only very slight changes were observed after participants commenced medication. Although this suggests that participants' negative psychological experiences after starting a modulator were adverse events, it is also noteworthy because it suggests on this occasion that an improvement in CF symptomatology does not lead to improvements in mental health.

Similar findings have been observed in pre-modulator research, where female gender and undertaking therapy for anxiety and depression or receiving medication for anxiety and depression were stronger predictors of anxiety and depression than physical health (Quittner et al., 2014). The only factor that has been found to be predictive of anxiety and depression in CF is very severe illness (Quittner et al., 2014). Many of the studies included in this study, however, included participants who accessed the medication on a compassionate basis and were therefore experiencing severe illness. Nevertheless, the same pattern was observed. Overall, this suggests that the relationship between CF and mental health is more complex and impacted by more factors than direct physical health. Further research is needed to understand the nuances of this.

Strengths and Limitations

One of the key strengths of this review is its inclusion of both quantitative and qualitative studies. Although only one qualitative study was included, it offered more detailed insight into the experiences of pwCF. More specifically, this study illustrated the variances in the participants'

experiences, which offered unique insight into what factors may be driving the quantitative appraisal of experience represented in questionnaire answers or scores.

The quality assessment identified very few studies which consistently demonstrated good quality methodological design. Although most studies utilised similar and well-validated measures, study designs varied widely and only one study reported effect size. Even though significance testing, indicates whether the changes in scores after participants commenced the medication was due to chance or a real effect, it was unable to show its magnitude and therefore how impactful of a change it was. A large effect size would indicate that CFTR modulators are having a considerable impact on the psychological wellbeing of pwCF, whilst a small effect size would suggest it is not. Moreover, effect sizes can be calculated irrespective of sample size and would therefore be important to report when working in research with small populations (Sullivan & Feinn, 2012). The lack of effect sizes reported in the studies in this review limits the claims that it can make.

Clinical Implications

This research highlights the importance of continued monitoring of psychological wellbeing by CF teams. It suggests that despite pwCF's physical health improving and to a certain extent, their overall QoL, anxiety and depression remain constant. Both factors are associated with poorer outcomes for pwCF including treatment non-compliance (Goodfellow et al., 2015) and poor QoL (Yohannes et al., 2012). Continued monitoring of anxiety, depression and QoL by members of the CF team will allow pwCF to access appropriate support by the team's clinical psychologist, a role that this review suggests remains important, despite improvements in health.

Areas for future research

Further and higher quality research is needed to understand the implications of CFTR modulator therapies on psychological wellbeing. This includes larger studies, which take into account the impact of a number of additional variables including the genetics of its participants, gender, ethnicity as well as other physical health elements. This may be difficult due to there being relatively small numbers of pwCF, however, it will be important in establishing whether there have indeed been changes in psychological wellbeing following the introduction of modulators.

Further qualitative research should also be undertaken to help contextualise and add meaning to the findings. Qualitative research has gained increasing prominence in healthcare research due to its ability to give reason to experience (Tuckerman et al., 2020). This may, in turn, give insight into any non-physical factors that are influencing participants' psychological wellbeing.

Conclusion

This review aimed to explore the impact of CFTR modulators on the psychological wellbeing of pwCF. Overall, there was evidence of some improvement in QoL measures, but little to no change in levels of anxiety and depression. These findings corroborate current thinking that new or worsening instances of anxiety and depression in pwCF after they have started taking a CFTR modulator are related to adverse events, rather than an overall trend. It also supports a holistic understanding of wellbeing in chronic illness and suggests that pwCF's psychological wellbeing in relation to CFTR extend beyond improvements associated with improved general physical health and reduced CF symptomatology, to consider more psychological experiences such as feelings of uncertainty. Further and high-quality research is needed to better understand this relationship.

References

Abbott, J., & Gee, L. (2003). Quality of life in children and adolescents with cystic fibrosis: implications for optimizing treatments and clinical trial design. *Paediatr Drugs, 5*(1), 41-56. https://doi.org/10.2165/00128072-200305010-00004

Abbott, J., & Hart, A. (2005). Measuring and reporting quality of life outcomes in clinical trials in cystic fibrosis: a critical review. *Health Qual Life Outcomes, 3*, 19. https://doi.org/10.1186/1477-7525-3-19

Acaster, S., Pinder, B., Mukuria, C., & Copans, A. (2015). Mapping the EQ-5D index from the cystic fibrosis questionnaire-revised using multiple modelling approaches. *Health Qual Life Outcomes, 13*, 33. https://doi.org/10.1186/s12955-015-0224-6

Alexandra, L. Q., Janice, A., Anna, M. G., Lutz, G., Beth, S., Sarah, E. H., Bruce, M., Kathryn, A. S., & Stuart, E. (2016). International Committee on Mental Health in Cystic Fibrosis: Cystic Fibrosis Foundation and European Cystic Fibrosis Society consensus statements for screening and treating depression and anxiety. *Thorax, 71*(1), 26. https://doi.org/10.1136/thoraxjnl-2015-207488

Ancel, J., Launois, C., Perotin, J. M., Ravoninjatovo, B., Mulette, P., Hagenburg, J., Malet, J., Griffon, M., Carré, S., Lebargy, F., Deslée, G., & Dury, S. (2022). Health-Related Quality of Life in Adults with Cystic Fibrosis: Familial, Occupational, Social, and Mental Health Predictors. *Healthcare (Basel), 10(*7). https://doi.org/10.3390/healthcare10071351

Arslan, M., Chalmers, S., Rentfrow, K., Olson, J. M., Dean, V., Wylam, M. E., & Demirel, N. (2023). Suicide attempts in adolescents with cystic fibrosis on Elexacaftor/Tezacaftor/Ivacaftor

therapy [Article]. *Journal of Cystic Fibrosis, 22*(3), 427-430. https://doi.org/10.1016/j.jcf.2023.01.015

Bardin, E., Pastor, A., Semeraro, M., Golec, A., Hayes, K., Chevalier, B., Berhal, F., Prestat, G., Hinzpeter, A., Gravier-Pelletier, C., Pranke, I., & Sermet-Gaudelus, I. (2021). Modulators of CFTR. Updates on clinical development and future directions. *European Journal of Medicinal Chemistry, 213*, 113195. https://doi.org/https://doi.org/10.1016/j.ejmech.2021.113195

Bower, J. K., Volkova, N., Ahluwalia, N., Sahota, G., Xuan, F., Chin, A., Weinstock, T. G., Ostrenga, J., & 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. *J Cyst Fibrosis, 22*(4), 730-737. https://doi.org/10.1016/j.jcf.2023.03.002

DiMango, E., Overdevest, J., Keating, C., Francis, S. F., Dansky, D., & Gudis, D. (2021). Effect of highly effective modulator treatment on sinonasal symptoms in cystic fibrosis [Article]. *Journal of Cystic Fibrosis, 20*(3), 460-463. https://doi.org/10.1016/j.jcf.2020.07.002

Edmondson, C., Course, C. W., & Doull, I. (2021). Cystic fibrosis transmembrane conductance regulator modulators for cystic fibrosis: a new dawn? *Archives of Disease in Childhood, 106*(10), 941-945. https://doi.org/10.1136/archdischild-2020-320680

Feng, Y.-S., Kohlmann, T., Janssen, M. F., & Buchholz, I. (2021). Psychometric properties of the EQ-5D-5L: a systematic review of the literature. *Quality of Life Research, 30*(3), 647-673. https://doi.org/10.1007/s11136-020-02688-y

Goodfellow, N. A., Hawwa, A. F., Reid, A. J. M., Horne, R., Shields, M. D., & McElnay, J. C. (2015). Adherence to treatment in children and adolescents with cystic fibrosis: a cross-sectional, multi-method study investigating the influence of beliefs about treatment and parental depressive symptoms. *BMC Pulmonary Medicine, 15*(1), 43. https://doi.org/10.1186/s12890-015-0038-7

Guta, M. T., Tekalign, T., Awoke, N., Fite, R. O., Dendir, G., & Lenjebo, T. L. (2021). Global Burden of Anxiety and Depression among Cystic Fibrosis Patient: Systematic Review and Meta-Analysis. *Int J Chronic Dis, 2021,* 6708865. https://doi.org/10.1155/2021/6708865

Habib, A. R., Kajbafzadeh, M., Desai, S., Yang, C. L., Skolnik, K., & Quon, B. S. (2019). A Systematic Review of the Clinical Efficacy and Safety of CFTR Modulators in Cystic Fibrosis. *Sci Rep, 9*(1), 7234. https://doi.org/10.1038/s41598-019-43652-2

Harrison, R., Jones, B., Gardner, P., & Lawton, R. (2021). Quality assessment with diverse studies (QuADS): an appraisal tool for methodological and reporting quality in systematic reviews of mixed- or multi-method studies. *BMC Health Services Research, 21*(1), 144. https://doi.org/10.1186/s12913-021-06122-y

Jacqui, W. (2023). Cystic fibrosis: What next for the "wonder drug" Kaftrio? *BMJ, 383,* p2766. https://doi.org/10.1136/bmj.p2766

Lopes-Pacheco, M. (2020). CFTR Modulators: The Changing Face of Cystic Fibrosis in the Era of Precision Medicine [Review]. *Frontiers in Pharmacology, 10*, Article 1662. https://doi.org/10.3389/fphar.2019.01662

Lord, L., McKernon, D., Grzeskowiak, L., Kirsa, S., & Ilomaki, J. (2023). Depression and anxiety prevalence in people with cystic fibrosis and their caregivers: a systematic review and meta-analysis. *Social Psychiatry and Psychiatric Epidemiology, 58*(2), 287-298. https://doi.org/10.1007/s00127-022-02307-w

McHugh, M. L. (2012). Interrater reliability: the kappa statistic. *Biochem Med (Zagreb), 22*(3), 276-282.

Michael, M., Saima, A., Beth, S., Gerry, M. L., Jessica, O., Chris, G., & Tony, K. (2012). Depression management in primary care: an observational study of management changes related to PHQ-9 score for depression monitoring. *British Journal of General Practice, 62*(599), e451. https://doi.org/10.3399/bjgp12X649151

Natio, Y., Charman, S., Duckers, J., & Clarke, S. (2023*). UK Cystic Fibrosis Registry: 2022 Annual Data Report*. Cystic Fibrosis Trust. https://www.cysticfibrosis.org.uk/sites/default/files/2023-10/CFT_2022_Annual_Data_Report_FINAL_v8.pdf

National Institute of Healthcare and Excellent [NICE]. (2017). *Cystic fibrosis: diagnosis and management(ng78).* https://www.nice.org.uk/guidance/ng78

Piehler, L., Thalemann, R., Lehmann, C., Thee, S., Röhmel, J., Syunyaeva, Z., Stahl, M., Mall, M. A., & Graeber, S. Y. (2023). Effects of elexacaftor/tezacaftor/ivacaftor therapy on mental health of patients with cystic fibrosis. *Front Pharmacol, 14*, 1179208. https://doi.org/10.3389/fphar.2023.1179208

Quittner, A. L., Goldbeck, L., Abbott, J., Duff, A., Lambrecht, P., Solé, A., Tibosch, M. M., Bergsten Brucefors, A., Yüksel, H., Catastini, P., Blackwell, L., & Barker, D. (2014). 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), 1090-1097. https://doi.org/10.1136/thoraxjnl-2014-205983

Quittner, A. L., Sawicki, G. S., McMullen, A., Rasouliyan, L., Pasta, D. J., Yegin, A., & Konstan, M. W. (2012). Psychometric evaluation of the Cystic Fibrosis Questionnaire-Revised in a national sample. *Quality of Life Research, 21*(7), 1267-1278. https://doi.org/10.1007/s11136-011-0036-z

Saluzzo, F., Riberi, L., Messore, B., Loré, N. I., Esposito, I., Bignamini, E., & De Rose, V. (2022). CFTR Modulator Therapies: Potential Impact on Airway Infections in Cystic Fibrosis. *Cells, 11*(7). https://doi.org/10.3390/cells11071243

Serdar, C. C., Cihan, M., Yücel, D., & Serdar, M. A. (2021). Sample size, power and effect size revisited: simplified and practical approaches in pre-clinical, clinical and laboratory studies. *Biochemia Medica*, *31*(1), 27-53. https://doi.org/10.11613/bm.2021.010502

Sullivan, G. M., & Feinn, R. (2012). Using Effect Size-or Why the P Value Is Not Enough. *Journal of graduate medical education, 4*(3), 279–282. https://doi.org/10.4300/JGME-D-12-00156.1

Talwalkar, J. S., Koff, J. L., Lee, H. B., Britto, C. J., Mulenos, A. M., & Georgiopoulos, A. M. (2017). Cystic Fibrosis Transmembrane Regulator Modulators: Implications for the Management of Depression and Anxiety in Cystic Fibrosis. *Psychosomatics, 58*(4), 343-354. https://doi.org/10.1016/j.psym.2017.04.001

Tuckerman, J., Kaufman, J., & Danchin, M. (2020). How to use qualitative methods for health and health services research. *Journal of Paediatrics and Child Health, 56*(5), 818-820. https://doi.org/10.1111/jpc.14849

VanElzakker, M. B., Tillman, E. M., Yonker, L. M., Ratai, E.-M., & Georgiopoulos, A. M. (2023). Neuropsychiatric adverse effects from CFTR modulators deserve a serious research effort. *Current Opinion in Pulmonary Medicine, 29*(6), 603-609. https://doi.org/10.1097/MCP.0000000000001014

Verkleij, M., de Winter, D., Hurley, M. A., & Abbott, J. (2018). Implementing the International Committee on Mental Health in Cystic Fibrosis (ICMH) guidelines: Screening accuracy and referral-treatment pathways. *Journal of Cystic Fibrosis, 17*(6), 821-827. https://doi.org/https://doi.org/10.1016/j.jcf.2018.02.005

World Health Organisation [WHO). (2023a). *Anxiety disorders*. https://www.who.int/news-room/fact-sheets/detail/anxiety-disorders

World Health Organisation(2023b). *Depressive disorder (depression).* https://www.who.int/news-room/fact-sheets/detail/depression

Yohannes, A. M., Willgoss, T. G., Fatoye, F. A., Dip, M. D., & Webb, K. (2012). Relationship between anxiety, depression, and quality of life in adult patients with cystic fibrosis. *Respir Care, 57*(4), 550-556. https://doi.org/10.4187/respcare.01328

Zolin, A., Bossi, A., Cirilli, N., Kashirskaya, N., & Padoan, R. (2018). Cystic Fibrosis Mortality in Childhood. Data from European Cystic Fibrosis Society Patient Registry. *International Journal of Environmental Research and Public Health, 15*(9).

References of Included Studies

Allgood, S., Levy, R., Bubaris, D., Riekert, K., Psoter, K. J., & Lechtzin, N. (2023). The effect of elexacaftor/tezacaftor/ivacaftor on non-pulmonary symptoms in adults with cystic fibrosis. *Heliyon, 9*(9), e20110. https://doi.org/10.1016/j.heliyon.2023.e20110

Aspinall, S. A., Mackintosh, K. A., Hill, D. M., Cope, B., & McNarry, M. A. (2022). Evaluating the Effect of Kaftrio on Perspectives of Health and Wellbeing in Individuals with Cystic Fibrosis [Article]. *International Journal of Environmental Research and Public Health, 19*(10), Article 6114. https://doi.org/10.3390/ijerph19106114

Bell, S. C., Mainz, J. G., MacGregor, G., Madge, S., Macey, J., Fridman, M., Suthoff, E. D., Narayanan, S., & Kinnman, N. (2019). Patient-reported outcomes in patients with cystic fibrosis with a G551D mutation on ivacaftor treatment: results from a cross-sectional study. *BMC Pulmonary Medicine, 19*(1), N.PAG-N.PAG. https://doi.org/10.1186/s12890-019-0887-6

Carrasco Hernández, L., Girón Moreno, R. M., Balaguer Cartagena, M. N., Peláez, A., Sole, A., Álvarez Fernández, A., Felipe Montiel, A., Olveira, C., Olveira, G., Gómez Bonilla, A., Gómez Crespo, B., García Clemente, M., Solís García, M., Quaresma Vázquez, J., Blitz Castro, E., Rodríguez González, J., Expósito Marrero, A., Diab-Cáceres, L., Ramos Hernández, C., . . . Quintana Gallego, E. (2023). Experience With Elexacaftor/Tezacaftor/Ivacaftor in Patients With Cystic Fibrosis and Advanced Disease. *Archivos de Bronconeumologia, 59*(9), 556-565. https://doi.org/https://doi.org/10.1016/j.arbres.2023.05.017

DiMango, E., Overdevest, J., Keating, C., Francis, S. F., Dansky, D., & Gudis, D. (2021). Effect of highly effective modulator treatment on sinonasal symptoms in cystic fibrosis [Article]. *Journal of Cystic Fibrosis, 20*(3), 460-463. https://doi.org/10.1016/j.jcf.2020.07.002

Ejiofor, L. C. K., Mathiesen, I. H. M., Jensen-Fangel, S., Olesen, H. V., Skov, M., Philipsen, L. K. D., Pedersen, C. L., & Pressler, T. (2020). Patients with cystic fibrosis and advanced lung disease benefit from lumacaftor/ivacaftor treatment. *Paediatric Pulmonology, 55*(12), 3364-3370. https://doi.org/10.1002/ppul.25059

McCoy, K. S., Blind, J., Johnson, T., Olson, P., Raterman, L., Bai, S., Eisner, M., Sheikh, S. I., Druhan, S., Young, C., & Pasley, K. (2023). Clinical change 2 years from start of elexacaftor-tezacaftor-ivacaftor in severe cystic fibrosis [Article]. *Paediatric Pulmonology, 58*(4), 1178-1184. https://doi.org/10.1002/ppul.26318

Migliorisi, G., Collura, M., Ficili, F., Pensabene, T., Bongiorno, D., Collura, A., Di Bernardo, F., & 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 (Basel, Switzerland), 15*(5). https://doi.org/10.3390/ph15050606

Piehler, L., Thalemann, R., Lehmann, C., Thee, S., Röhmel, J., Syunyaeva, Z., Stahl, M., Mall, M. A., & Graeber, S. Y. (2023). Effects of elexacaftor/tezacaftor/ivacaftor therapy on mental health of patients with cystic fibrosis. *Front Pharmacol, 14*, 1179208. https://doi.org/10.3389/fphar.2023.1179208

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

Chapter Three: Bridging Chapter

Chapter two showed the paucity of research exploring the impact of Cystic Fibrosis transmembrane conductance regulator (CFTR) modulator therapies on psychological wellbeing. The review confirmed the positive impact CFTR modulators can have on people with CF (pwCF)'s physical wellbeing and overall quality of life (QoL), but not on their experiences of anxiety and depression. The review implied that direct improvements in Cystic Fibrosis (CF) symptomatology do not necessarily equate to improvements in pwCF's psychological wellbeing. This suggested that the relationship between CF, CFTR modulator and psychological wellbeing was more complex and further research is needed to understand this.

