A mixed methods study in cystic fibrosis following the widespread availability of elexacaftor/tezacaftor/ivacaftor. Understanding the impact of context change in long-term condition care.

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Abstract

This study explored how the introduction of elexacaftor/tezacaftor/ivacaftor (ETI) has shaped cystic fibrosis (CF) care. This pragmatic, mixed-methods Realist Evaluation examined how clinicians and people with CF (pwCF) made sense of and responded to this contextual change, focussing on adherence to inhaled medicines and the evolving configuration of specialist CF services.

Initial Programme Theory was developed through interviews with CF clinicians across the UK. It was refined through a national survey and realist focus groups with pwCF. Feasible elements of Programme Theory were tested in a multivariable regression analysis.

The refined Programme Theory identified key mechanisms shaping post-ETI care. Restored wellness has led pwCF and clinicians to re-evaluate the role of burdensome inhaled medicines and models of care. Many pwCF feel empowered to autonomously reduce inhaled medicines, giving primacy to subjective health indicators, such as symptom burden. In the absence of published evidence, many clinicians are hesitant to support these approaches. Clinicians often prioritise objective health indicators, such as lung function, over subjective measures. The resulting epistemological dissonance between pwCF and clinicians leads to concealment of actual behaviour, uncertainty, and variation, leaving some clinicians feeling professionally disempowered. While some pwCF find adoption of virtual appointments liberating in the context of improved health, others experience abrupt transitions as abandonment, highlighting the enduring importance of relational continuity.

These findings reinforce the need for shared decision-making and personalised care in the post-ETI era. Ten recommendations aim to guide service design, including an acknowledgement of emotional and relational needs, adoption of shared decision-making, and a more holistic model of care. As the first Realist Evaluation in CF, this thesis provides novel insights into the generative mechanisms underpinning behaviours. It introduced the PLUTO framework to support shared decision-making and emphasised habit as key mediator of adherence behaviours, which can generalise to other long-term conditions.

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Declaration

I, the author, confirm that the Thesis is my own work. I am aware of the University's Guidance on the Use of Unfair Means (www.sheffield.ac.uk/ssid/unfair-means). This work has not previously been presented for an award at this, or any other, university.

Publications directly related to the thesis

Peer-reviewed publications

Sandler RD *et al*. The CFHealthHub Learning Health System: Using Real-Time Adherence Data to Support a Community of Practice to Deliver Continuous Improvement in an Archetypal Long-Term Condition. *Healthcare* (Basel). 2022 Dec 21;11(1):20. doi: 10.3390/healthcare11010020.

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Publications arising from wider work during PhD study

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Sandler RD, Lai L, Dawson S, *et al*. Development of data processing algorithm to calculate adherence for adults with cystic fibrosis using inhaled therapy - a multi-center observational study within the CFHealthHub learning health system. *Expert Rev Pharmacoecon Outcomes Res*. 2024 Jul;24(6):759-771. doi: 10.1080/14737167.2024.2328085. Epub 2024 Mar 12. PMID: 38458615.

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1. Introduction

In this thesis, I examined the impact of the novel oral medicine elexacaftor/tezacaftor/ivacaftor (ETI) on the care of people with cystic fibrosis (pwCF) in the United Kingdom (UK) with a particular focus on the implications for specialist adult CF care service design and delivery. I explored how clinicians and pwCF across the UK understood and responded to this significant contextual change using a pragmatic, mixed-methods Realist Evaluation study design.

Chapter 2 outlines the broader context of optimising care in long-term conditions, with an emphasis on personalised care and medicines adherence. It introduces the clinical background of CF and the structure of specialist adult CF services in the UK. I also detail the development of the CFHealthHub learning health system, co-designed within a UK CF community of practice to support adherence to inhaled medicines via a digital platform and behavioural intervention. I describe its evolution in response to contextual changes, using the Non-adoption, Abandonment, Scale-up, Spread and Sustainability (NASSS) framework. The introduction of ETI represented a major contextual change, prompting the development of a new observational study and clinical framework aimed at maintaining a focus on adherence to inhaled medicines in the post-ETI therapeutic landscape.

Chapter 3 presents the study's realist methodological approach, which enabled exploration of how contextual factors influence the activation of mechanisms to generate specific outcomes in complex settings. The study used both qualitative and quantitative data to examine changes in the behaviours, interactions, and decision-making processes of clinicians and pwCF following the introduction of ETI. I also give a reflexive account of my position as the researcher and how this shaped the work of the thesis.

Chapter 4 reports findings from semi-structured interviews with specialist adult CF clinicians across multiple Centres. Reflexive thematic analysis was employed to identify key aspects of CF care that have been shaped by the introduction of ETI.

In Chapter 5, an Initial Programme Theory (IPT) was developed by re-analysing interview transcripts using realist approaches, to identify key aspects of context that may be leading to different outcomes the theorise on the underlying mechanisms driving these changes. Key theory areas are discussed, and elements of theory are articulated in an index of Context (C), Mechanism (M), Outcome (O) configurations (CMOC). Chapters 4 and 5 sought to qualitatively answer the first research question: *"How have ETI and the COVID-19 pandemic shaped perspectives of CF clinicians on inhaled medicines and the demands on their services?*"

Chapter 6 refines the Programme Theory using data from interviews with specific clinicians at a single adult CF Centre. These interviews focussed on the practical delivery of inhaled medicines adherence support to pwCF since the introduction of ETI.

Chapter 7 presents the findings of a national survey of over 300 pwCF, designed to explore perspectives on inhaled medicines. Both quantitative and qualitative data were analysed to test and refine the evolving Programme Theory and identify priority areas for exploration in subsequent realist focus groups.