The review also highlighted the potential importance of qualitative studies in aiding understanding of this complexity, a notable strength of qualitative studies that are highly valued in healthcare research (Renjith et al., 2021). Aspinall et al. (2022)'s qualitative study illustrated participants' differing experiences of the medication and indicated that negative side effects of the medication led to poorer QoL. Side effects is not a variable that has been accounted for in any of the studies identified in the review but may have helped to explain some of the variance. This demonstrated the importance of qualitative studies to gather context and reasoning for patterns within quantitative data.

Aspinall et al., (2022) also illuminated other factors that may have a bearing on participants' psychological wellbeing. This included the impact of uncertainty around continuing to be able to have the medication on their experiences of anxiety, the guilt associated with being able to access a medication that others may not be able to and the difficulties in identity some were experiencing due to their improvement in physical health. The latter two were outside of the scope of this review, but all may have had an impact on participants' psychological wellbeing.

These experiences are corroborated by a further two qualitative studies, which explore the lived experiences and psychological impact of CFTR modulator therapies on adults with CF. Both studies were excluded due to including participants who were not taking a CFTR modulator therapy (Keyte et al., 2023) or because they did not focus on either anxiety, depression or QoL (Page et al., 2022). Both studies emphasised the complexity of their feelings with regards to CFTR modulator therapies, including the role of hope and potential CFTR modulators provided them (Page et al., 2022) as well as the anxiety and uncertainty associated with these medications (Keyte et al., 2022). These experiences may go towards explaining why despite changes in their physical health, participants did not experience an improved psychological wellbeing, as the presence of CFTR modulators in themselves brought different but still difficult emotional experiences.

The evidence of the importance of qualitative research in enhancing understanding of the impact of CFTR modulator therapies informed the approach taken in the empirical paper presented in chapter four of this thesis portfolio.

As discussed in chapter one, CF is known to have a negative impact on pwCF's psychological wellbeing (Ernst et al., 2010). But it can also have an impact on the psychological wellbeing of their families, namely their parents (Daly et al., 2022). As will be explored further in chapter four, parents of children with CF play an important role in the treatment of CF (Bryon & Wallis, 2011). From the point of diagnosis, parents of children with CF (cwCF) hold primary responsibility for the day-to-day management of their children's health, including their engagement with their treatment regime, the management and organisation of their treatment regime and adapting their day-to-day activities to limit their risks of becoming unwell (Fitzgerald et al., 2018; Grossoehme et al., 2014; Cystic Fibrosis [CF] Trust, 2015). For instance, some children with CF have a pancreatic insufficiency, which means the pancreas is unable to produce enough enzymes to digest food. They, therefore, must take an enzyme replacement known as Creon with all of their meals (Somaraju & Solis-Moya, 2016). Parents, therefore, have to ensure the enzyme is available to their children at all times they wish to eat. This is only one part of their treatment regime and cwCF often have to take a number of different medications, all of which have their own instructions (Altabee et al., 2022) .

Parents of cwCF also have an impact on their child's psychological wellbeing. Parents' own psychological wellbeing, such as whether they are experiencing anxiety and depression, has been found to have an impact on children's treatment adherence (Goodfellow et al., 2015) and parental coping has also been found to influence their children's psychological wellbeing (Wong & Heriot, 2008). Understanding and supporting parents is therefore key to being to ensuring the health and wellbeing of cwCF.

The following qualitative paper seeks to explore parents' experiences of the new CFTR modulators. The paper hopes that parents will be able to provide novel insight into the impact of CFTR modulators as well as how and whether their own psychological experiences are changed by their child having a potentially lifesaving medication. Such understanding will not only add to knowledge about CFTR modulators, but also provide important insight into the needs of cwCF and their parents upon starting CFTR modulators.

Chapter Four: Empirical Paper

Tentative Hope: An exploration of the experiences of parents of children with Cystic Fibrosis as they commence the new Cystic Fibrosis conductance regulator modulator therapies.

Hannah Edwards, Dr Gail Clare, Dr Louise Morgan, Jack Johnson and Dr Amy Carroll

Department of Clinical Psychology and Psychological Therapies, University of East Anglia, UK.

Cambridge and Peterborough NHS Foundation Trust

The Queen Elizabeth Hospital King's Lynn NHS Foundation Trust

Norfolk and Norwich University Hospitals NHS Foundation Trust

Prepared for: Health Psychology Review (see Appendix L for author guidelines)

Word Count excluding abstract, titles, tables and references: 7317

Word Count: including titles, tables/figures: 8639

Any queries regarding this review should be directed to Hannah Edwards, Norwich Medical School, University of East Anglia, Norwich, Norfolk, NR4 7TJ, UK

Email: h.edwards3@uea.ac.uk

Abstract

Background. Cystic Fibrosis transmembrane conductance regulator (CFTR) modulator therapies are a highly anticipated new treatment for Cystic Fibrosis (CF) (Lopes-Pacheco, 2020). Though research into CFTR medication is in its infancy, the medications have been shown to have significant positive impact on the physical health of people with CF (Gramegna et al., 2020) and are expected to considerably increase their life expectancy (Natio et al., 2023) representing a significant breakthrough in CF treatment.

Parents of children with CF have an important role in the treatment and management of CF (Bryon & Wallis, 2011). Caregiver burden is significant and negatively associated with the physical health outcomes for children themselves (Daly et al., 2022). Very little research has explored parental experiences and perspectives of CFTR modulator therapies.

Aim. This study aims to explore the lived experiences of parents of children with CF who are taking CFTR modulators using Interpretative Phenomenological Analysis.

Methods. Ten qualitative interviews were conducted with parents of children with CF to explore their experiences of their child starting a CFTR modulator.

Results. Five key themes were identified through the analysis, namely: experience as context, living alongside CF, the impact of the medication, the special role of CF and the socio-political context. These illustrated the complex and sometimes contradictory feelings of parents as their children lived with CF, started this medication.

Conclusion. Parents of children with CF have a complex relationship with their child starting CFTR modulators, which is influenced by several different non-physical factors. Understanding this is essential for future care.

Introduction

CF is a life limiting genetic condition, affecting a person's physical, social, occupational, and psychological functioning (Dill et al., 2013). Since the introduction of the newborn bloodspot screening (NBS) in 2007, children in the UK are typically diagnosed with Cystic Fibrosis (CF) before they are a month old (Schlüter et al., 2020). For parents and caregivers, this often-unexpected diagnosis marks the beginning of their CF journey (Chudleigh & Chinnery, 2020). Parents and caregivers (referred to as parents going forward) of children with CF (cwCF) are required to make a rapid adjustment, learning about CF and the various treatments and lifestyle changes required for the continued health and wellbeing of their child (Cystic Fibrosis [CF]Trust, 2015) whilst also parenting a newborn. This can be an overwhelming experience, with an often-reported sense of grief or loss in response to receiving the diagnosis (CF Trust, 2015).

Parenting a child with Cystic Fibrosis

CF has a high treatment burden and for children, their parents have the primary responsibility for administering this to ensure the wellbeing of their child. Parents are required to support their child to engage in their treatment, which includes administering a variety of medications, supporting them with daily physiotherapy, attending multiple hospital appointments and managing their day-to-day lifestyle and activities to minimise their risk of becoming unwell (Fitzgerald et al., 2018).

Owing to this high treatment burden, and the responsibility of parenting a child with a serious and chronic health condition, parents of cwCF often report poor psychological wellbeing (Daly et al., 2022). Parents of cwCF experience higher levels of anxiety and depression in comparison to parents in the general population (Daly et al., 2022) and parental mental health and adjustment has been found to have a significant impact on the physical health and wellbeing of cwCF (Wong & Heriot, 2008). For example, cwCF whose parents are experiencing depression have poorer treatment adherence and are more likely to become unwell requiring hospitalisation (Smith et al., 2010). Similarly, cwCF whose parents are anxious are more likely to be anxious themselves, something that, as noted in chapter three, has a negative impact on quality of life (Quittner et al., 2016). Consequently, understanding and supporting the psychological wellbeing of parents has become an important aspect of CF care (National Institute of Healthcare and Excellence [NICE], 2017).

Cystic Fibrosis transmembrane conductance regulator modulator therapies

Traditionally, CF treatment has focused on managing the complex array of CF symptomatology. Cystic Fibrosis transmembrane conductance regulator (CFTR) modulator therapies are a new form of Cystic Fibrosis treatment (Lopes-Pacheco, 2020). Unlike traditional CF treatment,

which is often multi-faceted and burdensome, CFTR modulators are a relatively simple oral medication, which target the cause of CF symptomatology (Lopes-Pacheco, 2020). CFTR modulators have been shown to significantly improve physical health outcomes in pwCF (Gramegna et al., 2020) and the introduction of the medication is expected to have a significant positive impact on life expectancy for pwCF. For example, in 2022 in the United Kingdom (UK) the median age of death of someone with CF was 33 years old, however, since the medication has become widely accessible in the UK it is now estimated that for someone born in 2022, the median age of death will be 56.1 years (Natio et al., 2023).

The positive impact of CFTR modulators on the physical health of pwCF has been widely observed (Bower et al., 2023) and researchers have now begun to explore the impact of CFTR modulators from a more holistic stance (e.g. (Page et al., 2022). Researchers have started to utilise qualitative methods to try and gather a more nuanced and detailed understanding of the experiences of pwCF taking the medication. Researchers have observed that adults with CF (awCF) experience a real sense of hope when starting the medication and begin to be able to make concrete plans for the future (Page et al., 2022). Hope has been found to be an important factor in coping and adjustment with regards to CF (Abbott et al., 2023), and increased levels of hope due to the medication could be seen as positive. In contrast (Keyte et al., 2023) found awCF to be struggling with a change in identity upon taking the medication and highlighted the importance of psychological support during this process. This experiential research offers important insight into the impact of CFTR modulators on pwCF's psychological experiences. Unlike the research in chapter two, it suggests that the medication may be having an impact on pwCF's psychological wellbeing, particularly with regards to coping and adjustment.

The following study will continue this experiential exploration of CFTR modulator therapies. However, rather than investigating the experiences of pwCF, it will focus on the parents of children and young people with CF, a group who have been referred to as "the hidden and unacknowledged members of the CF multidisciplinary team." (p.31) (Bryon & Wallis, 2011)

Research including the perspectives and experiences of parents is becoming increasingly common within childhood chronic illness research (Baker & Claridge, 2023). Smith et al. (2015) argues that studying parents' perspectives of their child's health, helps health professionals to better understand the needs and wishes of both parents and children. They state that doing so, supports health professionals to create care systems that can better meet and respond to the needs of that group (Smith et al., 2015). Including parents in research into CFTR modulators is therefore essential, however, since CFTR modulators have become more widely available, very little research has

included parents' perspectives or experiences of their child's treatment. This is an important gap in the literature.

Research Aims

This study aims to explore what it is like for parents of cwCF to commence CFTR modulators. Specifically, it aims to discover the shared and differing experiences of parents as their children start this new stage in their CF journey and how they make sense of this important and potentially life altering transition in the context of parenting a child with CF.

Methods

Design

This study used Interpretative Phenomenological Analysis (IPA) to capture and explore parents' experiences of their children starting CFTR modulator therapies. IPA is principally concerned with the in-depth examination of the lived experience of a particular phenomenology and how people make sense of this (Smith et al., 2022). It is well established within health psychology, as it privileges the perspective of the individual, encouraging a nuanced and detailed exploration of a phenomenon in all complexity (Biggerstaff & Thompson, 2008). As a result, this was thought to be an appropriate approach for understanding parents' experiences of their child beginning CFTR therapy, making space for their thoughts, feelings and opinions, which are yet to be understood in the literature to date.

Participants

Participants were recruited from the UK. More specifically, they came from one paediatric CF centre and one district general hospital paediatric CF clinic, aligned with the CF centre.

Inclusion criteria for the study were: parents or carers of cwCF who were taking one of the four CFTR modulators. Their child needed to have started the medication for at least a month before taking part in the study, which is the minimum amount of time the researchers were recommended would need to occur before change was noted. Parents' children also had to receive their diagnosis to June 2019, a year before CFTR modulators became widely available in England.

Exclusion criteria for the study were that another parent was already involved in the study or that the parent did not regularly attend appointments in which they were informed about the medication.

A total of 24 parents expressed interest in the study. Of these, 14 decided not to take part, were ineligible or were not able to be recruited within the time frame available, leaving a total of 10 participants.

A sample size of 10 is considered large in IPA research, which typically benefits from small samples to allow the experiences of each participant to be looked at in detail (Smith & Osborn, 2015). That said, a sample size of 10 is appropriate and within the range recommended for professional doctorates (Smith et al., 2022).

Participant Characteristics

All participants who took part identified as mothers, with a mean age of 30.7 years (SD 5.19). With regards to their children, there was an even gender split, with a mean age of 9.60 years (SD = 3.20). Most of the children were taking Kaftrio at the time of the interviews, and many had taken previous types of CFTR modulator therapy before this. On average, participants' children had been taking the medication for 36 months (SD 25.50), though the high standard deviation denotes significant variation here. Further detail participant characteristics can be found on table 2.1, though details have been kept minimal here to preserve anonymity in a small community of parents overall.

Table 2.1

Participant characteristics

Participant Identifier	CFTR Modulators Commenced	Estimated time on CFTR modulators (months)
Parent 1*	Orkambi and Kaftrio	19
Parent 2*	Orkmabi and Kaftrio	31
Parent 3	Kalydeco	22
Parent 4	Kalydeco, Orkambi, Symkevi and Kaftrio	43
Parent 5	Kalydeco and Kaftrio	20
Parent 6	Kalydeco and Kaftrio	10
Parent 7*	Kalydeco, Orkambi and Symkevi	48
Parent 8*	Kalydeco	98
Parent 9*	Kalydeco and Kaftrio	21
Parent 10*	Kalydeco and Kaftrio	48

*denotes participants who completed the interview after National Institute of Healthcare and Excellent's announcement about the future of CFTR modulator therapy availability in the UK (CF Trust, 2024).

Materials

The topic guide (see appendix D) used to facilitate the interviews was constructed with input from the supervisory team, all of whom had clinical experience working with pwCf and in specialist CF clinics and teams. The preliminary guide was then discussed in detail with a parent of a child with CF who had commenced CFTR modulators, and who assisted with further development and refinement.

Procedure

Eligible participants from each centre were invited to take part in the study by letter which was disseminated by clinical teams. The primary researcher (HE) then attended outpatient CF clinics, where she was introduced to eligible participants by members of the clinical team, to discuss the purpose of the research and gain expressions of interest. Those who expressed interest were asked to complete a consent to contact form (appendix E). HE then contacted consenting parents to explain the study in more depth and if interested, complete screening questions to confirm eligibility. Approximately a third of parents who expressed interest in the study initially did not

respond to attempts to contact. Once eligibility screening was complete, potential participants were given time to review the information provided about the study before beginning the consent process. Once consent was taken, interviews were arranged on Microsoft Teams or in person as per the participants' preference.

Interviews were completed by the primary researcher (HE) and lasted approximately one hour. The topic guide was used to structure the interviews, however, additional follow up questions to clarify a participant's point or gather more detailed information were permitted. This is in accordance with IPA methodology, which encourages flexibility in order to access experiences in detail (Smith et al., 2022).

Demographic information (see appendix F) was collected at the beginning of the interview. Following completion of the interview, participants were debriefed (see appendix G for copy of the debrief form). Each participant was sent a £10.00 shopping voucher as a token of thanks for participation in the study.

Each interview was automatically transcribed by Microsoft Teams and then reviewed for accuracy and edited by HE. Analysis was then conducted following the guidelines detailed in Smith et al. (2022). A detailed description of this can be found in chapter seven.

Procedural note

Partway through the recruitment and running of this study, NICE (CF Trust, 2024) made an announcement about the potential removal of access to CFTR modulators. Participants who were interviewed after this are denoted in table 2.1. The announcement confirmed that access to CFTR modulators would not be taken away if a pwCF had already been initiated on them, but that future availability of the medication would be restricted. This confirmed that the announcement would not affect participants' children's direct access to the medication but might have impacted on the parents' experience of this. In consultation with the supervisory team, the decision was made to note this phenomenon but continue to adhere to the original topic guide and protocol, which would allow participants to reflect on this potential change to availability if they so wished. In this context, where access to life altering medication might be restricted due to economic reasons, parents' views of the CFTR modulators are deemed to be even more important.

Position of the primary researcher

The primary researcher is a trainee clinical psychologist who had no personal or professional experience of CF, the individuals affected by the condition or their families. This project took the ontological and epistemological position of critical realism, recognising that there is objective

experience, but that is influenced by both the participants' and the primary researcher's interpretation of that experience. The primary researcher's own experience was that of an outsider and initially that of naivety, believing that the introduction of medication would be a wholly positive thing. The advantage of this position was that the researcher came with limited preconceived ideas of the experiences of the participants', meaning analysis was strongly connected to the data. To promote reflexivity the primary researcher kept a reflective diary throughout the project, helping them to keep note of the impact of their interpretation and biases on the research and how their understanding of it became increasingly more nuanced and complex. Regular supervision further supported this. The research supervisors were all Clinical Psychologists who had worked or were actively working with pwCF and their families. Their expertise helped the primary researcher to understand more about the context and the experiences of the participants.