In Chapter 8, findings from three realist focus groups with pwCF are described. Data collecting during these focus groups offered deeper insight into the mechanisms influencing behaviour and engagement with care for pwCF. Chapters 7 and 8 sought to build on previous insights and qualitatively answer the second and third research questions,: "*How have ETI and the COVID-19 pandemic shaped the experiences and care needs/preferences of pwCF?"* and "*What factors are associated with adherence to inhaled medicines for pwCF in the post-ETI era?*"

Chapter 9 presents a multivariable linear regression analysis, where elements of Programme Theory and other relevant factors were tested for association with objectively measured adherence data. Twenty-five variables across demographic, socioeconomic, health-related, and psychological domains were analysed using routinely collected data from the electronic health records of all pwCF on a single adult CF Centre caseload. This chapter sought to quantitatively answer the third research question: "*What factors are associated with adherence to inhaled medicines for pwCF in the post-ETI era?*".

Chapter 10 discusses the findings from Chapters 4 to 9, presenting a refined Programme Theory, answering the three research questions and identifying key elements of context and mechanisms which are shaping CF care delivery and experience in the post-ETI era. The thesis concludes in Chapter 11, with recommendations for specialist CF service providers in the UK and outlines the study's contribution to knowledge.

2. Background

2.1 Introduction

In this chapter, I provide a background to key topics which inform the importance and setting for this study. First, I discuss the scale of the challenges posed by providing care for people with long-term conditions and particularly focus on medicines adherence. Research findings in specific long-term conditions, such as CF, may inform developments across other, more prevalent long-term conditions, such as asthma.

I then give an overview of the clinical manifestations of CF and how supporting adherence to inhaled medicines is considered an important aspect of care optimisation. With this in mind, I then describe the development of CFHealthHub, a multi-centre learning health system, across UK adult CF Centres and academic partners. I describe the different aspects of the CFHealthHub programme, including a community of practice, a digital platform and behaviour change intervention, and how the programme was shaped by different complexities and contextual factors.

2.2 Long-term conditions

2.2.1 The scale of the problem

A long-term condition is "*a condition that cannot, at present, be cured but is controlled by medication and/or other treatment/therapies*" (1). Examples include CF, diabetes, hypertension, and asthma. In 2012, it was estimated that between 15 and 26 million people in the UK (30 to 40% of the total population) suffered from one or more long-term conditions (2, 3). Providing care for people with long-term conditions accounts for 70% of the total National Health Service (NHS) spend, which includes 50% of all General Practice (GP) visits, 64% of secondary care outpatient appointments and 70% of all inpatient bed days (1). Despite this proportion of healthcare utilisation, individuals with long-term conditions themselves are likely to spend less than 1% of their time in contact with health professionals, meaning they are required to self-manage for the majority of their time (4). Supporting self-management is therefore a key step to optimising long-term condition care and forms a key aspect of personalised care.

2.2.2 Personalised care

The requirement to personalise care is an important aspect of supporting people with long-term conditions. For acute (short-term) conditions, such as pneumonia, there may be an initial, significant disruption to the person with pneumonia's life (i.e. an acute period of ill health), which requires them to adjust their other commitments for a fixed period whilst they recover. Whilst personal contexts differ, the disruption from a short-term illness is mostly short-lived and may either involve a short hospital stay or short-term medication. People with long-term conditions are required to self-manage daily and must incorporate these required behaviours into their lives. For example, people with diabetes are asked to monitor their blood sugar levels, and people with CF or asthma are asked to adhere to regimens of prescribed inhaled medicines.

Many people with long-term conditions do not want to be in hospital unless absolutely necessary and want to be supported to self-manage (5). Supporting self-management is involves engaging people in decisions about their health, which may depend on the quality of information provided and both their desired and realised level of involvement (6, 7). The NHS Long-Term Plan (2019) also outlined an ambition to improve access to evidence-based self-management tools or interventions (8).

2.2.3 Patient activation and engagement

Patient activation is a behavioural concept, defined as the "*an individual's knowledge, skill, and confidence for managing their health and health care*" (9). An estimated 25-40% of the population have low levels of activation (10). Patients with higher levels of activation tend to have better health outcomes, demonstrate better self-management behaviour and use less unscheduled emergency care (11-14). Interestingly, patient activation levels have demonstrated superior predictive value for health outcomes compared to more classically considered socio-demographic determinants of health, such as age and ethnicity (15). A key self-management behaviour that is likely related to activation, is medicines adherence.

2.2.4 Medicines adherence

The taking of medicine is a key facet of care in long-term conditions where efficacious treatments exist. Not taking a medicine as prescribed is considered a key reason for suboptimal clinical response (16, 17). The extent to which someone with a long-term condition takes treatment is dependent on a complex bio-psycho-social process, considering the properties of the medicine but also the person's choice and behaviour. Three terms commonly used to describe treatment-taking are compliance, adherence, and concordance.

Compliance refers to "*the extent to which the patient's behaviour matches the prescriber's recommendations*" (18). This term can be problematic as it may perpetuate a paternalistic approach to medicine, where decisions are made by a clinician and non-compliance may be considered an inability of the person to understand a treatment regimen or an irrational, maladaptive behaviour (19).

Concordance recognises that clinicians and people with a condition can have equally pertinent views on treatment, which may contrast, and that a treatment regimen is agreed on consensus (18). This view encourages an open, two-way discussion but also risks the situation where a person is choosing to either take (or not take) a treatment in contravention to evidence-based medical recommendations. This may result in people choosing treatments which are less efficacious or potentially harmful, creating an ethical dilemma for care providers.

Adherence can be defined as the extent to which a person's behaviour, such as taking medicines or changing their lifestyle, corresponds with agreed recommendations from a health care provider (20). Explicitly stating that recommendations should be agreed between the person and their health care provider supports the partnership theme underpinning personalised care. Adherence can therefore be considered a continuum, from complete refusal to take prescribed medicines, to partial or full following of a treatment regimen. In contrast, compliance/non-compliance is often considered binary. There is also a distinction between "intentional non-adherence", where there is a considered decisions not to take treatment, and "unintentional non-adherence", where

other barriers, such as competing priorities/pressures (e.g. work or family commitments) prevent someone taking medicines as prescribed (21, 22).

The dependence of the adherence definition on agreement can be problematic, should people with a condition hold strong beliefs which compete with the evidence-based opinion of their care provider. The concept of "informed adherence" looks to address this balance but is dependent on the person being provided sufficient information in such a way as to develop adequate self-knowledge, alongside self-efficacy around treatment taking and the ability to take a scientifically reasoned approach to decision-making (23). In this thesis, in keeping with current medical culture, I use the term adherence, recognising the limitations of this construct.

In developed countries, adherence to medicines is estimated at around 50% and adherence problems are observed whenever there is the need for self-administration of medicine (20, 24). Thresholds of defining "good" and "bad" adherence are used, but without an evidence base in many cases. In reality, categorising adherence as "good" or "bad" based on arbitrary measurement may be inappropriate, as the dose–response phenomenon, common to most medicines, is a continuum function (20). Adherence is a key aspect of self-management, therefore interventions which support adherence can be considered a steppingstone to optimising long-term condition care.

2.2.5 Interventions to support adherence

Interventions which support adherence are usually complex, including features such as a non-linear causal pathway between intervention and outcome, several interacting components/dependencies, and the inherent need to balance fidelity and tailoring (24-26). The Medical Research Council (MRC) Framework for Developing and Evaluating Complex Interventions advises theory-informed intervention development, continual refinement and concurrent implementation, evaluation, and health economic assessment (25, 27, 28).

Up to 50% of health interventions with proven benefits are never implemented in routine care. For those which are, there is an average delay of 17 years between the original research and implementation (29, 30). Implementation science is a field dedicated to studying and promoting the uptake of evidence-based practices into routine care (31, 32). Implementation scientists recognise that classical "efficacy" trials, which identify whether an intervention works or not, may not identify implementable interventions. Therefore, innovatively designed "effectiveness" trials, which identify the extent to which an intervention works, may be more appropriate for complex interventions (32, 33). The setting for the study in this thesis was the implementation of a complex intervention to support medicines adherence for people with CF (pwCF), which had successfully improved adherence in a recent randomised controlled trial (RCT) (34).

2.3 Cystic fibrosis

2.3.1 Epidemiology

CF is an archetypal, life-limiting, long-term condition, resulting from mutations in the CF transmembrane conductance regulator (*CFTR*) gene, affecting around 160,000 people worldwide (35-37). There are approximately 11,000 pwCF in the UK, with around 200 new diagnoses per year, of which the majority are identified by newborn screening (38). The median age of pwCF in the UK is 22 years and around 7,200 are ≥ 16 years-old, where CF "adulthood" is usually defined in the UK (38). The median age of death in 2023 was 46

years and median predicted survival age for a child born with CF in 2024 was 64 years (38).

2.3.2 Respiratory manifestations

The *CFTR* gene codes for the CFTR protein, which is involved in the transport of chloride and bicarbonate ions across epithelial cell membranes (39-41). Disruption of ion channel function results in the production of thick mucus in multiple organ systems. The two systems which have the most common and significant manifestations of CFTR protein dysfunction are the respiratory and pancreatic systems (42). Structural organ damage is recognised early in infancy, even before clinical symptoms of CF are detected (43, 44).

Lung function is usually measured by the forced expiratory volume in 1 second (FEV_1). This value, in litres, is then typically converted to percentage of predicted FEV_1 ($\%FEV_1$), accounting for age, gender, height and ethnicity, using the Global Lung Initiative (GLI) equation (45). For example, a 20-year-old Caucasian man with CF, with a height of 180cm and an FEV_1 of 3.5L would have a %FEV1 of 73.2%. If the same man had an FEV_1 of 3.0L, $\%FEV_1$ would be 62.8%. If their FEV_1 remained static at 3.0L then their % FEV_1 at the age of 25 would be 63.1%.

In this thesis, in keeping with the preferred terminology of the CF community, the terms "lung function," "FEV_1" and "$\%FEV_1$" are used somewhat interchangeably when describing health measures and outcomes. Description of percentage changes in lung function and/or FEV_1 represent an absolute percentage point change in $\%FEV_1$ rather than a relative percentage change. For example, "a 2% decline in FEV_1" or "a 2% decline in lung function" would both describe a reduction in $\%FEV_1$ from 34% to 32%.

Respiratory mucus, produced by epithelial cells which line the airways, captures inspired pathogenic particles, transporting them back up the airways via the muco-ciliary escalator, allowing them to be removed via cough or swallow (46). CFTR protein dysfunction results in the production of dehydrated, thick mucus which cannot be cleared as effectively by the muco-ciliary escalator. Mucus stasis in hypoxic small airways promotes persistence of pathogenic bacteria, such as *Staphylococcus aureus*

and *Pseudomonas aeruginosa* (42, 47). In line with CF literature and the language used by the UK CF community, I refer to *P. aeruginosa* using only its genus "*Pseudomonas"* throughout the rest of this thesis. Other species of *Pseudomonas* exist, but only infection with *P. aeruginosa* is considered clinically relevant in CF.