Ethics

The research was reviewed and granted ethical approval from the NHS Health and Social Care Research Ethics Committee A (HSC REC A). Due to CF being a relatively small community, special consideration has been taken throughout this process to remove any identifiable information.

Results

Following an in-depth analysis of each individual interview, patterns of similarity and difference were identified across the transcripts for all ten participants. These were formulated into Group Experiential Themes (themes), designed to "highlight the shared and unique features of the experience across the contributing participants" (Smith et al., 2022, p.100). A detailed description of analysis can be found in chapter six.

A total of five GETs were identified, examples of which can be found in the table below, along with 11 associated subthemes. Many of the themes and subthemes were interlinked.

Table 2.2

A summary of the Group Experiential Themes and their related subthemes and experiential statements.

Group Experiential Themes	Sub themes	Example Quote
Experiences as context	Impact of diagnosis	I remember for probably a few months I didn't even kiss her on the lips because I was so worried about giving her germs or anything like that. And so that like, I hate that now. The thought of not kissing her. So yeah…I worry about it less now (Parent 8).
	Child's relationship with CF	But I find the older he gets, obviously the more understanding he has, the more awareness he has, and it bothers him more…He knows he's different from his peers and that bothers him. And that obviously upsets me. Cause I can't change that and I can't do anything about that for him and I can't make it better (Parent 1).
	Stories of unknown people with CF	I'm obviously on Facebook groups with other CF mums and you know you do hear some really sad stories, and you know [child's name] is a really healthy kid with or without CF. So yeah we're really, really lucky (Parent 8).
Living alongside CF	Conscious Adjustment	We had heard about the possibility of new medication coming out…but we hadn't pinned hopes on it (Parent 10).
	Unconscious Adjustment	Yeah, it has it, I'm actually, I think sometimes again, you have to kind of ground yourself and thank back to those days (Parent 9).
Impact of medication	Tangible	That sounds awful, but it's been nice that having to not do all the things that we have to do (Parent 7)
	Intangible	I think I'd find it really hard to pin it down to the medication because he's between five and eight. He's had all sorts of mood changes (Parent 6).

Special role of CF team		They are incredible and I don't honestly know where we would be without them a lot of the time. But I think they were really, really supportive, really, really encouraging (Parent 1).
Socio-political context	Privilege	You know, but it's kind of that bizarre thing of how much it is worth (Parent 7).
	Uncertainty of removal	As a parent with a child that is on it, it makes me really sad…I'm not going to lie. That made my heart break a little bit to think that these children coming up are [not] able to access something that my son has. Because of the cost. I mean I appreciate it is an issue, but the difference it does make is massive (Parent 1).

A more detailed description of the themes and their associated subthemes is presented in the narrative below.

Experiences as context

Parents' narratives of their children starting CFTR modulator therapies often included reflections on their experiences of CF prior to starting the medication. Parents reflected on both their own experiences, represented in the subthemes ***impact of diagnosis*** and ***child's relationship with CF*** and the experiences of others illustrated in the subtheme ***stories of unknown people with CF.*** These experiences offered important context for both the meaning of the medication and their expectations for it.

Many parents reflected on the ***impact of the diagnosis***, referring to it as a "big shock" (Parent 3) and "devastating" (Parent 5). They reflected on the contradiction of having a newborn baby, which signified a future and then being informed of their life expectancy. Parent five said:

> It's so hard to kind of describe how devastating it is…It's like, it's dangling a life carrot in front of you and they're never ever going to be able to have it. And it seems so cruel, so cruel. But obviously once you've got this medication, it's, it's literally, it's it's given you a new life.

Here, parent five illustrates the grief they experienced upon receiving the diagnosis; the meaning of the medication is demonstrated in contrast to this. The medication is seen to offer a reprieve from this grief, and instead offer a future. This is echoed by many parents, stating that the medication means their child will no longer have "limitations" and instead have "opportunities". This

was often an emotive topic for parents, which emphasised its importance. For many of the parents, the medication was seen to offer a future they had previously thought they could not have:

> It meant actually she'd be able to live longer…she's going to be able to fulfil some of the things that we thought would not be possible. (Parent 4)

However, despite the importance of the medication, parents differed on how certain they were of this. Some were confident that the medication meant their child would have a future, whereas others were much more tentative. These different approaches could reflect different strategies, a theme that will be elaborated on later. Nevertheless, in the context of the initial diagnosis, the medication was highly important.

In contrast, when parents spoke about the medication in the context of their ***child's relationship with CF,*** prior to starting the medication, the feeling was more muted. Most parents described their child as being "well" prior to starting the medication and because of this, they did not expect the medication to significantly change their lives. In fact, one parent expressed anxiety towards the medication because of this:

> [child's name] has a major fear of blood tests because he has been poked and prodded so much…and the thought that he was going to have to have these regular blood tests like…every 3 months. I'm just like, the stress that that is going to cause is ridiculous. Like can we not. (Parent 1)

This quote illustrates how both their child's health status and their relationship with treatment influenced their feelings towards the medication. It highlights a conflict in the parent between the potential the medication offers and the realities of taking it for their child. All in all, the importance of the medication appeared to lie in its contrast between the implications of the diagnosis and the future, rather than what it could offer in the present.

Another key source of contextualisation for the parents can be summed up in the subtheme ***the stories of other unknown people with CF*****.** Many parents positioned their experience of their child's condition, their decisions around commencing the medication and their decision making with regards to CF in general, in reference to stories of other people with CF. It was not always clear where these stories came from, however, social media and the CF team seemed to be the source of some. For example:

> One person in particular, we were following and seeing like not only her point of view of how it changes, like there was where you've seen that they're on a waiting list for

> transplants…but one particular person, I just remember and just drastically seeing like that change in her and thinking ah. (Parent 9)

In the above example, the story of other people with CF, seemed to be a source of encouragement, evidencing why this medication was important. For others, however, such stories would lead them to minimise the importance of their experience, as it was not seen as drastic as those of "others", for example:

> so my story isn't, isn't as amazing as other parents who had really poorly children at the beginning (Parent 5).

All in all, parents' experiences of their child starting the medication was mediated by their own and others' experiences of CF.

Living alongside Cystic Fibrosis

The theme **living alongside CF** represents how parents' various strategies to manage the impact of CF influenced their experiences of their child starting the medication. These strategies were employed both consciously, reflected in the subtheme ***conscious adjustment*** and unconsciously, illustrated in the subtheme ***unconscious adjustment.***

Conscious adjustment refers to the decisions that some of the parents made to not centralise CF in their children's lives. Instead, they emphasised the importance of their child having a "normal life" and seeing their child as "normal". Many recognised the contradiction of this positioning, noting that there were aspects of their life that were different to other people and that they hoped to be different. However, rather than normal meaning typical, it instead appeared to be used to denote a level of acceptance.

For some, this decision also applied to their relationship with the medication, both in the run up to and after having the medication. For instance:

> I think because obviously, we tried not to let it affect us, it hasn't, it hasn't massively changed. It changed in the way that she's on a lot less other medications now…but other than that, not really (Parent 8).

In the above quote, parent eight illustrates how their decision not to focus on CF in their day to day lives minimised how they experienced the impact of the medication, even when there was a tangible effect. A similar approach was taken by Parent ten, who emphasised the importance of not putting your hopes into the medication, they said:

> don't waste the privilege…don't think it's a miracle…it's just part of…looking after your child (Parent 10).

Here, the parent demonstrates a more reserved attitude towards the medication, emphasising the importance of continuing to complete their CF treatment as normal. This emphasis of continuing CF treatment as normal is shared by many of the parents and where, for some, it means they are more reserved towards the medication, for others, they remain openly excited and hopeful about it.

However, even when parents reported excitement about the medication, this was often noted to be for short periods of time due to ***unconscious adjustment***. This subtheme reflects parents' natural adjustment to life with CF, something that occurs without intention. For example parent nine stated:

> This is on a time scale, like in the early days, it took over my life. It was never not there, just like up in the morning and I wouldn't even think about CF, but I just have this feeling in my tummy, and then it'll be…that kind of overwhelming worry…but yeah, as you get older, seeing him running around football mad. So you see him…just like any other child.

Here, parent nine illustrates how the initial grief of being told their child has CF, lessens or changes over time, instead being replaced with who their child is. This view is shared by other parents, reflecting on how the identity of their child, overtime, subsumes the child having CF. Similarly, parents shared how the day-to-day realities of having a child meant adjustment was inevitable. Parent six emphasises this:

> But I think at that moment, at diagnosis, it did, you know, certainly at least for a day. And then we went out in the car and the kids both filled their nappies and we had no spaces. Suddenly it was like here we are, here's reality. Stuck in a car on a hot date, with two poopy children, this is now the priority. So you know, life sort of comes back and brings down and keeps you in the moment (Parent 6).

This exemplifies how, despite experiencing difficult emotions, parents are still responsible for the care of their children and that this becomes their focus. This was similarly observed in the positive emotions around the medication, whereby one parent stated:

> I think unless you sit and think about it…I think it's when you go to these appointments and they say, oh, we're gonna take this away again. It's like instant… and I have adapted again (Parent 9).

Here, the good news of having the medication reduced, quickly becomes part of the norm. Another parent echoed this, sharing that they had to ground themselves with videos of what life was like prior to the medication, in order to truly recognise how things had changed. All in all, parental decisions around how to view CF and the medication, as well as parents' natural ability to adapt meant that excitement about the medication was often short lived.

The impact of the medication

Another key theme was the impact of the medication. Parents would reflect on what they noticed and felt had changed for themselves and their children after commencing the medication. This is further illustrated in the two subthemes ***tangible impact*** and ***intangible impact.***

Tangible impact refers to the explicit changes parents noted after their child started the medication. Despite CF being a physical health condition and the medication leading to physical changes, parents spoke more about practical and emotional changes they experienced. For instance, some parents found they had more time to spend with their children because since starting the medication, the number of other treatments they had to do had decreased. Parent eight stated:

> It's changed in a way that she's on a lot less other medications now. A big thing was the Creon that she had with food. So it was sort of me having to be a lot more organised to remember, to remember to always have Creon with me when we go out and things like that. And I don't have to worry about that now because she is not unwell anymore (Parent 8).

Creon is a digestive enzyme that some people with CF have to take with every meal (Somaraju & Solis-Moya, 2016). For this parent, an important change was the reduction in mental load associated with having to incorporate less medication into their daily lives. The excitement of this was shared by a number of parents in a similar position. This reduction in organisational responsibilities did not occur for everyone, in fact for many their day-to-day experience of CF had not changed at all. What had changed, however, was how they felt about CF.

All ten parents spoke about the medication offering a sense of relief. For example, parent one stated:

> I still do everything I did before, I think. Like I said, the only difference is I don't have that extra worry.

The medication was seen to allow parents to worry less about their children. One parent described the medication as offering another layer of protection for their child, providing a more explicit reason as to why it offered relief, for others it was less clear. They shared that although the

medication had not meant changes in the here and now, it gave them more "room to breathe". This sense of relief without clear reasoning may be due to difficulties associated with CF being in the future rather than in the present. It could also be due to there continuing to be a sense of uncertainty associated with it. This is demonstrated in the quote below by parent nine:

> he's still got…CF and it's still got that uncertainty about it. And then part of me thinks, you know these drugs are amazing. But long term effect. Like there's still, you've got little worries along the way.

Here you see how the parent's feelings about the medication shifts, between the uncertainty of the future with the medication and the potential of the medication, a state of flux shared by many of the parents.

This sense of uncertainty was emphasised for parents where they had not seen tangible evidence of the medication working. Parent seven, for example, states

> Yeah you've got this thing of not really knowing whether she would be like she is (Parent 7).

This is an example of the theme ***intangible impact,*** which refers to the difficulties that many parents had in describing what had changed for their children. Parents expressed a hesitancy towards ascribing change to the medication as it could also be other things such as normal developmental changes. For example, parent 2 shared:

> so it's difficult to say whether changes are due…whether it's just…him growing up.

This sense of unsureness was shared by several of the parents, both in regard to whether the medication was having a positive impact, but also whether their child was experiencing side effects. For instance, one parent reflected on their difficulty distinguishing whether their child's mood changes were due to the medication, or because they were a child.

The special role of the paediatric CF team

All ten parents described their relationship with their paediatric CF team as positive. The teams were portrayed as both knowledgeable and highly accessible, something that was understood as special in contrast to an NHS where long waiting lists are seen as the norm. This is evidenced by Parent 7:

> Not that I have another team to go on, but they're always there for you when you need it. And they always said that, you know, just e-mail us if you've got a ridiculous question…which I know so many other people don't understand. It's like, no, seriously I can just email the nurse…and one of them will get back to me in like half an hour.

Parents also demonstrated a high degree of trust in the team, but in slightly different ways. Some showed it in their willingness to try any treatment the team offered, whereas others trusted that they could ask any question and be treated with integrity.

Parents shared that the CF teams had spent much time preparing them for this medication. For some, this was highly valued and gave them assurance that the medication was indeed coming. For others, they were more sceptical and felt that if this appeared, it was likely to be a long time in the future. All parents, however, felt well supported to access the medication.

The socio-political context

The final theme illustrates parents' awareness of their access to this medication in its broader socio-political context. This is illuminated further in the two subthemes: ***privilege*** and ***uncertainty of removal.***

As part of the subtheme ***privilege***, many parents expressed a strong sense of gratitude for being given access to this medication. One parent stated:

> We were quite humbled…aren't we damn lucky, so we need to seize the opportunity (Parent 4).

Here the use of the term 'humbled' suggests that access to the medication was not seen as the norm, but something that they have access to due to another kind of privilege. This was echoed by other parents highlighting an awareness of other families who do not have access to this medication and that CF is a relatively rare health condition to receive such a high level of input. It also shows the pressure that comes with this sense of privilege. Some parents shared a need to get the medication right and not to waste anything. They described feeling guilty if they missed a dose. This was added to by an understanding of the cost of the medication, with most parents commenting on this. For instanced parent two states:

> We recognise how valuable they are, so there was kind of, there was a bit of fear around how expensive they are…

This quote highlights the discomfort and pressure that comes with having access to such a medication, particularly as it is funded.

The knowledge of how expensive it was intensified the sense of fear expressed by some parents, when speaking about its potential removal. In the subtheme ***uncertainty of removal,*** parents who were interviewed after NICE's announcement that they could not recommend that the

NHS continue to offer three out of the four modulators reported feeling a sense of anger and sadness.

> when I first read the post that NICE [was] not going to renew the modulated drugs. So that's how I read it…my heart sunk. I was like, what? What? That can't happen. And they can't dangle that or give us hope (Parent 2).

Here, the parent questions the ethics of being offered a potentially life saving medication and removing this for them or others like them. This was reiterated by other parents who saw this as an act of injustice. This anger and sadness was similarly felt by parents who had positioned themselves as not focusing on the importance of the medication. This highlights that despite parents taking a reserved position towards the medication, it is still incredibly important and meaningful to them.

Although it was confirmed that the parents in this study's children would still have access to medication, the idea of removal still struck a chord with them, with one parent stating:

> You know, if he had to come off it. He is going to be at risk of becoming more unwell…if he becomes more unwell? If his lung function is less and he can't play, or he's not as, he's such a good little footballer and and a good rugby player…If he couldn't play sports…it would be devastating for him. And I think the emotional impact. I don't think we would be quite prepared for. Of what that would be like (Parent 2).

This suggests that coming off the medication would act as another point of crisis for them, with those opportunities granted to them once more removed.

All in all, the socio-political context of CFTR modulators was noted to have a big impact on parents' emotions around their children starting CFTR modulators, adding a layer of complexity and increased pressure to the experience.

Discussion

This study aimed to explore parents' experiences of their children starting CFTR modulator therapy. To this author's knowledge, it is one of a small number of studies to include parents in the research of modulators and the first to explore parents' experiences of this treatment.

The results highlighted the complex interplay between several key themes. These included the direct impact of the medication, how it was positioned in their wider story with CF and the tools they used to manage and make sense of their experiences. Overall, the direct physical impact of the medication was given the least attention by parents. One explanation for this is the sample consisted

of parents with children whom the parents considered as relatively healthy. The medication is, therefore, less likely to have an observable physical impact on their children. However, it was also evident that parental coping, both conscious and unconscious, meant that some parents were not as focused on the physical changes or markers of physical change. Interestingly, in the interviews, many parents reflected on it being either the first, or the first for a while, opportunity to really reflect on what had changed. The intangibility of some of the changes, due to them occurring in children who are also developing and changing all the time, may have accentuated this.

Parents were more explicit in describing the psychological impact this medication had on themselves. The modulators were seen as a source of relief from the day-to-day management of CF for some, but predominantly from their grief at what a future with CF looks like. These feelings were mediated by the context in which they were being discussed and once more by parents' conscious and unconscious adjustment. For instance, parent narratives were much more emotive when talking about the medication in the context of the diagnosis or the fear of removal. Whilst when speaking about the medication as it impacted them in the present moment, parents reflected on how normalised it had become. This is arguably reflective of Tonkin (1996)'s growing around grief model. In Tonkin's model, grief is a stable presence in people's lives, it does not reduce over time, but instead people's lives grow around it. It states that there are times when grief becomes the emotion of focus, and times when it is not. Parents' narratives around CF could be understood in a similar way. The grief from CF remains the same, however, their and their children's lives grow around it. Events such as the availability of new potentially lifesaving medication, draw this grief back into focus, however, it is not the focus of everyday life.

Throughout parents' narratives, there was evidence of the use of different coping strategies. Some parents were optimistic about the medication, whereas others were more reserved, not wishing to place too much hope in them. Some parents were confident in the medication meaning a future for their children, whereas others struggled with the uncertainty and wished not to think too much about it. More often than not, all of the differing positions were observed within the same parent at different points in the interviews. Parents of children with CF are known to use a range of different coping strategies (Arslan Şahbaz & Cankurtaran,2023). Optimism and hopefulness have been associated with greater psychological wellbeing for both parents and their children, whereas parents who are seen to be more negative have been shown to have poorer outcomes (Wong & Heriot, 2008). Taking a more reserved approach, although not explicitly negative, could be seen as such, as it is used to defend against getting your hopes up and experiencing disappointment. Alternatively, it could be seen as an example of acceptance uncertainty, a key attribute of psychological flexibility which has been found to improve outcomes in parents of children with

chronic illness (Lappalainen et al., 2021). In these instances, parents may be accepting that they do not know what is going to happen, a position that those who were optimistic also took.