Pseudomonas is the most common respiratory pathogen in adults with CF. When it is first detected, eradication treatment with antibiotics is recommended (48). *Pseudomonas* is characterised by the ability to persist despite treatment and eradication is often unsuccessful, resulting in chronic *Pseudomonas* infection (49). Chronic *Pseudomonas* infection is associated with an increased rate of lung function decline and earlier mortality (50, 51). On the other hand, for pwCF with chronic *Pseudomonas* infection, long-term suppressive treatment with inhaled antibiotics is associated with improvements in lung function and reduced frequency of pulmonary exacerbations (52, 53). Long-term inhaled antibiotics are therefore recommended for all pwCF with chronic *Pseudomonas* infection (54).

Pulmonary exacerbations describe acute deterioration in respiratory symptoms (such as cough, mucus production and breathlessness) with an associated drop in lung function (42). Repeated exacerbations drive cumulative lung damage, and approximately a quarter of pwCF do not recover to their pre-exacerbation level of lung function (55, 56).

Daily airway clearance physical therapy is recommended for all pwCF to promote expectoration of mucus (57, 58). If there is evidence of lung disease then daily inhaled therapy with mucolytic medicines, such as dornase alfa (DNase), hypertonic saline or mannitol is recommended, which cleave and rehydrate mucus to promote clearance (59, 60). Use of any of these three agents is associated with reduced pulmonary exacerbations, increased lung function and increased quality of life (61-63). In the UK, DNase is prescribed more commonly than hypertonic saline or mannitol (38).

Should lung function continue to decline, despite the optimised use of aforementioned treatments, then PwCF may be considered for lung transplantation (64, 65). Prior to the Coronavirus disease 2019 (COVID-19) pandemic over 90 lung transplants were performed for pwCF each year in the UK, though these numbers have since reduced, with

only 21 being performed in 2023 (35, 38). PwCF have better outcomes post-transplant than those with other conditions, with a 5-year survival rate of approximately 60% and relatively greater improvements in quality of life (66-70).

2.3.3 Pancreatic manifestations

Pancreatic CFTR protein malfunction also manifests as thick secretions, impairing release of digestive enzymes into the gastrointestinal tract. Impaired chloride and bicarbonate transfer results in the secretion of more acidic and lower volume fluid, causing digestive enzymes to precipitate, rather than remain soluble. These precipitations can then cause obstruction of pancreatic ducts, leading to chronic inflammation and atrophy (71). Pancreatic disease is a very early manifestation of CF, even detectable in utero (72).

In clinical practice, it is commonplace to classify pwCF by a “pancreatic sufficient” or “pancreatic insufficient” phenotype, which appears directly influenced by genotype (73). Approximately 85% of all PwCF are pancreatic insufficient, with over 60% being pancreatic insufficient at the point of diagnosis through newborn screening (74, 75). Malabsorption, as a result of pancreatic insufficiency, leads to malnutrition, and contributes to “failure to thrive”, which is commonly described in children with CF (76).

Orally administered pancreatic enzyme replacement therapy is recommended for all pwCF with pancreatic insufficiency (77). Whilst there is a lack of clinical trial data to inform the ideal diet for pwCF, good nutrition is associated with better outcomes (78). Therefore, typical recommendations include a high-volume, high-calorie diet with consideration of vitamin supplementation, usually overseen by a specialist CF dietician. If these measures are ineffective then oral nutrition supplementation is recommended, though there is a lack of evidence relating to its impact on outcomes (79, 80). Should oral supplementation be ineffective, then parenteral feeding, via nasogastric, nasojejunal or gastrostomy tubes is considered (79) .

CF-related diabetes (CFRD) is distinct from other forms of diabetes, with insulin deficiency from pancreatic islet cell damage as a larger driver of disease than insulin resistance (81, 82). As CFRD does not tend to present with the typical osmotic symptoms

of type 1 diabetes mellitus (e.g. polydipsia, polyuria and weight loss) routine screening from 10 years of age is recommended (60). Screening for CFRD with serum glycosylated haemoglobin (HbA1c) and oral glucose tolerance testing is recommended as part of the CF Annual Review (83). The newer method of continuous glucose monitoring is now the most widely used screening test for CFRD in the UK (35, 60, 84). Over a third of adults with CF have CFRD, and it is associated with worse outcomes, including mortality and chronic infection (38, 85, 86). The mainstay of CFRD management is insulin therapy, as opposed to oral diabetic agents, though a recent Cochrane review highlighted a lack of high-quality long-term evidence (54, 87). Eighty five per cent of people with CFRD in the UK are treated with insulin (35).

2.3.4 CFTR modulators

The aforementioned treatments (inhaled medicines, pancreatic enzyme replacement, nutritional supplementation, and insulin) are designed to compensate for the physiological abnormalities caused by defective CFTR protein. Since the discovery of the *CFTR* gene in 1989, there has been an interest in developing medicines which may modulate the production and function of the CFTR protein itself (37, 88). This drug discovery journey was complicated by the recognition of over 1500 pathogenic variants in the *CFTR* gene, grouped into distinct 6 classes, meaning that an individual medicine acting on the CFTR protein may only be effective for people with specific pathogenic variants. Since 2012, four oral CFTR modulator (CFTRm) medicines have been made commercially available and have revolutionised the care of pwCF.

The first therapeutic CFTRm, ivacaftor (Kalydeco®, Vertex Pharmaceuticals, Boston, MA, USA), demonstrated improvements of 10.6% in FEV_1, increases in weight and reduced rate of pulmonary exacerbations in a pivotal RCT (89). Ivacaftor was subsequently approved for use in Europe in 2012 (90). However, whilst highly effective, only 5% of the UK CF population were eligible for ivacaftor, as eligibility was restricted to those with specific, less common *CFTR* pathogenic variants (91). The uptake of ivacaftor for eligible pwCF was over 80% and improvements in weight, quality of life, infections and exacerbations were sustained in other RCTs, open-label extension trials and real-world

studies (92-97). Five-year data also demonstrated reduced need for lung transplantation (98).

A second CFTRm, combination lumacaftor/ivacaftor (LUM/IVA, Orkambi®, Vertex Pharmaceuticals), was trialled in in pwCF who were homozygous for the most common *CFTR* pathogenic variant (Phe508del). Studies demonstrated an initial 4% increase in FEV_1, lower rates of pulmonary exacerbation and reduced rate of FEV_1 decline (99, 100). LUM/IVA was also efficacious in people with more severe lung disease, who were excluded from the earlier trials of ivacaftor (101).

A third CFTRm, combination tezacaftor/ivacaftor (TEZ/IVA, Symkevi®, Vertex Pharmaceuticals) demonstrated similar results to LUM/IVA, with a 3.4% increase in FEV_1 and fewer exacerbations in pwCF with homozygous Phe508del *CFTR* pathogenic variant (102). TEZ/IVA was also studied in pwCF with heterozygous Phe508del *CFTR* pathogenic variant and an additional "residual function" *CFTR* pathogenic variant, and led to a 6.5% improvement in FEV_1 compared to placebo, which was 2.1% higher than the improvement seen in participants randomised to take ivacaftor monotherapy (103). LUM/IVA and TEZ/IVA are licensed in the UK, as is ivacaftor, dependent on age and genotype (104).

Elexacaftor/tezacaftor/ivacaftor (ETI, Kaftrio®, Vertex Pharmaceuticals) was the first triple combination CFTRm. The landmark RCT demonstrated a 14.3% increase in FEV_1, surpassing improvements seen with ivacaftor (105). ETI also demonstrated additional benefits in those who already had CFTRm exposure (106). In August 2020, ETI was commissioned in the UK and 80-90% of pwCF are eligible to receive it, including those who were eligible for and/or prescribed earlier CFTRm (104). Of all pwCF prescribed CFTRm in the UK , over 90% are now prescribed ETI (38).

Whilst ivacaftor, LUM/IVA and TEZ/IVA may have transformed health outcomes for many of the pwCF who were eligible for them, it was the availability and widespread eligibility for ETI which revolutionised CF care in the broadest sense and for the most people. ETI is generally well tolerated and real-world data support that the improvements in lung function demonstrated in the clinical trials may be sustained out to four years (107-109).

In this thesis, the term *post-ETI era* refers to the period following the introduction and widespread availability of ETI in the UK from August 2020 onwards, rather than implying a time in which it is no longer available.

The improvements in lung function seen in clinical trials, however, appear to exceed those seen in real-world data. The average increase in lung function in pwCF starting ivacaftor, using real-world data, was approximately 6%, showing an efficacy-effectiveness gap when compared to the 10.6% improvements seen in the 2011 RCT (89, 98). Furthermore, within five years, lung function appeared to decline back to pre-ivacaftor levels, despite sustained increases in weight. This suggests that the observed pattern may not simply reflect a 'wearing off' effect of the drug. (110). An alternative explanation may relate to the recognised reduction in the use of inhaled medicines among pwCF prescribed CFTRm, despite pre-existing inhaled medicine regimens being continued alongside CFTRm in the key clinical trials. (111-114).

There is considerable interest in the CF community in the potential of ETI to reduce the overall treatment burden for pwCF, which may be driving this reduction in the use of inhaled medicines (115). Studies examining the long-term impacts of withdrawing inhaled medicines are ongoing. Preliminary results from the SIMPLIFY study, showed that, in pwCF prescribed ETI with a near-normal lung function (mean %FEV_1 = 96.9%), the withdrawal of inhaled mucolytics did not result in a reduction in lung function at a very short 6-week time period (116). Whilst this gives confidence to the potential of CFTRm to allow some pwCF to reduce their treatment burden, the short time frame and near-normal lung function in the study cohort means clinicians are advised to use this evidence with caution when making clinical recommendations (79, 117). The recent European Cystic Fibrosis Society (ECFS) Standards of Care highlight the important role of inhaled medicines, particularly in those with moderate-severe lung disease and the lack of evidence to confidently recommend therapeutic rationalisation via treatment withdrawal (118). This uncertainty became a key area for theory development throughout the work of this thesis.

2.3.5 CF care delivery in the UK

At the commencement of this study, commissioning of NHS services for pwCF was informed by the CF Trust "*Standards for the Clinical Care of Children and Adults with Cystic Fibrosis in the UK*", first published in 2001(119). The CF Trust is the only UK-wide CF charity, whose mission is "*to make sure everyone with CF can live a life unlimited*" (120). The CF Trust supports research, campaigns for change, and produces information to benefit both clinicians and pwCF.

In 2001, only a third of the approximately 6,500 pwCF in the UK were adults (defined as ≥16 years of age) and it was recommended that care be delivered at specialist CF Centres. All care was intended to take place face-to-face, which created challenges for pwCF who live far from a specialist Centre. Recognising this, the CF Trust advised that, children and young pwCF (but not adults) from remote areas could be seen in a local clinic which was also attended by health care professionals from the nearest specialist CF Centre.