Clinical Implications

This study illustrates the complex feelings parents of children with CF may navigate upon starting the CFTR modulator therapy. The findings illustrate that despite the modulators being proclaimed as an incredibly positive advance in treatment, that not all parents may feel this way and there remains a lot of uncertainty about the impact and future of both the treatment availability and course of CF for these children and families. The findings also demonstrate that parents may be using both helpful and unhelpful coping strategies to manage their feelings around the medication. It is, therefore, important that parents are given space by the staff within the CF team and clinic to process these complex feelings. Clinical psychologists may be able to help identify when parents are using unhelpful coping strategies and help them make sense of the uncertainty. This is particularly noteworthy as it may have been expected that following gaining access to a potentially lifesaving medication, parents' psychological wellbeing may improve, which in turn may lead to clinical psychologists not being invested in as part of CF teams. This study highlights that this is not the case and that there is still a need for psychological support, despite the trajectory for their child's life potentially being different.

The CF team, in general, was highly valued by the parents in this study, particularly their accessibility, time, and familiarity. The CF team was seen as a key source of information and guidance throughout their entire CF journey. It is, therefore, important that CF teams are supported to continue to offer such comprehensive support.

This study also demonstrates the potential importance of this medication for the wellbeing of parents. This could be due to both the reduction in organisation and planning this medication may lead to, as well as the sense of relief they are provided with, to see their child's health improve. Parents of children with CF are known to experience higher rates of anxiety and depression (Daly et al., 2022) and the presence of this medication may go towards reducing this. It is, therefore, important that the value of this medication is not only measured in its impact on physical health. In NICE's recent report into the clinical and cost effectiveness of CFTR modulator therapies, no measure of parental wellbeing or quality of life was included as an outcome (Edwards et al., 2023). It is important that the impact on parents is included in this appraisal process and that factors such as the time parents may gain back due to CFTR modulators or a potential reduction in ongoing stress, are seen as valid outcomes and included in measures of cost-effectiveness.

Strengths and Limitations

One of the main strengths of this study is its parental focus. Parents are known to have a pivotal role in the care and management of their children with CF (Bryon & Wallis, 2011), but little research has been completed in this area. The parents in this study offered a unique perspective into what it is like to commence this medication, prioritising the power of adaptation and coping in their narratives more than depression and anxiety. Further research may wish to focus on this part of the narrative in its attempt to understand the impact of CFTR modulators on psychological wellbeing more broadly.

Another strength of this study was the opportunity it gave parents to reflect. Parents reported the experience to be a positive one and valued being given time to connect with their experiences. Once more, this highlights the importance of the role of clinical psychologists, but also of researchers in giving voice to differing perspectives.

Another example of this is the inclusion of a parent as a patient and public involvement (PPI) resource. By including the parent in the development of the topic guide, it helped to ensure the questions reflected what the parent felt was important to their experiences. Unfortunately, due to confidentiality needs and the potential for the PPI parent to recognise the participants involved, they were not invited to be a part of the analysis, which would have helped to better ensure that analysis represented parental perspectives.

One of this study's main limitations is its lack of diversity in the sample. This includes both the severity of the children's CF and the gender of the parents. Most of the parents described their children as being generally in good health prior to them commencing a CFTR modulator therapy, which the parents felt influenced their experiences. A broader representation of illness severity may have added further nuance and richness to the data.

Furthermore, all the parents who took part in this study self-identified as mothers. This is not unusual in research into caregivers of children with chronic health difficulties, as women tend to be primary caregivers (Chu et al., 2022). Research has shown, however, that male and female caregivers can have different perceptions of illness (Chu et al., 2022) and it is, therefore, important to have all genders represented in research.

With regards to other demographic factors such as ethnicity, this information was not collected as part of this research. This decision was made because CF is known to most affect those of white ethnicity, with 94.6% of pwCF in the UK being white (Natio et al., 2023). Owing to this, ethnic diversity in the sample was likely to be limited and reporting of this may have led to

participants becoming identifiable. The decision was, therefore, made not to collect this data. It is, however, important to recognise cwCF and the parents of cwCF from ethnic minorities, who are known to experience health inequalities (Palla, 2023; Palla & Laguna, 2023). This study cannot represent those experiences and it would, therefore, be important to capture this in order identify the needs of ethnic minorities with regards to CFTR modulators.

Implications for further research

This study illustrates the importance of parents' perspectives in the CF treatment. It suggests that the medication is having an important yet complex emotional impact. Further research is needed to better understand the modulators' impact on parental wellbeing and parental mental health.

Further research is also needed representing people from a diverse range of backgrounds and experiences of CF. This study did not take into account the genetics of the children with CF, but this is known to have an impact on the effectiveness of the medication (Egan, 2016) and further research taking this into account may be helpful.

This study also highlights the complexity parents of children with chronic illness may feel when starting new treatment. It is, therefore, important that parental research occurs alongside the development of any new treatment for a paediatric chronic condition.

Conclusion

This study represents shared and differing experiences of parents of children with CF as they commence the highly anticipated CFTR modulator therapy. It shows that despite the medication being important, parents have more complex feelings towards it, mediated by their experiences of their child's CF, coping strategies and opportunity to reflect. Further research is needed into CFTR modulators including the experiences and perspectives of parents, as well as how they may impact parental psychological wellbeing. These factors need to be included when evaluating the cost effectiveness of the treatment.

In the following chapter the researcher will reflect upon their experiences of conducting the studies in this research portfolio.

References

Abbott, J., Hurley, M. A., Chadwick, H., & Peckham, D. (2023). Ways of coping and survival in Cystic Fibrosis: a 20-year longitudinal study. *Journal of Cystic Fibrosis, 22*(1), 112-118. https://doi.org/10.1016/j.jcf.2022.04.011

Arslan Şahbaz, E. E., & Cankurtaran, Ö. Evaluation of coping strategies of parents of children with cystic fibrosis. *Social Work in Health Care,* 1-21. https://doi.org/10.1080/00981389.2024.2324858

Baker, K., & Claridge, A. M. (2023). "I have a Ph.D. in my daughter": Mother and Child Experiences of Living with Childhood Chronic Illness. *Journal of Child and Family Studies, 32*(9), 2625-2636. https://doi.org/10.1007/s10826-022-02506-8

Biggerstaff, D., & Thompson, A. (2008). Interpretative Phenomenological Analysis (IPA): A Qualitative Methodology of Choice in Healthcare Research. *Qual Res Psychol, 5.* https://doi.org/10.1080/14780880802314304

Bower, J. K., Volkova, N., Ahluwalia, N., Sahota, G., Xuan, F., Chin, A., Weinstock, T. G., Ostrenga, J., & 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. *J Cyst Fibros, 22*(4), 730-737. https://doi.org/10.1016/j.jcf.2023.03.002

Bryon, M., & Wallis, C. (2011). Parents as equal partners in the paediatric cystic fibrosis multidisciplinary team. *Journal of the Royal Society of Medicine, 104*(1_suppl), 30-35. https://doi.org/10.1258/jrsm.2011.s11105

Chu, S. Y., Wen, C. C., & Weng, C. Y. (2022). Gender Differences in Caring for Children with Genetic or Rare Diseases: A Mixed-Methods Study. *Children (Basel), 9*(5). https://doi.org/10.3390/children9050627

Chudleigh, J., & Chinnery, H. (2020). Psychological Impact of NBS for CF. *International Journal of Neonatal Screening, 6*(2), 27. https://doi.org/10.3390/ijns6020027

Daly, C., Ruane, P., O'Reilly, K., Longworth, L., & Vega-Hernandez, G. (2022). Caregiver burden in cystic fibrosis: a systematic literature review. *Ther Adv Respir Dis, 16*, 17534666221086416. https://doi.org/10.1177/17534666221086416

Dill, E. J., Dawson, R., Sellers, D. E., Robinson, W. M., & Sawicki, G. S. (2013). Longitudinal trends in health-related quality of life in adults with cystic fibrosis. *Chest, 144*(3), 981-989. https://doi.org/10.1378/chest.12-1404

Edwards, S., Farrar, B., Ennis, K., Downes, N., Wakefield, V., Mackenzie, I., Walters, A., & Jhita, T. (2023). *Ivacaftor–tezacaftor–elexacaftor, tezacaftor–ivacaftor and lumacaftor–ivacaftor for treating cystic fibrosis: A Multiple Technology Appraisal.*

Egan, M. E. (2016). Genetics of Cystic Fibrosis: Clinical Implications. *Clin Chest Med, 37*(1), 9-16. https://doi.org/10.1016/j.ccm.2015.11.002

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

Gramegna, A., Contarini, M., Aliberti, S., Casciaro, R., Blasi, F., & Castellani, C. (2020). From Ivacaftor to Triple Combination: A Systematic Review of Efficacy and Safety of CFTR Modulators in People with Cystic Fibrosis. *International Journal of Molecular Sciences, 21*(16), 5882. https://doi.org/10.3390/ijms21165882

Keyte, R., Kauser, S., Mantzios, M., & Egan, H. (2023). The psychological implications and health risks of cystic fibrosis pre- and post- CFTR modulator therapy. *Chronic Illness, 19*(3), 539-556. https://doi.org/10.1177/17423953221099042

Lappalainen, P., Pakkala, I., Strömmer, J., Sairanen, E., Kaipainen, K., & Lappalainen, R. (2021). Supporting parents of children with chronic conditions: A randomized controlled trial of web-based and self-help ACT interventions. *Internet Interv, 24*, 100382. https://doi.org/10.1016/j.invent.2021.100382

Lopes-Pacheco, M. (2020). CFTR Modulators: The Changing Face of Cystic Fibrosis in the Era of Precision Medicine [Review]. *Frontiers in Pharmacology, 10.* https://doi.org/10.3389/fphar.2019.01662

Natio, Y., Charman, S., Duckers, J., & Clarke, S. (2023). *UK Cystic Fibrosis Registry: 2022 Annual Data Report. Cystic Fibrosis Trust*. https://www.cysticfibrosis.org.uk/sites/default/files/2023-10/CFT_2022_Annual_Data_Report_FINAL_v8.pdf

National Institute of Healthcare and Excellent [NICE]. (2017). *Cystic fibrosis: diagnosis and management(ng78).* https://www.nice.org.uk/guidance/ng78

Page, A., Goldenberg, A., & Matthews, A. L. (2022). Lived experiences of individuals with cystic fibrosis on CFTR-modulators. *BMC Pulmonary Medicine, 22*(1), 42. Retrieved 2022/01//, from http://europepmc.org/abstract/MED/35062937

Chapter Five: Personal Reflections of the Researcher

The following chapter is a personal reflection on this portfolio as well as the experiences of the researcher creating it. The chapter will be written in the first person and will include a reflection on the researcher's own relationship with CF and a reflection on the experience of completing research in an area in which there is great political change.

Researcher's relationship with Cystic Fibrosis

Prior to beginning this thesis portfolio, I had no personal or professional experience of Cystic Fibrosis (CF). What little I knew about the condition, I had learned from biology lessons years ago and that had predominantly focused on the genetics of the condition, rather than what it was like for people with CF. Upon starting this, I was acutely aware of this position and its potential impact on my interpretation and engagement with the research. I wondered, particularly as I was going to work qualitatively, if I would truly be able to represent the experiences of parents of children with CF.

First, I began familiarising myself with CF. I spent much of my time exploring the Cystic Fibrosis Trust website and talking to my supervisors, all of whom had worked as Clinical Psychologists in CF. I quickly became aware of how technical an area it is, especially as my portfolio focuses on a medication that links with CF's genetic components. I also became aware of the extent and impact it had on people's lives, learning from the stories of my supervisors and various articles and blog posts. As a researcher focusing on a particular project, I am aware that I have only been able to scratch the surface of this condition, but still found the amount of information and its complexity overwhelming as I continued through this process.

My initial position was, "having CF must be difficult and being a parent of a child with CF, must also be really tricky". However, through the process of this portfolio, my position has slightly changed, and this was reflected in my conversations with my supervisors as well as how I chose to write this thesis. Rather than focusing on how difficult it is to have CF, which I agree is still the case, my position shifted to "it is amazing how resilient people with CF and their families are". This shift in my perspective, arguably reflects some of the experiences I observed in the parents whom I interviewed. With parents reporting the diagnosis initially to be devastating, but then their focus shifting to something more resilient and optimistic.

Throughout this process I have had to be open and reflexive in my understanding of CF. I have voraciously absorbed the stories of those with experience in CF whom I have connected with during this process, including my supervisors and the paediatric team who supported recruitment, to

the parent PPI member and the parents whom I interviewed. It has been quite a journey, heightened by the current politics of the medication, namely whether it will continue to be offered as a funded medication on the NHS.

In the spirit of IPA research, this thesis portfolio reflects the experiences and stories of people with CF and their families that I have gathered and how I have then made sense of them. I believe that despite my lack of experience in CF, I have gained a nuanced and detailed perspective of the condition and hope this is reflected in this work.

Completing research in an active political area

As I set out to complete this research, I became increasingly aware of its socio-political context. I was aware that this medication was highly important for the CF community and that people had fought for access to it on the NHS. I initially saw my research in the context of celebrating the CF's community's success in accessing this medication and demonstrating the extent to which this was an important decision.

However, over halfway through this portfolio, I became aware of National Institute of Healthcare and Excellent (NICE)'s statement that they could not recommend the NHS to continue to offer this medication to pwCF due to the costs associated with it. Upon hearing this I was angry and frustrated. I had spent months collecting stories of parents telling me how important this medication was to their families, to then be informed that this was not considered valuable enough to the NHS to continue to offer it. This led me to reflect on how conditions are funded in the NHS and what information is needed in order to demonstrate the cost effectiveness of a medication. I then saw my research as offering a unique perspective on the value of this medication. Expressing what CFTR modulators mean to the families of pwCF and how our understanding of the psychological implications of this medication are yet to really be established but should not be underestimated in terms of value of impact.

All in all, these experiences emphasised the importance of research as a political tool and how we as Clinical Psychologists are responsible for creating high quality research that can be used to direct policy, which in turn can have huge implications for the wider community.

Chapter Six: Discussion and Critical Evaluation

Overall Discussion

In this concluding chapter, a synthesis of the entire thesis portfolio will be presented. This will include a summary of the key findings from both the systematic review and the empirical paper, a discussion of the portfolio's strengths and weaknesses, a reflection on the portfolio's implications for clinical work and finally, suggestions for future research.

The first chapter of this portfolio set the context for the rest of the body of work. The chapter offered a broad overview of Cystic Fibrosis (CF) and how the condition impacted the physical, functional and psychological lives of people with CF (pwCF) (Ernst et al., 2010). Readers were introduced to Cystic Fibrosis transmembrane conductance regulator (CFTR) modulator therapy and their importance to the CF community (Lopes-Pacheco, 2020). Attention was brought to the paucity of research into CFTR modulators' implications for the psychological wellbeing of pwCF, which became an important driver for this portfolio.

The systematic review aimed to explore whether CFTR modulators had an impact on the psychological wellbeing of pwCF. To this author's knowledge, no other review has been completed on this topic. Research into CFTR modulators has primarily focused on physical health outcomes and safety (e.g (Habib et al., 2019) and is in its infancy (Allen et al., 2023). There is growing concern, however, that some people's psychological wellbeing was being negatively impacted by CFTR modulators and a call was made for more research into the topic (VanElzakker et al., 2023). The systematic review was designed with this in mind, aiming to explore and critically appraise current research into the impact of CFTR modulators on psychological wellbeing with the view to answer the question: What is the impact of CFTR modulator therapies on the psychological wellbeing of pwCF?

Within the systematic review, ten papers were identified for inclusion with all but one being quantitative in design. Psychological wellbeing was operationalised into three core components: quality of life (QoL), anxiety and depression. These components reflected the areas of psychological wellbeing that have been highlighted as important within previous CF research (Abbott & Gee, 2003; Quittner et al., 2016). The review produced mixed results, with some evidence that pwCF's QoL improved after starting CFTR modulator therapy, particularly when related to their physical experiences of QoL. However, because of the heterogeneity of study designs, the extent of this could not be illuminated. No significant changes were observed in reported outcomes of anxiety and depression.

The lack of significant change observed in this review is of interest. It corroborates current thought that negative psychological experiences associated with the medication are related to

adverse events associated with initiating or remaining on CFTR modulators, rather than a more general experience (VanElzakker et al., 2023). The strength of this position is limited, however, due to the paucity of research in this area. The findings also suggest that despite participants commencing medication that aims to relieve their CF symptomatology, this is not necessarily leading to an improvement in their psychological wellbeing. This implies that the relationship between CF, CFTR modulators and psychological wellbeing is more complex, and a more nuanced understanding was needed. The beginnings of this were found in the qualitative paper included in this review, with the suggestions of additional factors such as side effects and uncertainty impacting their experiences. This highlighted the potential for qualitative research to provide possible explanations for the quantitative answer.

The potential importance of qualitative research in understanding the nuance of the impact of CFTR modulators, helped to inform the development of the empirical paper, along with the recognition of the importance of parents' roles in the care and management of children with CF. From the moment of diagnosis, parents have primary responsibility for managing and monitoring their child's health (Bryon & Wallis, 2011). It is therefore important to include their perspective and views in any new treatment. To this author's knowledge, no research into CFTR modulator therapies has focused on parents, an important gap in the literature. The empirical paper was developed to help address this. It aimed to explore the lived experiences of parents of children with CF (cwCF) who were commencing CFTR modulator therapies. The study sought to utilise qualitative methodology to capture the nuance of this experience and in doing so, add unique perspectives to current understanding of CFTR modulators.

Interpretative Phenomenological Analysis (IPA) was used to explore parents' narratives of their experiences of their children starting one of the CFTR modulator therapies. IPA is an important, experientially focused methodology, which is widely used in healthcare research (Smith & Osborn, 2015). IPA is valued for being able to construct in-depth and nuanced interpretations of particular phenomena, which are also strongly connected to the individual experiences of participants (Biggerstaff & Thompson, 2008). Such detail is important when attempting to understand a potential complex phenomenon, such as the impact of a new medication.