Each specialist CF Centre should be staffed by a multi-disciplinary team (MDT) covering each of the following disciplines: physicians; clinical nurse specialists; physiotherapists; dieticians; social workers; psychologists; pharmacists; clerks and secretaries. Fifteen functions of a specialist CF Centre were outlined, including provision of specialist clinical services for pwCF, psychosocial support for problems related to CF and ensuring smooth transition from paediatric to adult care. Furthermore, staff were expected to participate in research, attend national meetings and share data in the UK CF Database. Centres were asked to ensure adequate capacity to permit same-day admissions for pwCF who require inpatient care, for example when experiencing an exacerbation, and adhere to strict hygiene and separation procedures to reduce the risk of nosocomial infection or person-to-person transmission of dangerous pathogens, such as *Pseudomonas*.

Regular outpatient appointments were recommended at least every 3 months but ideally every 6-8 weeks, where specific clinical outcome measures (e.g. lung function, weight) and sputum samples are collected and current symptoms reviewed. The more

structured “Annual Review” appointment remains a cornerstone of care where additional investigations, such as blood glucose monitoring and chest x-rays are performed once a year.

The second edition of the CF Trust Standards of Care (2011) built on this and explicitly recommended models of care (121). Key relevant features included a sustained commitment to delivery of care under the supervision of recognised specialist CF Centres and, whilst shared care with a local clinic may be used for children, it should only be offered in exceptional circumstances (such as long travelling distances) for adults. When this is the case, at least the Annual Review should be undertaken at a specialist CF Centre and at least one other review at the local clinic must be attended by members of the specialist CF Centre MDT.

This document also outlined minimal whole time equivalent staffing levels for each MDT discipline based on the number of pwCF in the specialist CF Centre population. Routine outpatient appointments every 2-3 months was recommended, though frequency could be increased if necessary. The 2017 Nationale Institute for Health and Care Excellence (NICE) guideline for the diagnosis and management of CF mostly aligns with CF Trust Standards of Care but adds that telemedicine or home visits for routine monitoring can be considered and the frequency of routine appointments for adults is somewhat relaxed to every 3 to 6 months (60).

The area of investigation in this study is specialist adult CF services in the UK, where care is currently delivered across 26 specialist CF Centres and two standalone clinics (one in London and one in Cornwall). Midway through this study, in August 2024, the CF Trust published an updated third edition of the CF Standards of Care which included a new, specific emphasis on person-centred care and the role of virtual consultations and remote monitoring in light of the impact of ETI alongside digital acceleration resulting from the COVID-19 pandemic (122). The CF Trust advise that *“The needs of most people with CF are likely to be met by a ‘blended model’ of virtual and face-to-face appointments. A bespoke approach should be considered on a case-by-case basis.”* Hence, exploration of the views of clinicians and pwCF, as sought in this study provided

useful insights into the factors that might influence the bespoke and personalised approach to decision-making.

There were further insights in the Standards of Care third edition which may have important implications for care delivery. Real-world evidence demonstrates that CFTRm, and in particular ETI, have reduced the number of pwCF experiencing pulmonary exacerbations and thus reduced the demand for hospital admissions for intravenous (IV) antibiotics (123-125). Whilst this has reduced the inpatient workload for specialist CF Centres, workloads in other areas have increased, such as remote monitoring and prescribing. Furthermore, whilst the numbers of children with CF is anticipated to remain stable, the numbers of adults with CF will continue to increase owing to improved health outcomes and reduced mortality.

Recognising the changes that CF care is undergoing, it is recommended that these Standards of Care are reviewed after 3 years, rather than waiting 10 years between reviews, as was previously done. Additionally, the ECFS produced four Standards of Care documents towards the end of this study, which are largely consistent with UK guidance (79, 118, 126, 127). The recommendations in these documents are considered in the discussion of work presented in this thesis.

2.3.6 CF as a testbed for optimising long-term condition care

As a condition, CF has some characteristics which can make for a useful testbed when it comes to developing an understanding of how to optimise the care of people with long-term conditions. Almost all pwCF in the UK are “known”, due to a combination of standardised newborn screening for all babies and the UK CF Registry, which collects data on over 99% of the UK CF population, and is maintained by the CF Trust (128). This provides accurate population denominators for epidemiological studies exploring issues such as health inequalities and the effects of changing models of care on outcomes.

Culturally, CF has a rich history in quality improvement and data collection, for example through national registries and sharing of information and best practice (129). Care for pwCF is provided only at a limited number of specialist CF Centres, meaning national communities of practice can be established and innovation scaled across the nation for

a much lower resource cost than in the case of other conditions, such as asthma, where care is provided across hundreds of primary and secondary care settings. There are other inherited conditions, such as primary ciliary dyskinesia, which may have some similarities to CF, but the case volume and number of specialist care Centres are too small for robust evaluation of implementation at scale.

CF is genetically determined, meaning its incidence is not influenced by socio-economic status. This makes CF a valuable condition for studying how health inequalities arise, providing insights that can inform effective interventions for pwCF and potentially extend to other long-term conditions (130). Interventions to improve the quality of care in long-term conditions are complex, and as such no one intervention could be directly taken from one setting to another with the expectation of the same outcomes without paying attention to the contextual factors that may influence the outcomes (131). Therefore, using CF as an exemplar, may offer insights and generate vicarious self-efficacy to likeminded people working to improve care in other long-term conditions (132).