A number of important themes were highlighted within parents' narratives, most notably the importance of this medication and the hope it offered them. This was demonstrated in parents' reflections on their experiences of receiving their child's diagnosis, the sense of relief they felt when their child started CFTR modulator therapy and the uncertainty around access. These feelings co-existed with the theme "coping", in which parents were observed to use both conscious and

unconscious coping strategies to adapt to the realities of living with CF. Consequently, parents' narratives were seen to constantly shift between highlighting the importance of CFTR modulator therapy, to highlighting their lives as normal, arguably an act of adaptation in action.

This evidence of adaptability offers one explanation with regards to the lack of significant change in pwCF's experiences of anxiety and depression upon starting CFTR modulator therapy. PwCF may simply be adapting to the impact of the medication. Moreover, in the theme "impact of medication" many parents reported that their day-to-day experiences of managing CF had not changed, which in turn may mean that many of the difficulties that contribute to current levels of anxiety and depression in pwCF did not change either. However, parents did express a real sense of relief upon their child commencing the medication and optimism for the future, something that has been echoed in experiential research into pwCF's starting CFTR modulator therapy (e.g. (Page et al., 2022)). Such factors have been observed to improve psychological wellbeing in parents of cwCF (Wong & Heriot, 2008) and this could in turn have a positive impact on the psychological wellbeing of pwCF. This is beyond the scope of current research into CFTR modulator therapies but could be another variable of interest.

In summary, the experiences and impact of CFTR modulator therapies on pwCF and parents of cwCF are complex. There is evidence that they may have a positive impact on the QoL of pwCF, but that other factors such as uncertainty, hope, identity, side effects and coping are also contributing and further complicating these experiences. Further research, both exploring these further and accounting for them, is needed to gain a better understanding of the impact of CFTR modulator therapies.

Strengths and Limitations

The individual strengths and limitations of the systematic review and empirical paper have been discussed in their respective chapters and will not be repeated here. The following will focus on the broader strengths and limitations of the thesis portfolio.

One of the core strengths of this portfolio is its focus on the psychological experiences of pwCF. Over the years the importance of understanding the relationship between chronic illness and mental health has been increasingly recognised (Trudy & Doris, 2016) and research such as this, not only informs understanding but also has implications for how pwCF and their families are supported by healthcare professionals. Examples of this will be further explored in the clinical implications section.

Another strength of this portfolio is the inclusion of parent perspectives. Parents have been important voices in the campaigns for CFTR modulator therapies becoming funded by the NHS, something that has taken approximately ten years (Cystic Fibrosis [CF] Trust, n.d) and remains a point of uncertainty (CF Trust, 2024). The description of parents as "the hidden and unacknowledged members of the CF multidisciplinary team." (p.31) (Bryon & Wallis, 2011), highlights both their importance in CF care, but also their tendency to be under-represented and under-valued. This portfolio acts in opposition to this, instead giving voice to and representing parents of cwCF. This is not only important clinically, as services which involve parents are often found to better meet the needs of their patients (Smith et al., 2015), but also as poor representation in research can have widespread negative connotations including undermining trust, stopping innovation and heightening health inequalities (National Academies of Sciences et al., 2022).

The importance of representation also highlights one of the limitations of this portfolio. There is very little exploration of the impact of factors such as ethnicity. This was initially noted as a limitation in the systematic review and continued in the empirical paper. CF is a condition that primarily impacts those of a white ethnicity (Natio et al., 2023) and for the purposes of confidentiality, ethnicity was not collected in the empirical paper, however, research should still endeavour to be representative and inclusive.

One of the limitations of this portfolio is that it did not take note of the individual impact of specific CFTR modulator therapies or particular genetic profiles, factors which are known to impact pwCF's experience of their condition (Egan, 2016b). People's experiences may differ due to these factors, and this cannot be identified as part of this portfolio. However, due to there being relatively little research into the impact of CFTR modulator therapies at this stage, it would be challenging to break this down meaningfully at present by specific medication, but this is perhaps a direction for future research.

Future research directions

Research into CFTR modulator therapies is in its infancy. The medications have only been available for the past 12 years internationally and only widely available in the UK for the past four (Jacqui, 2023). Much research is needed into the long-term effects of the medication as well as their long-term implications for psychological wellbeing. Such research will help to inform the development and focus of CF care and the role of CF teams. It is important that this research includes both quantitative and qualitative approaches and, as highlighted in this portfolio, qualitative research can offer important insight into people's experiences (Renjith et al., 2021) .

The participants who took part in the empirical paper, and likely the systematic review, were born in a period where this medication was unavailable, and they were therefore informed of their shortened life expectancy. If the NHS is to continue to offer this medication, cwCF who are born now, will potentially live with a vastly different prognosis and outlook, representing real progress in the treatment of CF (McBennett et al., 2022). Understanding the impact this change has on the psychological wellbeing of pwCF and their families will be important. This may have implications for services, including how they are structured, the content of usual care and what information is shared with families upon diagnosis. Moreover, with pwCF potentially living longer, services may have to enhance their usual provision so that it can support people for longer periods of time. PwCF may also experience some of the health conditions and psychological experiences associated with ageing, which would need to be understood and supported. The scope of CF research may need to expand beyond its current focus to be more holistic and life long.

CF is a complex genetic condition, with a wide variety of presentations (Egan, 2016a). As discussed in strengths and limitations, these may potentially impact pwCF's experiences of CFTR modulator therapies. It will be important to include these variables in future research in order to best inform pwCF and their families of what to expect from the medication and the development of appropriate treatment pathways. Other important factors to consider are gender and ethnicity. Due to the relative rareness of CF (Chen et al., 2021), such research may be difficult to complete by individual groups of clinicians or researchers. Cooperation will be needed to recruit large enough sample sizes to manage this to ensure that underrepresentation does not lead to health inequalities. Health inequalities for minoritised groups in CF recognised (DiMango et al., 2021). They have been reported to have worse physical health outcomes prior to CFTR modulators being developed but are also less likely to have access to the CFTR modulators, as they are less likely to have the required genetics for the medication (McGarry et al., 2022). It is therefore important to include minoritised groups in research to better ensure that systems and treatment being developed for CF is keeping them in mind, and not furthering health inequalities.

Clinical Implications

One of the main clinical implications of this portfolio is an understanding that both parents and pwCF may experience complex emotions upon starting CFTR modulator therapies. It is therefore important that space is made for such complex emotions, so that pwCF and their families do not feel distressed, unusual or isolated from having such feelings.

These findings suggest that CF teams should be having open conversations with their patients and their families about their potentially complex feelings, normalising them and, if needed,

bringing them to the attention of the clinical psychologists in the team if it is felt they would benefit from more in-depth support.

The portfolio emphasises the continuing need for clinical psychologists in CF teams, as despite improvements in physical health, which may in time have an impact on the role and configuration of CF teams, psychological wellbeing does not appear to be directly impacted by this. Clinical psychologists will therefore still have a role in supporting the psychological wellbeing of pwCF and their families, including with adherence to CFTR modulator therapies.

At the time of writing, National Institute for Health and Care Excellence (NICE) are in the process of negotiating with CFTR modulator therapy manufacturers with regards to the costs associated with continuing to offer CFTR modulator therapies as part of the NHS (CF Trust, 2024). To do this, NICE has engaged with an appraisal process, which involves collecting information about the cost-effectiveness of CFTR modulator therapies (CF Trust, 2024). The current protocol for exploring this does not include research into the modulators' impact on psychological wellbeing, apart from QoL, although this is once more limited to the respiratory domain or overall QoL scores. Neither does the protocol include measures regarding CFTR modulators impact on parents (Edwards et al., 2023). This portfolio emphasised the importance of these factors with regards to understanding the medication and their exclusion limits this. Future appraisal of CFTR modulator therapies, in order to best represent the impact of the medication, should include both qualitative analysis and experiential data in decision making.

Overall Conclusion

In conclusion, CFTR modulator therapies are an important development in the treatment of CF. They have been highly anticipated by the CF community and are hoped to be lifesaving. With this, however, come more complex psychological experiences for pwCF and their families. Further research is needed to capture this in its complexity to help families navigate such changes.

Chapter Seven: Extended Methodology for the Empirical Paper

The following chapter provides a more detailed explanation of the empirical paper's methodology. It will include a description of the analytic process and how good quality analysis was ensured.

Analytic Process

As stated in the empirical paper, analysis followed the steps set out by *Smith et al. (2022)*

Each transcript was automatically transcribed by Microsoft teams. In order to immerse themself in the data, the primary researcher then listened to each interview more than once and updated the transcripts for accuracy. During this process, the researcher made notes of their initial thoughts about each transcript.

Following this, the first transcript was printed off, read and re-read. Initial comments on points of interest were recorded on the transcript. These are known as exploratory notes. An example of exploratory notes is "in the present moment".

Next, experiential statements were added to the transcript. These are statements that reflect the experiential quality of the data, whilst summarising and synthesising the exploratory notes, for example: "Life does not give you time to be sad".

The experiential statements were then copied onto post-stick notes for further analysis. During this process a number of experiential statements were removed, with the researcher only including statements that felt relevant. The choice to do this reflects a key aspect of IPA philosophy, which emphasises the researcher as an active interpreter and curator of participants' experiences, known as the double hermeneutic. The post-stick notes were then placed in a random order and the primary researcher moved them into groups according to connections they observed across the statements. This was an active and reflexive process, with the primary researcher changing the groups several times.

Once the experiential statements were grouped, the primary researcher then assigned each group a name according to its core characteristics. These core characteristics are known as Personal Experiential Themes (PETs). This process was repeated for each individual transcript.

An example of an early PET created during analysis was: "Coping Strategies in Cystic Fibrosis (CF)". This contained three subthemes: avoidance, gratefulness and unconscious, all of which comprised experiential statements such as "Put CF to back of mind" and "reassuring to see child acting like any other child". These were tabulated for reference.

Once each transcript had its own table of PETs, the primary researcher looked for connections between the PETs in order to form Group Experiential Themes (GETs). This involved a similarly reflexive process of moving PETs and their subthemes into different groupings. This process was fluid and the PETs and GETs were reconfigured a number of times. Table 1 illustrates an early form of a GET, including its subthemes and associated experiential statements.

The process of analysis was fluid and often changing. The main researcher used supervision as support in this process.

Table 3.1

An early example of a Group Experiential Theme

Part of a larger story
Contextualised by impact of diagnosis
The diagnosis itself was shocking
I was not prepared to receive this diagnosis
Fear of the future
I was afraid of the future for my child
Fear of going back to premedication life
Death sentence
Stories heard of not of those in old age
Contrast of new life and death sentence
Contextualised by child's relationship with CF
Experience of having an unwell child is devastating
My child was incredibly poorly prior to starting the medication
It was devastating and overwhelming to see my child undergoing so many interventions
Lucky did not have a unwell child
Luck around severity of CF impacts wellbeing
Feel lucky in comparison to more unwell children
Recognises severity of CF contextualises approach to it
Impact of medication is less because child is well
Previous health status
Did not think the drugs would make a difference to my well child
Hope that children are not aware of the work you put in

Easier when child's relationship with it is easier

Compliance makes it easier

Proud of child's resilience

Feel grateful for compliant child

Contextualised by other unknown people with CF

The practical elements of medication are the foremost importance

There is a sense of relief with my child being compliant

Stories heard of not of those in old age

There are other children who are worse off

Our experience is less dramatic than others

Reflection on Quality

IPA emphasises the validity of a single researcher's interpretation of phenomena *(Smith et al., 2022).* It therefore does not typically advocate the use of a second coder to ensure the validity and reliability of the data. Instead researchers have established a set of criteria, which must be present for IPA research to be considered as high quality Nizza et al. (2021). These criteria, described below, guided how the results were written.

1. Constructing a compelling unfolding narrative

    1. The analysis tells a persuasive and coherent story. The narrative is built cumulatively through an unfolding analytic dialogue between carefully selected and interpreted extracts from participants.
    2. Developing a vigorous experiential and/ or existential account
    3. Focus on the important experiential and/or existential meaning of participants' accounts gives depth to the analysis.

2. Close analytic reading of participants' words

    1. Thorough analysis and interpretation of quoted material within the narrative helps give meaning to the data and the experience it describes.
    2. Attending to convergence and divergence
    3. Idiographic depth and systematic comparison between participants create a dynamic interweaving of patterns of similarity and individual idiosyncrasy. (Nizza et al., 2021, p.4)

Portfolio References

Abbott, J., & Gee, L. (2003). Quality of Life in Children and Adolescents with Cystic Fibrosis. *Pediatric Drugs, 5*(1), 41-56. https://doi.org/10.2165/00128072-200305010-00004

Abbott, J., Hart, A., Havermans, T., Matossian, A., Goldbeck, L., Barreto, C., Bergsten-Brucefors, A., Besier, T., Catastini, P., Lupi, F., & Staab, D. (2011). Measuring health-related quality of life in clinical trials in cystic fibrosis. *J Cyst Fibros, 10* Suppl 2, S82-85. https://doi.org/10.1016/s1569-1993(11)60013-1

Allen, L., Allen, L., Carr, S. B., Davies, G., Downey, D., Egan, M., Forton, J. T., Gray, R., Haworth, C., Horsley, A., Smyth, A. R., Southern, K. W., & Davies, J. C. (2023). Future therapies for cystic fibrosis. *Nature Communications, 14(*1). https://doi.org/10.1038/s41467-023-36244-2

Altabee, R., Carr, S. B., Abbott, J., Cameron, R., Office, D., Matthews, J., Simmonds, N., Cosgriff, R., Turner, D., & Whitty, J. (2022). Exploring the nature of perceived treatment burden: a study to compare treatment burden measures in adults with cystic fibrosis. *NIHR open research, 2*, 36. https://doi.org/10.3310/nihropenres.13260.1

Ancel, J., Launois, C., Perotin, J. M., Ravoninjatovo, B., Mulette, P., Hagenburg, J., Malet, J., Griffon, M., Carré, S., Lebargy, F., Deslée, G., & Dury, S. (2022). Health-Related Quality of Life in Adults with Cystic Fibrosis: Familial, Occupational, Social, and Mental Health Predictors. *Healthcare (Basel), 10*(7). https://doi.org/10.3390/healthcare10071351

Aspinall, S. A., Mackintosh, K. A., Hill, D. M., Cope, B., & McNarry, M. A. (2022). Evaluating the Effect of Kaftrio on Perspectives of Health and Wellbeing in Individuals with Cystic Fibrosis. *Int J Environ Res Public Health, 19*(10). https://doi.org/10.3390/ijerph19106114

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

Bentley, S., Bowman, E., & Makhecha, S. (2022). Clinical impact of CFTR modulator therapy roll-out [Article]. *Pharmaceutical Journal, 309*(7966). https://doi.org/10.1211/PJ.2022.1.158712

Bierlaagh, M. C., Muilwijk, D., Beekman, J. M., & van der Ent, C. K. (2021). A new era for people with cystic fibrosis [Review]. *European Journal of Pediatrics, 180*(9), 2731-2739. https://doi.org/10.1007/s00431-021-04168-y

Biggerstaff, D., & Thompson, A. (2008). Interpretative Phenomenological Analysis (IPA): A Qualitative Methodology of Choice in Healthcare Research. *Qual Res Psychol, 5.* https://doi.org/10.1080/14780880802314304

Brendbekken, A., & Bhopal, A. (2024). Putting Kaftrio into perspective: a test case for fair and open priority setting. *BMJ*, q182. https://doi.org/10.1136/bmj.q182

Bryon, M., & Wallis, C. (2011). Parents as equal partners in the paediatric cystic fibrosis multidisciplinary team. *Journal of the Royal Society of Medicine, 104*(1_suppl), 30-35. https://doi.org/10.1258/jrsm.2011.s11105

Cameron, R. A., Office, D., Matthews, J., Rowley, M., Abbott, J., Simmonds, N. J., Whitty, J. A., & Carr, S. B. (2022). Treatment Preference Among People With Cystic Fibrosis: The Importance of Reducing Treatment Burden. *Chest, 162*(6), 1241-1254. https://doi.org/https://doi.org/10.1016/j.chest.2022.07.008

Chen, Q., Shen, Y., & Zheng, J. (2021). A review of cystic fibrosis: Basic and clinical aspects. *Animal Model Exp Med*, 4(3), 220-232. https://doi.org/10.1002/ame2.12180

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., & Peckham, D. (2014). European Cystic Fibrosis Society Standards of Care: Framework for the Cystic Fibrosis Centre. *Journal of Cystic Fibrosis, 13*, S3-S22. https://doi.org/https://doi.org/10.1016/j.jcf.2014.03.009

Daly, C., Ruane, P., O'Reilly, K., Longworth, L., & Vega-Hernandez, G. (2022). Caregiver burden in cystic fibrosis: a systematic literature review. *Ther Adv Respir Dis, 16,* 17534666221086416. https://doi.org/10.1177/17534666221086416

Davies, G., Rowbotham, N. J., Smith, S., Elliot, Z. C., Gathercole, K., Rayner, O., Leighton, P. A., Herbert, S., Duff, A. J. A., Chandran, S., Daniels, T., Nash, E. F., & Smyth, A. R. (2020). Characterising burden of treatment in cystic fibrosis to identify priority areas for clinical trials. *Journal of Cystic Fibrosis, 19*(3), 499-502. https://doi.org/10.1016/j.jcf.2019.10.025

Dellon, E. P., Shores, M. D., Nelson, K. I., Wolfe, J., Noah, T. L., & Hanson, L. C. (2010). Family Caregiver Perspectives on Symptoms and Treatments for Patients Dying From Complications of Cystic Fibrosis. *Journal of Pain and Symptom Management, 40*(6), 829-837. https://doi.org/10.1016/j.jpainsymman.2010.03.024

DiMango, E., Simpson, K., Menten, E., Keating, C., Fan, W., & Leu, C.-S. (2021). Health Disparities among adults cared for at an urban cystic fibrosis program. *Orphanet Journal of Rare Diseases, 16*(1), 332. https://doi.org/10.1186/s13023-021-01965-4