There are, however, some limitations in broadly generalising findings from studies in CF. Compared to other long-term conditions such asthma or hypertension, the UK CF population are younger and overwhelmingly Caucasian. Whilst the lack of social gradient for the incidence of the condition is helpful, it also does differentiate the CF population from other long-term conditions with a clear social gradient for incidence. Additionally, CF care in the NHS is relatively well-resourced compared to other long-term conditions, such as asthma, meaning that care models which are dependent on the CF resource/funding structure may not generalise to other conditions. Associations of pwCF have played a crucial role in the shaping of CF care and research, beyond their support of pwCF and their families/carers (133). Again, other disease areas with less active or effective advocacy groups may not be able to replicate advancements seen in CF.

Over the past decade, clinicians, academics and pwCF across multiple Centres collaborated to develop the CFHealthHub learning health system: a community of practice, digital platform and behaviour change intervention aiming to enable pwCF to live as normal a life as possible by supporting adherence to inhaled medicines.

The study presented in this thesis began in 2022, as CFHealthHub was in an implementation phase, following completion of an RCT demonstrating that the CFHealthHub intervention improved adherence to inhaled medicines for pwCF compared to usual care (34). Next, I introduce CFHealthHub and discuss the journey from conception to implementation.

2.4 CFHealthHub

2.4.1 Introduction

CFHealthHub was conceptualised following improvement work in a single adult CF Centre. From 2012 to 2016, members of the adult CF MDT identified that supporting adherence to inhaled medicines would allow them to achieve a shared goal, which was "*to enable pwCF to live as normal a life as possible*". Further study and academic collaboration led to the development of the CFHealthHub complex behavioural intervention and digital platform, which intended to support adherence to inhaled medicines through habit formation. Following a successful 2-centre pilot study in 2016 (134), a full 19-centre RCT was undertaken from 2017 to 2019, which demonstrated that the CFHealthHub intervention increased adherence to inhaled medicines by a mean of 9.5 percentage points compared to usual care, which was sustained to 12 months (34).

I joined the CFHealthHub programme in August 2021 as a CF Clinical Research Fellow. At this point, CFHealthHub was functioning as a learning health system, with the intention to drive quality improvement and research across multiple UK adult CF Centres. A learning health system can be defined as "*a health system in which outcomes and experience are continually improved by applying science, informatics, incentives and culture to generate and use knowledge in the delivery of care*"(135). Learning health systems are predicated on a continuous cycle with three recurring processes (135). Firstly, "Practice to Data", where data is captured from routine healthcare practice, e.g. within an electronic medical record (EMR) with highly structured input fields. Secondly, "Data to Knowledge" where insights are generated from the captured data e.g. recognising patterns in healthcare utilisation within a hospital. Thirdly, "Knowledge to

Practice", where these insights can be used to develop improvement initiatives, e.g. new protocols for clinical staffing levels based on resource usage.

In a 2022 Health Foundation report, CFHealthHub was recognised as the only disease-specific learning health system with national reach in the UK (136). In April 2022, when I officially started my PhD programme, 14 UK adult CF Centres were part of CFHealthHub.

In this section, I describe how complexity shaped the development and evolution of CFHealthHub using the NASSS framework, which is designed to support evaluation of complexity in the development and implementation of health and care technologies (137). Non-adoption (N) refers to a failure for individuals or organisations to make the changes required to implement an innovation, whereas abandonment (A) refers to when attempts to implement changes are not continued to completion. Scale-up (S) refers to local attempts at implementing successful innovations from a smaller setting in larger settings, whereas spread (S) refers to similar attempts at implementation in more distant settings. Finally, sustainability (S) refers to the need to sustain the innovation long-term, at either the individual or system level (137).

Innovations characterised by complexity across any or all of seven domains within the NASSS framework rarely, if ever, become mainstreamed. These seven domains are captured in Table 1 and include: the condition; the technology; the value proposition; adopter systems; health and care organisations; wider systems and continuous embedding and adaptation over time.

Table 1: Overview of NASSS framework domains

NASSS Framework domain	Brief description
The condition	The clinical, psychological and socio-cultural characteristics of the health condition for which the intervention is designed.
The technology	The material features of the technology, as well as the technical knowledge and skills required for its use.
The value proposition	The anticipated value of the intervention from both a supply-side perspective (e.g. developers, investors) and a demand-side perspective (e.g. patients, clinicians, commissioners).
The adopter system	The individuals or groups expected to adopt the technology, such as staff, patients and carers, and the potential implications for roles, relationships and identities.
The healthcare organisation	The organisational capacity for innovation, including technological readiness, and the degree of change required to existing structures, processes and workflows
The wider system	The broader institutional and policy context, encompassing regulatory requirements, professional norms and inter-organisational networks.
Adaptation over time	The extent to which the intervention is capable of evolving in response to contextual shifts and supporting long-term sustainability.

NASSS = Non-adoption, Abandonment, Scale-up, Spread and Sustainability.

Considerations within each domain can be simple (few components, fairly predictable), complicated (many components, but largely predictable) or complex (many components interacting dynamically and unpredictably) (138). Implementation is more likely to fail when there is more complexity. Using this framework allowed exploration of context surrounding CFHealthHub, which is considered essential for successful implementation (139). By understanding where complexity exists, developmental priorities can be set to address complexity and support implementation. The NASSS framework is specifically recommended for the evaluation of complexity in learning health systems (135).