Edmondson, C., Course, C. W., & Doull, I. (2021). Cystic fibrosis transmembrane conductance regulator modulators for cystic fibrosis: a new dawn? *Archives of Disease in Childhood, 106*(10), 941-945. https://doi.org/10.1136/archdischild-2020-320680

Edwards, S., Farrar, B., Ennis, K., Downes, N., Wakefield, V., Mackenzie, I., Walters, A., & Jhita, T. (2023). *Ivacaftor–tezacaftor–elexacaftor, tezacaftor–ivacaftor and lumacaftor–ivacaftor for treating cystic fibrosis: A Multiple Technology Appraisal.*

Egan, M. E. (2016a). Genetics of Cystic Fibrosis. Clinical Implications [Review]. Clinics in Chest *Medicine, 37*(1), 9-16. https://doi.org/10.1016/j.ccm.2015.11.002

Egan, M. E. (2016b). Genetics of Cystic Fibrosis: Clinical Implications. *Clin Chest Med, 37*(1), 9-16. https://doi.org/10.1016/j.ccm.2015.11.002

NHS England. (2015). A01/P/c Ivacaftor for Cystic Fibrosis (G551D Mutation). https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2015/10/a01pc-ivacftr-cystic-fibrosis.pdf

Ernst, M. M., Johnson, M. C., & Stark, L. J. (2010). Developmental and psychosocial issues in cystic fibrosis. *Child Adolesc Psychiatr Clin N Am, 19*(2), 263-283, viii. https://doi.org/10.1016/j.chc.2010.01.004

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

Goodfellow, N. A., Hawwa, A. F., Reid, A. J. M., Horne, R., Shields, M. D., & McElnay, J. C. (2015). Adherence to treatment in children and adolescents with cystic fibrosis: a cross-sectional, multi-method study investigating the influence of beliefs about treatment and parental depressive symptoms. *BMC Pulmonary Medicine, 15*(1), 43. https://doi.org/10.1186/s12890-015-0038-7

Grossoehme, D. H., Filigno, S. S., & Bishop, M. (2014). Parent routines for managing cystic fibrosis in children. *J Clin Psychol Med Settings, 21*(2), 125-135. https://doi.org/10.1007/s10880-014-9396-1

Gulledge, A., Miller, S., & Mueller, M. (2021). Social support and social isolation in adults with cystic fibrosis: An integrative review. *Journal of Psychosomatic Research, 150*, 110607. https://doi.org/https://doi.org/10.1016/j.jpsychores.2021.110607

Guta, M. T., Tekalign, T., Awoke, N., Fite, R. O., Dendir, G., & Lenjebo, T. L. (2021). Global Burden of Anxiety and Depression among Cystic Fibrosis Patient: Systematic Review and Meta-Analysis. *Int J Chronic Dis, 2021*, 6708865. https://doi.org/10.1155/2021/6708865

Habib, A. R., Kajbafzadeh, M., Desai, S., Yang, C. L., Skolnik, K., & Quon, B. S. (2019). A Systematic Review of the Clinical Efficacy and Safety of CFTR Modulators in Cystic Fibrosis. *Sci Rep, 9*(1), 7234. https://doi.org/10.1038/s41598-019-43652-2

Harvey, C., Weldon, S., Elborn, S., Downey, D. G., & Taggart, C. (2022). The Effect of CFTR Modulators on Airway Infection in Cystic Fibrosis. *Int J Mol Sci, 23*(7). https://doi.org/10.3390/ijms23073513

Jacqui, W. (2023). Cystic fibrosis: What next for the "wonder drug" Kaftrio? *BMJ, 383,* p2766. https://doi.org/10.1136/bmj.p2766

Jaques, R., Shakeel, A., & Hoyle, C. (2020). Novel therapeutic approaches for the management of cystic fibrosis. *Multidiscip Respir Med, 15*(1), 690. https://doi.org/10.4081/mrm.2020.690

Kaplan, R. M. (2003). The significance of quality of life in health care. *Qual Life Res, 12* Suppl 1, 3-16. https://doi.org/10.1023/a:1023547632545

Keyte, R., Kauser, S., Mantzios, M., & Egan, H. (2023). The psychological implications and health risks of cystic fibrosis pre- and post- CFTR modulator therapy. *Chronic Illness, 19*(3), 539-556. https://doi.org/10.1177/17423953221099042

Knudsen, K. B., Pressler, T., Mortensen, L. H., Jarden, M., Skov, M., Quittner, A. L., Katzenstein, T., & Boisen, K. A. (2016). Associations between adherence, depressive symptoms and health-related quality of life in young adults with cystic fibrosis. *Springerplus, 5*(1), 1216. https://doi.org/10.1186/s40064-016-2862-5

Li, Q., Liu, S., Ma, X., & Yu, J. (2022). Effectiveness and Safety of Cystic Fibrosis Transmembrane Conductance Regulator Modulators in Children With Cystic Fibrosis: A Meta-Analysis. *Frontiers in Pediatrics, 10.* https://doi.org/10.3389/fped.2022.937250

Lopes-Pacheco, M. (2020). CFTR Modulators: The Changing Face of Cystic Fibrosis in the Era of Precision Medicine [Review]. *Frontiers in Pharmacology, 10.* https://doi.org/10.3389/fphar.2019.01662

Lord, L., McKernon, D., Grzeskowiak, L., Kirsa, S., & Ilomaki, J. (2023). Depression and anxiety prevalence in people with cystic fibrosis and their caregivers: a systematic review and meta-analysis. *Social Psychiatry and Psychiatric Epidemiology, 58*(2), 287-298. https://doi.org/10.1007/s00127-022-02307-w

McBennett, K. A., Davis, P. B., & Konstan, M. W. (2022). Increasing life expectancy in cystic fibrosis: Advances and challenges [Review]. *Paediatric Pulmonology, 57*(S1), S5-S12. https://doi.org/10.1002/ppul.25733

McGarry, M. E., Gibb, E. R., Oates, G. R., & Schechter, M. S. (2022). Left behind: The potential impact of CFTR modulators on racial and ethnic disparities in cystic fibrosis. *Paediatr Respir Rev, 42*, 35-42. https://doi.org/10.1016/j.prrv.2021.12.001

Megari, K. (2013). Quality of Life in Chronic Disease Patients. *Health Psychol Res, 1*(3), e27. https://doi.org/10.4081/hpr.2013.e27

Natio, Y., Charman, S., Duckers, J., & Clarke, S. (2023). *UK Cystic Fibrosis Registry: 2022 Annual Data Report*. Cystic Fibrosis Trust. https://www.cysticfibrosis.org.uk/sites/default/files/2023-10/CFT_2022_Annual_Data_Report_FINAL_v8.pdf

National Academies of Sciences, E., and Medicine, Affairs, P. a. G., Committee on Women in Science, E., and Medicine, Research, C. o. I. t. R. o. W. a. U. M. i. C. T. a., Bibbins-Domingo, K., & Helman, A. (2022). *Improving Representation in Clinical Trials and Research: Building Research Equity for Women and Underrepresented Groups. In Why Diverse Representation in Clinical Research Matters and the Current State of Representation within the Clinical Research Ecosystem.* National Academies Press (US). https://www.ncbi.nlm.nih.gov/books/NBK584396/

NICE. (2013). *How NICE measures value for money in relation to public health interventions.* [LGB10]. https://www.nice.org.uk/media/default/guidance/lgb10-briefing-20150126.pdf

Nizza, I. E., Farr, J., & Smith, J. A. (2021). Achieving excellence in interpretative phenomenological analysis (IPA): Four markers of high quality. *Qualitative Research in Psychology, 18*(3), 369-386. https://doi.org/10.1080/14780887.2020.1854404

Oliver, K. N., Free, M. L., Bok, C., McCoy, K. S., Lemanek, K. L., & Emery, C. F. (2014). Stigma and optimism in adolescents and young adults with cystic fibrosis. *Journal of Cystic Fibrosis, 13*(6), 737-744. https://doi.org/https://doi.org/10.1016/j.jcf.2014.04.005

Oxley, H., & Webb, A. K. (2005). How a clinical psychologist manages the problems of adults with cystic fibrosis. *J R Soc Med, 98* Suppl 45(Suppl 45), 37-46.

Page, A., Goldenberg, A., & Matthews, A. L. (2022). Lived experiences of individuals with cystic fibrosis on CFTR-modulators. *BMC Pulmonary Medicine, 22*(1), 42. Retrieved 2022/01//, from http://europepmc.org/abstract/MED/35062937

Parekh, M. H., Ipatova, A., Dashputre, A. A., & Kamal, K. M. (2015). Quality of Life In Adult Patients with cystic Fibrosis a Systematic Review. *Value in Health, 18*(3), A288. https://doi.org/10.1016/j.jval.2015.03.1680

Pfeffer, P. E., Pfeffer, J. M., & Hodson, M. E. (2003). The psychosocial and psychiatric side of cystic fibrosis in adolescents and adults. *Journal of Cystic Fibrosis, 2(*2), 61-68. https://doi.org/https://doi.org/10.1016/S1569-1993(03)00020-1

Quittner, A. L., Abbott, J., Georgiopoulos, A. M., Goldbeck, L., Smith, B., Hempstead, S. E., Marshall, B., Sabadosa, K. A., & Elborn, S. (2016). International Committee on Mental Health in Cystic Fibrosis: Cystic Fibrosis Foundation and European Cystic Fibrosis Society consensus statements for screening and treating depression and anxiety. *Thorax, 71*(1), 26-34. https://doi.org/10.1136/thoraxjnl-2015-207488

Renjith, V., Yesodharan, R., Noronha, J. A., Ladd, E., & George, A. (2021). Qualitative Methods in Health Care Research. *Int J Prev Med, 12*, 20. https://doi.org/10.4103/ijpvm.IJPVM_321_19

Sawicki, G. S., Ren, C. L., Konstan, M. W., Millar, S. J., Pasta, D. J., & Quittner, A. L. (2013). Treatment complexity in cystic fibrosis: Trends over time and associations with site-specific outcomes. *Journal of Cystic Fibrosis, 12*(5), 461-467. https://doi.org/10.1016/j.jcf.2012.12.009

Sawicki, G. S., Sellers, D. E., & Robinson, W. M. (2008). Self-Reported Physical and Psychological Symptom Burden in Adults with Cystic Fibrosis. *Journal of Pain and Symptom Management, 35*(4), 372-380. https://doi.org/10.1016/j.jpainsymman.2007.06.005

Smith, J., Cheater, F., & Bekker, H. (2015). Parents' experiences of living with a child with a long-term condition: a rapid structured review of the literature. *Health Expectations, 18*(4), 452-474. https://doi.org/10.1111/hex.12040

Smith, J. A., Flowers, P., & Larkin, M. (2022*). Interpretative Phenomenological Analysis: Theory, Method and Research* (2nd ed.).

Smith, J. A., & Osborn, M. (2015). Interpretative phenomenological analysis as a useful methodology for research on the lived experience of pain. *Br J Pain, 9*(1), 41-42. https://doi.org/10.1177/2049463714541642

Snowdon, C. (2023). *Cystic fibrosis: The miracle drugs priced out of reach.* https://www.bbc.co.uk/news/health-67712269

Somaraju, U. R., & Solis-Moya, A. (2016). Pancreatic enzyme replacement therapy for people with cystic fibrosis. *Cochrane Database Syst Rev, 11*(11), Cd008227. https://doi.org/10.1002/14651858.CD008227.pub3

Talwalkar, J. S., Koff, J. L., Lee, H. B., Britto, C. J., Mulenos, A. M., & Georgiopoulos, A. M. (2017). Cystic Fibrosis Transmembrane Regulator Modulators: Implications for the Management of Depression and Anxiety in Cystic Fibrosis. *Psychosomatics, 58*(4), 343-354. https://doi.org/https://doi.org/10.1016/j.psym.2017.04.001

Trudy, H., & Doris, S. (2016). Mental health in cystic fibrosis: turning the tide. *Thorax, 71*(1), 1. https://doi.org/10.1136/thoraxjnl-2015-208076

Cystic Fibrosis Trust. (2011). *Standards for the Clinical Care of Children and Adults with cystic fibrosis in the UK.* https://www.cysticfibrosis.org.uk/sites/default/files/2020-12/Cystic%20Fibrosis%20Trust%20Standards%20of%20care.pdf

Cystic Fibrosis Trust. (2015). *Cystic Fibrosis: here for parents*. In C. F. Trust (Ed.). https://www.cysticfibrosis.org.uk/sites/default/files/2020-12/CFParentsPack_v6%20LRspreads.pdf

Cystic Fibrosis Trust. (2024*). NICE modulator appraisal*. https://www.cysticfibrosis.org.uk/the-work-we-do/campaigning-hard/life-saving-drugs/nice-modulator-appraisal

Trust, C. F. (n.d.). *Life-saving drugs campaign timeline*. https://www.cysticfibrosis.org.uk/the-work-we-do/campaigning-hard/life-saving-drugs/campaign-timeline

Turcios, N. L. (2020). Cystic Fibrosis Lung Disease: An Overview. *Respir Care, 65*(2), 233-251. https://doi.org/10.4187/respcare.06697

VanElzakker, M. B., Tillman, E. M., Yonker, L. M., Ratai, E.-M., & Georgiopoulos, A. M. (2023). Neuropsychiatric adverse effects from CFTR modulators deserve a serious research effort. *Current Opinion in Pulmonary Medicine, 29*(6). https://journals.lww.com/co-pulmonarymedicine/fulltext/2023/11000/neuropsychiatric_adverse_effects_from_cftr.12.aspx

Wong, M. G., & Heriot, S. A. (2008). Parents of children with cystic fibrosis: how they hope, cope and despair. *Child: Care, Health and Development, 34*(3), 344-354. https://doi.org/10.1111/j.1365-2214.2007.00804.x

Portfolio Appendices

Systematic Review Appendices

Appendix A: Search Strategy

Below is an example of the search strategy used as part of this Systematic Review. This search was run on the database: MEDLINE Ultimate.

"Cystic Fibrosis Transmembrane Conductance Regulator" OR "CFTR modulator therapy" OR Ivacaftor OR Lumacaftor OR Tezacaftor OR Elexacaftor OR Kalydeco OR Orkambi OR Symdeko OR Trikafta OR Kaftrio OR VX-770 OR VX-445 OR VX-809 OR VX-661

AND

"mental health" OR "quality of life" OR Psycholog* OR Emotion* OR Psychiatr* OR "mental illness" OR "mental outcomes" OR "mental disorder" OR Depress* OR Anxiety OR Stress OR Wellbeing OR Well-being OR Insomnia OR "coping" OR Sleep OR "Eating disorder" OR "Disordered Eating" OR "behavioural changes"

Appendix B: Quality Appraisal Tool Criteria

QuADS Criteria	0	1	2	3
1. Theoretical or conceptual underpinning to the research	No mention at all.	General reference to broad theories or concepts that frame the study. e.g. key concepts were identified in the introduction section.	Identification of specific theories or concepts that frame the study and how these informed the work undertaken. e.g. key concepts were identified in the introduction section and applied to the study.	Explicit discussion of the theories or concepts that inform the study, with application of the theory or concept evident through the design, materials and outcomes explored. e.g. key concepts were identified in the introduction section and the application apparent in each element of the study design.
2. Statement of research aim/s	No mention at all.	Reference to what the sought to achieve embedded within the report but no explicit aims statement.	Aims statement made but may only appear in the abstract or be lacking detail.	Explicit and detailed statement of aim/s in the main body of report.
3. Clear description of research setting and target population	No mention at all.	General description of research area but not of the specific research environment e.g. 'in primary care.'	Description of research setting is made but is lacking detail e.g. 'in primary care practices in region [x]'.	Specific description of the research setting and target population of study e.g. 'nurses and doctors from GP practices in [x] part of [x] city in [x] country.'
4. The study design is appropriate to address the stated research aim/s	No research aim/s stated or the design is entirely unsuitable e.g. a Y/N item survey for a study seeking to undertake exploratory work of lived experiences. .	The study design can only address some aspects of the stated research aim/s e.g. use of focus groups to capture data regarding the frequency and experience of a disease.	The study design can address the stated research aim/s but there is a more suitable alternative that could have been used or used in addition e.g. addition of a qualitative or	The study design selected appears to be the most suitable approach to attempt to answer the stated research aim/s.

			quantitative component could strengthen the design.	
5. Appropriate sampling to address the research aim/s	No mention of the sampling approach.	Evidence of consideration of the sample required e.g. the sample characteristics are described and appear appropriate to address the research aim/s.	Evidence of consideration of sample required to address the aim. e.g. the sample characteristics are described with reference to the aim/s.	Detailed evidence of consideration of the sample required to address the research aim/s. e.g. sample size calculation or discussion of an iterative sampling process with reference to the research aims or the case selected for study.
6. Rationale for choice of data collection tool/s	No mention of rationale for data collection tool used.	Very limited explanation for choice of data collection tool/s. e.g. based on availability of tool.	Basic explanation of rationale for choice of data collection tool/s. e.g. based on use in a prior similar study.	Detailed explanation of rationale for choice of data collection tool/s. e.g. relevance to the study aim/s, co-designed with the target population or assessments of tool quality.
7. The format and content of data collection tool is appropriate to address the stated research aim/s	No research aim/s stated and/or data collection tool not detailed.	Structure and/or content of tool/s suitable to address some aspects of the research aim/s or to address the aim/s superficially e.g. single item response that is very general or an open-response item to capture content which requires probing.	Structure and/or content of tool/s allow for data to be gathered broadly addressing the stated aim/s but could benefit from refinement. e.g. the framing of survey or interview questions are too broad or focused to one element of the research aim/s.	Structure and content of tool/s allow for detailed data to be gathered around all relevant issues required to address the stated research aim/s.
8. Description of data collection procedure	No mention of the data collection procedure.	Basic and brief outline of data collection procedure e.g. 'using a questionnaire distributed to staff'.	States each stage of data collection procedure but with limited detail or states some stages in detail but	Detailed description of each stage of the data collection procedure, including when, where and how

			omits others e.g. the recruitment process is mentioned but lacks important details.	data was gathered such that the procedure could be replicated.
9. Recruitment data provided	No mention of recruitment data.	Minimal and basic recruitment data e.g. number of people invited who agreed to take part.	Some recruitment data but not a complete account e.g. number of people who were invited and agreed.	Complete data allowing for full picture of recruitment outcomes e.g. number of people approached, recruited, and who completed with attrition data explained where relevant.
10. Justification for analytic method selected	No mention of the rationale for the analytic method chosen.	Very limited justification for choice of analytic method selected. e.g. previous use by the research team.	Basic justification for choice of analytic method selected e.g. method used in prior similar research.	Detailed justification for choice of analytic method selected e.g. relevance to the study aim/s or comment around of the strengths of the method selected.
11. The method of analysis was appropriate to answer the research aim/s	No mention at all.	Method of analysis can only address the research aim/s basically or broadly.	Method of analysis can address the research aim/s but there is a more suitable alternative that could have been used or used in addition to offer a stronger analysis.	Method of analysis selected is the most suitable approach to attempt answer the research aim/s in detail e.g. for qualitative interpretative phenomenological analysis might be considered preferable for experiences vs. content analysis to elicit frequency of occurrence of events.
12. Evidence that the research stakeholders have been considered in research design or conduct.	No mention at all.	Consideration of some the research stakeholders e.g. use of pilot study with target sample but no	Evidence of stakeholder input informing the research. e.g. use of pilot study with feedback influencing the study	Substantial consultation with stakeholders identifiable in planning of study design and in preliminary work e.g. consultation in the

		stakeholder involvement in planning stages of study design.	design/conduct or reference to a project reference group established to guide the research.	conceptualisation of the research, a project advisory group or evidence of stakeholder input informing the work.
13. Strengths and limitations critically discussed	No mention at all.	Very limited mention of strengths and limitations with omissions of many key issues. e.g. one or two strengths/limitations mentioned with limited detail.	Discussion of some of the key strengths and weaknesses of the study but not complete. e.g. several strengths/limitations explored but with notable omissions or lack of depth of explanation.	Thorough discussion of strengths and limitations of all aspects of study including design, methods, data collection tools, sample & analytic approach.

Appendix C: Full table of results

Table 1.6

A full summary of study characteristics and outcomes

Author	Country	Participant Number	Age Range, Gender and Ethnicity	CFTR Modulator Type	Average time on CFTR Modulator	Study Design and Analysis	Area of Psychological Wellbeing	Key findings relevant to the review question
Aspinall et al., (2022)	United Kingdom	12	**Mean age:** 28.1 (6.4) **Gender:** 83% female, 17% male **Ethnicity:** Not reported	ETI	6 months to over 1 year	Qualitative Content Analysis	Quality of life	**Improved Quality of life.** All individuals identified improved quality of life including reduced coughing, reduced breathlessness, more energy, increased appetite, improved sleep duration and quality, and the ability to complete daily tasks easier. **Side Effects:** A decrease in quality of life. Some individuals had experienced side effects to the point that their quality of life had deteriorated as to pre ETI levels. This included brain fog and weight gain.
McCoy et al., (2022	United States	18	**Mean age:** 33.8 (15 to 49) **Gender:** 44% female, 56% male **Ethnicity:** Not reported	ETI	2 years	Retrospective Chart Review Wilcoxon signed-rank test on paired differences	Quality of life	Mean baseline CFQ-R Subscales: CFQ-R: Physical Functioning: 25.00 CFQ-R: Role Functioning: 66.67 CFQ-R: Vitality: 45.83 CFQ-R: Emotional Functioning: 73.33 CFQ-R: Social Functioning: 55.56 CFQ-R: Body image: 33.33 CFQ-R: Eating Problems: 77.78 CFQ-R: Treatment Burden: 50.00 CFQ-R: Health perceptions: 38.89 CFQ-R: Weight: 0.00 CFQ-R: Respiratory symptoms: 50.00 CFQ-R: Digestive symptoms: 83.33

								Mean 24 month CFQ-R Subscales: CFQ-R: Physical Functioning: 75.00* CFQ-R: Role Functioning: 91.67 CFQ-R: Vitality: 75.00* CFQ-R: Emotional Functioning: 86.67 CFQ-R: Social Functioning: 72.22* CFQ-R: Body image: 55.56 CFQ-R: Eating Problems: 100.00 CFQ-R: Treatment Burden: 66.67* CFQ-R: Health perceptions: 77.78* CFQ-R: Weight: 100.00 CFQ-R: Respiratory symptoms: 88.89* CFQ-R: Digestive symptoms: 88.89
Hernández et al., (2023)	Spain	114	**Mean age:** 28.1 (SD 6.5) **Gender:** 48.2% female, 51.8% male **Ethnicity:** Not reported	ETI	24 months	Ambispective, multicentre, observational pre-post study. Parametric and Non parametric tests	Quality of life	The mean value of all QoL items showed a significant difference (p<0.001) between basal and 24 months. The CFQ-R domains of respiratory, vitality, physical activity, daily activities and emotional wellbeing showed a significant increase between baseline and 12 months, after which it plateaued or decreased. CFQ-R Subscales: CFQ-R respiratory: 5.8 [-10.7 - 22.3] CFQ-R digestive: -20.8 [-37.5 - - 4.1]* CFQ-R vitality: -0.1 [15.9 - 15.7] CFQ-R physical activity: 8.6 [-8.1- 25.4] CFQ-R food: -16.1 [-34.7 - 2.4]* CFQ-R daily activities: -4.4 [-21.9-13.0] CFQ-R treatment: 2.0 [-12.1 - 16.1] CFQ-R emotional: -12.8 [-29.1 - 3.5]
Eijofor et al., (2020)	Denmark	21	**Median age:** 33.0 (IQR 23,	Lumacaftor /ivacaftor	Median 68.7 weeks (IQR: 58.1,	Follow up study	Quality of life	A significant difference was observed between the fixed effects overall CFQ-R score estimate at baseline of 648.3 and 799.2 at 12 months.

			40) **Gender:** 46% female, 54% male **Ethnicity:** Not reported		77.7)	Linear mixed-effects models and repeated measures ANOVA		Fixed effect estimate baseline CFQ-R Subscales: CFQ-R: Physical Functioning: 49.3 CFQ-R: Role Functioning: 70.2 CFQ-R: Vitality: 41.6 CFQ-R: Emotional Functioning: 67.4 CFQ-R: Social Functioning: 55.5 CFQ-R: Body image: 60.8 CFQ-R: Eating Problems: 62.9 CFQ-R: Treatment Burden: 67.4 CFQ-R: Health perceptions: 32.5 CFQ-R: Weight: 50.1 CFQ-R: Respiratory symptoms: 59.8 CFQ-R: Digestive symptoms: 62.9 Fixed effect estimate 12 month CFQ-R Subscales: CFQ-R: Physical Functioning: 73.1* CFQ-R: Role Functioning: 75.9 CFQ-R: Vitality: 60.7* CFQ-R: Emotional Functioning: 72.7 CFQ-R: Social Functioning: 66.1* CFQ-R: Body image: 73.0* CFQ-R: Eating Problems: 81.6* CFQ-R: Treatment Burden: 72.7 CFQ-R: Health perceptions: 54.68* CFQ-R: Weight: 76.1* CFQ-R: Respiratory symptoms: 65.7 CFQ-R: Digestive symptoms: 76.4 * The repeated measures ANOVA showed a significant effect of time on physical, vitality, eating problems, health perceptions, social functioning and body image.
Migliori	Italy	26 (13	**Median**	ETI	12 months	Retrospecti	Quality of life	Overall CFQ-R score pre and post commencing medication:

si et al., (2022)		control)	**age:** 29.5.0 (IQR 22.25, 39.00) **Gender:** 50% female, 50% male **Ethnicity:** Not reported			ve case control study Descriptive Statistics		Pre: 1: 33 2: 34 3: 36.6 4: 22 5: 72.2 6: 49 7: 33.3 8: 44.4 9: 61 10: 77.8 11: 78.9 12: 44.4 13: 22	Post: 1: 100 2: 100 3: 100 4: 100 5: 100 6: 100 7: 100 8: 100 9: 100 10: 100 11: 100 12: 100 13: 100
DiMango et al (2021)	United States	43	**Mean age:** 34.0 (SD 37.5) **Gender:** 67% female, 33% male **Ethnicity:** Not reported	ETI	3 months	Prospective Cohort Study Paired t test analysis	Quality of life	Mean CFQ-R Score (95% CI) Baseline: Physical functioning: 65 (59.6–70.4) Vitality: 48.3 (45.4–51.2) Emotion: 73.3 (69.7–76.7) Eat: 78.9 (74.3–83.5) Treatment burden: 55.5 (51.4–59.6) Health perception: 60.0 (55.8–64.2) Social: 61.6 (58.1–65.1) Body: 75.5 (69.5–81.5) Role: 75.8 (71.3–80.3) Weight: 70.0 (61.2–78.8) Respiratory: 60.6 (57.1–64.1) Digestion: 80 (75.4–84.6) Post Treatment: Physical functioning: 78.3 (73.8–82.8)* Vitality: 60.8 (56.7–64.9)*	

								Emotion: 76.0 (72.5–79.5) Eat: 88.9 (85.8–92.0)* Treatment burden: 66.7 (62.4–71.0)* Health perception: 75.5 (72.6–78.4) Social: 68.3 (64.6–72.0)* Body: 77.8 (71.7–83.9) Role: 85.8 (82.3–89.3)* Weight: 86.7 (82.0–91.4)* Respiratory: 83.3 (79.4–87.2) Digestion: 81.1 (76.4–85.8)
Bell et al., (2019)	France, United Kingdom, Germany Australia and Ireland	209 (137 control)	**Mean age:** 24.3 (SD 12.1) **Gender:** 44% female, 56% male **Ethnicity:** Not reported	Ivacaftor	Mean = 21.8 (SD = 15.1) months	Cross-sectional study (control group) Multi-variate regression analysis	Quality of life	**CFQ-R Subscales** Mean CFQ-R Score for patient group Physical functioning: 74.6 Vitality: 63.5 Emotion: 78.8 Eat: 91.1 Treatment burden: 65.3 Health perception: 67.6 Social: 70.2 Body: 74.9 Role: 77.0 School: 83.1 Weight: 80.7 Respiratory: 75.4 Digestion: 85.5 Mean CFQ-R Score for control group Physical functioning: 66.6* Vitality: 55.9* Emotion: 75.0 Eat: 84.2* Treatment burden: 54.8* Health perception: 58.6*

								Social: 82.7 Body: 67.8 Role: 73.5 School: 82.7 Weight: 64.2 Respiratory: 62.5* Digestion: 78.0 EQ-5D-5L Index Score (0-1), n; LS mean (SE) Patient: 72; 0.90 (0.02) Modulator: 137; 70.0 (0.02)* VAS score (0-100), n; LS mean (SE) Modulator: 72; 75.7 (1.8) Control: 135; 70.0 (1.4) EQ-5D-5L domains Mobility: Significantly better scores for modulator group Self-care: No significant difference observed Usual Activites: Significantly better scores for modulator group Pain/Discomfort: Significantly better scores for modulator group Anxiety/Depression: Significantly better scores for modulator group
Allgood et al., (2023)	United States	22	**Median age:** 35.3 (IQR=11.1) **Gender:** 40.9% female,	ETI	14 weeks	Prospective observational study Unadjusted	Depression and Anxiety	PHQ8 Depression: Unadjusted β (95% CI): - 0.29 (- 1.28, 0.71) Adjusted β (95% CI): - 0.13 (- 1.12, 0.86) GAD7 Anxiety: Unadjusted β (95% CI) - 0.344 (- 1.41, 0.74) Adjusted β (95% CI) - 0.19 (- 1.25, 0.87)

			59.1% male **Ethnicity:** 100% white			and adjusted and multivariable linear regression models		Adjusted models were adjusted for age, sex and baseline value of measure
Piehler et al., (2023)	Germany	70	**Median age:** 27.9 (IQR=22.5 - 34.1) **Gender:** 51.4% female, 48.6% male **Ethnicity:** Not reported	ETI	8 to 16 weeks	Prospective observational study Wilcoxon Signed Rank test	Quality of life, Anxiety and Depression	Change between baseline and ETI median CFQ-R Subscales Physical functioning: 12.5 (4.2–29.2)* Vitality: 8.3 (0.0–25.0)* Emotion: 0.0 (−6.7 to 6.7) Eat: 0.0 (0.0–0.0)* Treatment burden: 11.1 (0.0–16.7)* Health perception: 11.1 (0.0–22.2)* Social/School: 5.6 (−5.6–16.7)* Body: 11.1 (0.0–11.1)* Weight: 0.0 (0.0–33.3) Respiratory: 22.2 (11.1–44.4) Digestion: 0.0 (−19.4 to 11.1) Role: 8.3 (0.0–16.7)* PHQ-9 Female: 0.0 (IQR -2.0 to 1.0) Male: −1.5 (IQR -4.0 to 0.0)* GAD-7 Female: 0.0 (IQR -1.0 to 1.0) Male: −1.0 (IQR -3.0 to 0.0)* BDI-FS Female: 0.0 (IQR -0.8 to 0.0) Male: 0.0 (IQR -1.0 to 0.0)

Zhang et al., (2022)	United States	100	**Mean age:** 35.3 (I11.3) **Gender:** 48% female, 52% male **Ethnicity:** 96% white, 4% black, biracial or multiracial	ETI	Unclear	Retrospective chart review Linear mixed models	Anxiety and Depression	PHQ9 Depression (Mean and SD): Pre: 4.99 ± 4.65 Post: 5.07 ± 4.84 Change: -0.059 (SE 0.488) GAD7 Anxiety (Mean and SD): Pre: 4.34 ± 4.34 Post:4.34 ± 4.34 Change: -0.140 (SE 0.466)

Experimental Paper Appendices

Appendix D: Topic Guide

Parent's experiences of their child starting Cystic Fibrosis transmembrane conductance regulator (CFTR) modulator therapy

Topic Guide

1. Could you tell me a bit about what life was like for you before your child began [Name of CFTR Medication]?
    a. What was a typical day like for you?
    b. How do you feel CF impacted your day to day lives?

2. Could you tell me a bit about your journey to getting [Name of CFTR Medication]?
    a. Can you remember what it was like when you found about this medication?
    b. Do you remember what it was like to find out that CFTR modulator therapy was available for your child?
    c. What was it like at that moment?
    d. What was it like when you found out your child got it?
    e. What was it like to get the first appointment?
    f. How did it feel?

3. What was it like for you when [Child's Name] first started taking [Name of CFTR Medication]?
    a. How did if feel when they took their first dose?
    b. Did you notice any changes in them – what was it like when you noticed this?
    c. Did you notice any changes in their mood in behaviour – what was this like for you?
    d. Did you notice any physical changes – what was it like seeing this?

4. Has life changed for you since [Child's Name] started taking [Name of CFTR Medication]? Could you tell me a bit about that?
    a. Has your day-to-day life changed - What has that felt like for you?
    b. Have you felt your role as a parent has changed - What has this meant to you?
    c. Has your relationship with your child changed – What has this been like?
    d. What do you think [Child's Name] would say has been the biggest change for you as a parent?

5. How does life for you now compare to your expectations or hopes for when [Child's Name] first started the medication?
    a. Is there anything about this that surprises you?

6. Can you tell me a bit about the role of the CF team in [Child's Name] starting [Name of modulator therapy]?

7. What advice would you give to another parent whose child has started CFTR modulator therapy?
    a. What do you think would be important for them to know?

8. What does your future as a parent of a child with CF, look like now?
    a. What do you expect will happen?
    b. What do you hope will happen?
    c. Could you tell me a bit about any worries or concerns you have?
    d. Have you noticed this change since your child started the medication? What has that been like/meant for y

Appendix E: Consent to Contact

Parent's experiences of their child starting Cystic Fibrosis transmembrane conductance regulator (CFTR) modulator therapy

Participant ID:

CONSENT TO CONTACT

Name of the Participant:

Email:

Home telephone:

Mobile:

Preferred method of contact:

Email ☐ Home number ☐ Mobile ☐

Is it okay to leave a message on your home telephone?

Yes ☐ No ☐

Is it okay to leave a message on your mobile?

Yes ☐ No ☐

Is it okay to leave a text message on your mobile?

Yes ☐ No ☐

1. I give my consent to be contacted by the researcher in the above study. By signing this I am not giving my consent to take part in the study but for the researcher to make contact to discuss the study with me further.

2. I understand that the contact details I provide below will be provided to the researcher.

3. I understand that my contact details will be stored securely and then destroyed at the end of the study.

_____	_____	_____
Name of Participant	Date	Signature

Appendix F: **Participant Information Sheet**

PARTICIPANT INFORMATION SHEET

Study Title: Parent's experiences of their child starting Cystic Fibrosis transmembrane conductance regulator (CFTR) modulator therapy

You have been invited to take part in a research study being run by the University of East Anglia and supported by your local Cystic Fibrosis Team. The below leaflet will tell you what this research is about and if you would like to take part, how to go about this.

Please take some time to read through the following information carefully and discuss it with others and your care team if you would like to. If there is anything that is not clear or if you would like more information, please do not hesitate to contact us using the details at the end of this leaflet.

What is the purpose of this study?

As you are aware, new treatments called CFTR modulator therapies (also known by their brand names of *Kalydeco, Orkambi, Symkevi or Kaftrio*) have been made available to many eligible adults and children with CF over the past year or so.

As with any new treatment it is important to not only do research into the physical effectiveness of the medication, but to also understand the real-life experiences of those affected by it. We know that parents of children with CF, such as yourselves, are key to supporting their child manage their condition. We therefore wish to hear from you about your experiences of your child taking this medication.

We would like to understand what it has been like for you, for your child to start this medication. We wish to explore this so that we can have a better understanding of the journey families undergo

when starting this medication as well the day-to-day experiences of it. We believe that learning such information will both improve our understanding of the effects of this new treatment and also how we can best support families as they take up this medication.

Why am I being sent this information?

You have been invited to take part in this research project as you are a parent of a child who has recently begun taking one of the CFTR modulator therapies.

Am I eligible to take part?

We are currently only inviting parents who are under the care of the Norfolk and Norwich or Queen Elizabeth Hospital paediatric CF teams. We ask that your child received the diagnosis of CF prior to June 2020 and that they have been taking the medication for more than a month.

Unfortunately, we are only able to invite one parent per child to take part and that the parent regularly attended the CF clinic appointments related to starting the medication.

What will happen if I decide to take part?

If you decide to take part, the researcher will then be in contact to arrange the best time and venue to conduct the interview. The researcher aims to be as flexible as possible to suit your needs and the interview will likely take an hour. You will be asked to sign and return a consent form.

You can choose whether you would like to complete the interview face to face or remotely using the video conferencing software Microsoft teams. If you would like to complete it face to face a researcher would be able to join you in your home or, if you would prefer, we could arrange a meeting space at the University of East Anglia. The interview will likely take an hour.

The interview will be recorded using the Microsoft Teams video conferencing software and the audio will later be transcribed.

The interview will be analysed for key themes about your experiences and written up into a research paper to be published. If you would like a summary of the results you can request this and they can be sent to you at the end of study. To do this your details will be stored securely up until the results are shared with you. After this they will be deleted.

Do I have to take part?

No. Taking part in this research project is entirely voluntary and it is up to you whether or not you would like to take part. Taking or not taking part in this study will not affect the care you receive from your CF team.

If you decide to take part, you are free to withdraw at any time, without explanation but we will keep information about you that has already been involved in analysis

What are the possible benefits of taking part?

If you do take part, you will be contributing to our knowledge and understanding of CFTR modulator therapies. We will also gift you a £10.00 Love to Shop voucher as a token of appreciation for your time.

What are the possible disadvantages of taking part?

The interview will take approximately one hour of your time. We are aware that some may find talking about your child's Cystic Fibrosis quite difficult and upsetting at times. We aim to always be sensitive and considerate and can signpost you to supporting organisations.

What if there is a problem?

If you have a concern about any aspect of this study, you can speak to the researcher who will do their best to answer your questions. Contact details are listed at the bottom of this sheet.

If you wish to make a complaint (or talk about making a complaint) you can contact Dr Sian Coker, programme director at the University of East Anglia. She can be contacted at sian.coker@uea.ac.uk

You could also your local Patient Advice Liaison Service (PALS) a confidential service designed to support patients, relatives and carers. For Norfolk and Norwich University Hospital CF team families please contact 01603 289036 or email palsandcomplaints@nnuh.nhs.uk. For Queen Elizabeth Hospital families please contact 01553 613351 or 01553 613343 or email pals@qehkl.nhs.uk

Will taking part in this study be confidential?

What you say in the interviews will be kept strictly confidential, in that the recordings will not be shared with anyone other than those within the research team. By signing our consent form you agree that we may quote some of things you have said when we write up the research and produce an information booklet for parents. Any information we use in this way would be completely anonymised, neither you or your child's name will appear in any reports or publications. We will keep all information about you safe and secure.

The only instance we would break confidentiality is if you were to mention something that suggested that you or someone else was at risk of harm. In this case we would have a duty of care to contact the safeguarding team at the Norfolk and Norwich University Foundation Trust. If this were to be the case, we endeavour to have an open conversation with you at the time.

How will data be kept secure?

Digital data, such as the recordings and transcription will be kept securely in password protected files, on the University of East Anglia secure One drive. This will only be accessible to the research team. The recordings and transcription will be destroyed at the end of the research.

Physical data will be kept in a locked cabinets at the University of Easy Anglia.

Identifiable information will be kept separately to research data and only used for the purposes of participant contact during the study. This will all be destroyed at the end of the research.

The University of East Anglia will act as the Data Controller for this study they are responsible for looking after your information, using it properly and ensuring this research project is compliant with GDPR.

How will we use information about you?

We will need to use information from you for this research project.

This information will include your name, contact details and demographic information such as your age and gender and your child's age, gender and the type of medication they are taking. 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.

What are your choices about how your information is used?

- 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.

Where can you find out more about how your information is used?

You can find out more about how we use your information:

- at www.hra.nhs.uk/information-about-patients/
- by sending an email to **H.edwards3@uea.ac.uk**
- by ringing us on 07749725728

Who is organising the research?

This research is being organised by the University of East Anglia as part of the researcher's professional doctorate in Clinical Psychology. The research is being supported by the Norfolk and Norwich University Hospitals Foundation Trust and the Queen Elizabeth Hospital Kings Lynn Foundation Trust.

Who has reviewed this study?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and approved by Health & Social Care Research Ethics Committee A (HSC REC A).

Contact for further information?

If you would like to hear more about this study or if you would like to take part, please contact:

Hannah Edwards
Trainee Clinical Psychologist

Email: H.edwards3@uea.ac.uk
Tel: 07749725728

Appendix G: Consent Form

Participant ID:

Parent's experiences of their child starting Cystic Fibrosis transmembrane conductance regulator (CFTR) modulator therapy

CONSENT FORM

Please initial box

1. I have read the Participant Information sheet for the above study. ☐
2. I have had the opportunity to consider the information above, ask questions and feel that these have been answered satisfactorily. ☐
3. I understand that taking part in this study is voluntary and know that I am free to withdraw at any time without giving a reason. ☐
4. I understand that withdrawing would not impact the care me or my child receives from the CF team. ☐
5. I understand that my interview will be video recorded using Microsoft teams but only the audio will be transcribed. ☐
6. I understand that this recording and further information collected about me for the purposes of this study will be stored securely. ☐
7. I understand that anonymised quotes from my interview may be used in a flyer for other parents commencing CFTR modulator therapy and in the dissemination of research. ☐
8. I understand that relevant sections of the data collected during the study may be looked at by individuals from the University of East Anglia, or from regulatory authorities where it is relevant to my taking part in this research. ☐
9. I agree to take part in the above study. ☐
10. I would like to receive a copy of the results of this study (optional). ☐

_____	_____	_____
Name of Participant	Date	Signature
_____	_____	_____
Name of Person seeking consent	Date	Signature

Appendix H: Demographic Form

DEMOGRAPHIC INFORMATION

Participant ID:

Parent Demographics

Gender

Male ☐

Female ☐

Other ☐

(Please state)

_____

Age (years) _____

Do you have Cystic Fibrosis?

Yes ☐

No ☐

Child Demographics

Gender

Male ☐

Female ☐

Other ☐

(Please state)

_____

Age (years) _____

Which medication has your child commenced?

Kaftrio ☐

Symkevi ☐

Orkambi ☐

Kalydeco ☐

When did your child commence the medication?

Month _____ Year _____

Appendix I: Debrief

Thank you for taking part in my study!

I really appreciate the time that you have taken to speak to me and the experiences that you have shared.

We hope that by understanding your experiences of your child starting CFTR modulator therapy we can add to our knowledge of the impact of the medication as well as what support would be useful to families.

Please remember:

1. You are free to withdraw from the study at any time. However, we will keep any information that has already been involved in analysis.
2. Your information will be kept confidential unless we have concerns for the safety of yourself or others.
3. If you have any concerns, please contact myself at h.edwards3@uea.ac.uk.
4. If you have asked to be informed of the results of the study, we aim to be in contact between June and August 2024.

Talking about your experiences may have been difficult and upsetting at times. If you find that you need further support with this, please contact your local paediatric CF team.

Alternatively, the Cystic Fibrosis Trust offers a helpline. Call 0300 373 1000 or 020 3795 2184, Monday–Friday 10am–4pm. Email helpline@cysticfibrosis.org.uk.

If you find that you are experiencing high levels of distress and feel you need urgent support please contact NHS 111 and choose option 2 or alternatively call 999.

Appendix J

HRA REC Confirmation

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

Miss Hannah Edwards
University of East Anglia
Norwich Research Park
Norwich
NR4 7TJ

Email: approvals@hra.nhs.uk
HCRW.approvals@wales.nhs.uk

21 March 2023

Dear Miss Edwards

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**Parent's experiences of their child starting Cystic Fibrosis transmembrane conductance regulator (CFTR) modulator therapy**
IRAS project ID:	**321325**
Protocol number:	**n/a**
REC reference:	**23/NI/0020**
Sponsor	**University of East Anglia**

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.

Please see IRAS Help for information on working with NHS/HSC organisations in Northern Ireland and Scotland.

How should I work with participating non-NHS organisations?
HRA and HCRW Approval does not apply to non-NHS organisations. You should work with your non-NHS organisations to obtain local agreement in accordance with their procedures.

What are my notification responsibilities during the study?

The standard conditions document "*After Ethical Review – guidance for sponsors and investigators*", issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

Who should I contact for further information?
Please do not hesitate to contact me for assistance with this application. My contact details are below.

Your IRAS project ID is **321325**. Please quote this on all correspondence.

Yours sincerely,
Anna Bannister

Approvals Specialist

Email: approvals@hra.nhs.uk

Copy to: *Polly Harrison*

List of Documents

The final document set assessed and approved by HRA and HCRW Approval is listed below.

Document	*Version*	*Date*
Contract/Study Agreement template [PIC Agreement NNUH]	1	11 January 2023
Contract/Study Agreement template [PIC Agreement QEKHL]	1	11 January 2023
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Sponsor Evidence of Professional Liability]	1	01 August 2022
Interview schedules or topic guides for participants [Topic Guide]	2	23 November 2022
IRAS Application Form [IRAS_Form_17012023]		17 January 2023
IRAS Application Form XML file [IRAS_Form_17012023]		17 January 2023
IRAS Checklist XML [Checklist_17012023]		17 January 2023
Letter from sponsor [Sponsor Cover Letter re insurance]	1	13 January 2023
Non-validated questionnaire [Demographics Form]	2	23 November 2022
Other [GCP Refresher Document]	1	24 November 2022
Other [CPFT Lone Working Policy]	3	01 May 2018
Other [Sponsor Evidence of Employers Liability]	1	01 August 2022
Other [Consent to Contact Form]	2	23 November 2022
Other [Distress Protocol]	1	02 March 2023
Other [Debrief Document]	2	13 March 2023
Other [IRAS Rec Response]	1	13 March 2023
Participant consent form [Consent Form]	3	02 March 2023
Participant information sheet (PIS) [Participant Information Sheet]	5	02 March 2023
Research protocol or project proposal [Thesis Protocol]	2	23 November 2022
Summary CV for Chief Investigator (CI) [Research CV Hannah Edwards]	1	23 November 2022
Summary CV for student [Research CV Hannah Edwards]	1	03 October 2022
Summary CV for supervisor (student research) [Research CV Amy Carroll]	1	22 November 2022

IRAS project ID	321325

Information to support study set up

The below provides all parties with information to support the arranging and confirming of capacity and capability with participating NHS organisations in England and Wales. This is intended to be an accurate reflection of the study at the time of issue of this letter.

Types of participating NHS organisation	Expectations related to confirmation of capacity and capability	Agreement to be used	Funding arrangements	Oversight expectations	HR Good Practice Resource Pack expectations
Activities at NHS organisations will involve PIC activity only, including the identification of participants, database searches and the mailing out of study documentation...(to be amended as appropriate)	Research activities should not commence at participating NHS organisations in England or Wales prior to their formal confirmation of capacity and capability to deliver the study in accordance with the contracting expectations detailed. Due to the nature of the activities involved, organisations will be expected to provide that confirmation to the sponsor Within 35 days of receipt of the local	The sponsor has provided the appropriate model commercial PIC agreement that it intends to use as a subcontract between participating organisations and NHS organisations acting as their Participant Identification Centres (PICs).	Sponsor is not providing funding to PICs	The Chief Investigator will be responsible for all study activities performed at PICs.	Where an external individual will be conducting any of the research activities that will be undertaken at this site type then they would be expected to hold a Letter of Access. This should be issued be on the basis of a Research Passport (if university employed) or an NHS to NHS confirmation of pre-engagement checks letter (if NHS employed). These should confirm Occupational Health Clearance. These should confirm standard DBS checks.

Appendix K: Guidelines for Journal of Cystic Fibrosis

Your Paper Your Way

We now differentiate between the requirements for new and revised submissions. You may choose to submit your manuscript as a single Word or PDF file to be used in the refereeing process. Only when your paper is at the revision stage, will you be requested to put your paper in to a 'correct format' for acceptance and provide the items required for the publication of your article.
To find out more, please visit the Preparation section below.

Journal of Cystic Fibrosis publishes original scientific articles, editorials, case reports, short communications and other information relevant to cystic fibrosis and is published six times a year. Papers are accepted on the understanding that they have not been published, and are not being considered for publication elsewhere and are subject to editorial revision.

Original articles Original research papers should contain no more than 3,000 words for the manuscript body (excluding title page, abstract and references) plus no more than 5 figures or tables in total and 30 references. The abstract should consist of 4 paragraphs, labelled Background, Methods, Results, and Conclusions.
Review articles Review papers should be authoritative, well-referenced reviews of a relevant subject and should not contain more than 5,000 words for the manuscript body and 30 references with no more than 6 figures or tables.
Letters Headings should not be used in a letter; no abstract or keywords are required. The text should be no more than 800 words; there should be a maximum of 5 references and 1 table or figure may be included.
Correspondence Short articles relating to papers recently published in the Journal, or containing brief reports of unusual or preliminary findings. Maximum length 400 words, 1 table or figure and a maximum of 10 references.
Editorials These tend to be invited papers but unsolicited editorials are welcome. There are no abstract, keywords or section headings.
Short Communications 1,200 words for manuscript body plus no more than

3 figures or tables in total and 20 references.
Case Reports These must be carefully documented and must be of importance because they illustrate or describe unusual features or have important therapeutic implications. Maximum length 1,200 words, no more than a page and a half in length and a maximum of 1 table or figure. Case reports do not require a structured abstract and should include no more than 5 references.

Page charges

This journal has no page charges.

Appendix L

Guidelines for Health Psychology Review

About the Journal

Health Psychology Review is an international, peer-reviewed journal publishing high-quality, original research. Please see the journal's Aims & Scope for information about its focus and peer-review policy.

Structure

Your paper should be compiled in the following order: title page; abstract; keywords; main text introduction, materials and methods, results, discussion; acknowledgments; declaration of interest statement; references; appendices (as appropriate); table(s) with caption(s) (on individual pages); figures; figure captions (as a list).

Format-Free Submission

Authors may submit their paper in any scholarly format or layout. Manuscripts may be supplied as single or multiple files. These can be Word, rich text format (rtf), open document format (odt), or PDF files. Figures and tables can be placed within the text or submitted as separate documents. Figures should be of sufficient resolution to enable refereeing.

- There are no strict formatting requirements, but all manuscripts must contain the essential elements needed to evaluate a manuscript: abstract, author affiliation, figures, tables, funder information, and references. Further details may be requested upon acceptance.
- References can be in any style or format, so long as a consistent scholarly citation format is applied. Author name(s), journal or book title, article or chapter title, year of publication, volume and issue (where appropriate) and page numbers are essential. All bibliographic entries must contain a corresponding in-text citation. The addition of DOI (Digital Object Identifier) numbers is recommended but not essential.
- The journal reference style will be applied to the paper post-acceptance by Taylor & Francis.
- Spelling can be US or UK English so long as usage is consistent.

Note that, regardless of the file format of the original submission, an editable version of the article must be supplied at the revision stage.

Checklist: What to Include

1. **The Title Page** (p. 1) should contain the article title, authors' names and affiliations and the address for manuscript correspondence (including e-mail, address and telephone and fax numbers). No information that would indicate authors' identity or affiliation should be contained in the manuscript itself; all such information should be included on the title page only. Read more on authorship.
2. **Author details** Please ensure all listed authors meet the Taylor & Francis authorship criteria.
3. **The Abstract** (p. 2) must be a single paragraph that summarizes the main findings of the paper in fewer than 200 words. After the abstract a list of six **Keywords** that will be useful for indexing or searching should be included.
4. **Figures.** Figures may be embedded in the manuscript file (preferred), provided at the end, or saved as separate files. All figures must be numbered in the order in which they appear in the manuscript (e.g. Figure 1, Figure 2) and have appropriate captions. Figures should be of sufficient resolution to enable refereeing.
5. **Tables.** Tables may be embedded in the manuscript file (preferred), provided at the end, or saved as separate files. All tables must be numbered in the order in which they appear in the manuscript (e.g. Table 1, Table 2) and have appropriate captions.
6. **Authors' contributions.** All authors are expected to have made substantive intellectual contributions to, and to have been involved in drafting or revising the manuscript. Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content. Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship. With the submission of a manuscript, it is assumed that all authors have read and approved the final manuscript.
7. **Acknowledgements.** All contributors who do not meet the above criteria for authorship, should be listed in an acknowledgements section in accordance with the APA guidelines. The acknowledgements should be contained on the title page of the manuscript as making acknowledgements available to reviewers will compromise the masked peer-review process. Examples of those who might be acknowledged include those who provided general, technical, or writing assistance. Acknowledgement of funding/grants are also included in this section.
8. **Funding details.** Please supply all details required by your funding and grant-awarding bodies as follows:
   For single agency grants

This work was supported by the [Funding Agency] under Grant [number xxxx].
For multiple agency grants
This work was supported by the [Funding Agency #1] under Grant [number xxxx]; [Funding Agency #2] under Grant [number xxxx]; and [Funding Agency #3] under Grant [number xxxx].

9. **Supplemental online material.** Supplemental material can be a video, dataset, fileset, sound file or anything which supports (and is pertinent to) your paper. We publish supplemental material online via Figshare. Find out more about supplemental material and how to submit it with your article.
10. **Disclosure statement.** This is to acknowledge any financial or non-financial interest that has arisen from the direct applications of your research. If there are no relevant competing interests to declare please state this within the article, for example: *The authors report there are no competing interests to declare.* Further guidance on what is a conflict of interest and how to disclose it.
11. **Data availability statement.** If there is a data set associated with the paper, please provide information about where the data supporting the results or analyses presented in the paper can be found. Where applicable, this should include the hyperlink, DOI or other persistent identifier associated with the data set(s). Templates are also available to support authors.
12. **Data deposition.** If you choose to share or make the data underlying the study open, please deposit your data in a recognized data repository prior to or at the time of submission. You will be asked to provide the DOI, pre-reserved DOI, or other persistent identifier for the data set.
13. **Equations.** If you are submitting your manuscript as a Word document, please ensure that equations are editable. More information about mathematical symbols and equations.
14. **Units.** Please use SI units (non-italicized).