According to established narrative study principles, my approach to the work in this section was designed to weave together a sequence of events using repeated interviews with a single source, the CFHealthHub programme director, ultimately aiming to highlight challenges and opportunities through identification of complexity (140). Whilst the interpretation of how the context changes affected CFHealthHub was my own, this was inevitably influenced by the information provided by the programme director. In particular, the programme director advised which complexities had the biggest influence on the development and evolution of the programme from his perspective. These distinct complexities are described as discrete “epochs” in this chapter and are summarised in Table 2.

Table 2: Overview of key epochs in the CFHealthHub journey

Epoch	Brief description
1) Inception of CFHealthHub and RCT	CFHealthHub was established to develop a complex behaviour change intervention, supported by a bespoke digital platform, to promote adherence to inhaled therapies among pwCF. A multi-centre RCT was designed to evaluate its clinical impact.
2) Transition to learning health system	CFHealthHub collaborated with NICE to co-develop the first national Quality Indicators for CF, related to average levels of adherence at a provider-level. These indicators were intended to support system-level quality improvement, leveraging CFHealthHub resources to promote implementation following the RCT.
3) RCT failed to meet primary endpoint	Although the RCT demonstrated improved adherence, it did not produce a statistically significant reduction in pulmonary exacerbations, whereas a significant reduction in exacerbations was assumed in the pre-trial economic modelling. In response, a new workstream was introduced to explore the cost-saving potential reducing excess medicines waste using CFHealthHub adherence data.
4) COVID-19 Pandemic	The pandemic precipitated rapid changes to NHS funding mechanisms, rendering the original implementation funding strategy unviable. However, the wider adoption of remote monitoring created new opportunities for integrating CFHealthHub into routine care.
5) Introduction of ETI	The introduction of ETI, a highlight effective CFTRm with broad eligibility fundamentally altered the clinical landscape, introducing new uncertainties regarding the ongoing role of inhaled therapies and, by extension, the relevance of adherence support through CFHealthHub.

RCT = randomised controlled trial. pwCF = people with cystic fibrosis. NICE = National Institute of Health and Care Excellence. COVID-19 = Coronavirus disease 2019. NHS = National health Service. ETI = elexacaftor/tezacaftor/ivacaftor. CFTRm = CF transmembrane regulatory protein modulator.

This influence leaves the description of complexity open to bias based on the programme director's personal experiences and beliefs. To mitigate the potential impact of that bias in this thesis, subsequent work was designed to collect data from other CF clinicians across multiple CF Centres and pwCF themselves. As this descriptive chapter was not the main focus of this thesis, and few key individuals from CFHealthHub's inception remained involved, using data from the programme director, who had been involved in all aspects of CFHealthHub from the beginning, was chosen as the optimum approach to provide the depth of contextual information required for this study and describe important aspects of the vision and development.

Within CF, the benefit of understanding a single leader's experience and the lessons they learnt in the process, albeit in the context of clinical trials, is recognised (141). Prior to submission of this thesis, three others member of the CFHealthHub central team: a

research physiotherapist who was involved in intervention development, study planning and conduct and later implementation as a steward of the CFHealthHub community of practice; a digital health software expert who was involved in development of the digital platform; and another clinical academic reviewed the content of this section to validate my interpretation of the programme director's account and ensure there were no overt omissions or inaccuracies.

2.4.2 Epoch 1: Inception of CFHealthHub and RCT (2014 to 2019)

In 2012, clinicians in the Sheffield adult CF MDT used "microsystems" methodology to support quality improvement (142). The microsystems approach to improvement, which is often used in health care, involves an initial assessment of the system, repeated cycles of change and testing of potential solutions before progressing to standardisation and ongoing audit/evaluation (143).

The first step is assessing the system through the lens of the 5 P's (patients, professionals, processes, patterns, purpose). This requires input from a wide range of stakeholders, not only senior leadership and management (144). A series of meetings over several weeks involved representation from all disciplines in the MDT. This approach was designed to flatten the traditional medical/management hierarchy and provide a comprehensive assessment of the current system through incorporating a range of views. The primary outcome of this exercise was the agreement of a shared purpose of the MDT: "*to enable pwCF to live as normal a life as possible*."

Hospitalisation due to pulmonary exacerbations was identified as a key disruptor for the lives of pwCF. Inhaled medicines had the potential to reduce the rate of pulmonary exacerbations (53, 54). Lower adherence to inhaled medicine regimens was associated with increased rates of exacerbation and hospitalisation (145). Therefore, supporting adherence was chosen as the focus for the improvement work and shaped the design of CFHealthHub.

A seminal CF study in 2011 found that, when adherence to inhaled medicines was assessed using objective measures from nebuliser devices with electronic data capture capability, median daily adherence to the prescribed regimen was 36%, meaning that the

typical person in the studied population was only taking one in every three of their prescribed doses of inhaled medicine each day (146). Alternative methods of adherence measurement in the study, including clinician report and self-report from pwCF, gave higher values (median adherence approximately 60% and 80% respectively), highlighting the value of using objective adherence data where available.

CF clinicians collaborated with software developers and digital health experts at the University of Manchester to develop a bespoke digital platform for CFHealthHub which was compatible with the two nebuliser devices with electronic data capture capability approved for use in the UK: the I-neb Adaptive Aerosol Delivery System (Philips Respironics, Chichester, UK), and eFlow Technology nebulisers with an eTrack data-logging Controller (PARI Pharma GmbH, Starnberg, Germany), subsequently referred to as “I-nebs” and “eTracks” respectively.

Collaboration with academics, psychologists, and behaviour change experts led to the development of a behavioural intervention, co-designed with pwCF, which aimed to help pwCF develop habits for taking inhaled medicines to drive increases in adherence (147). The CFHealthHub digital platform enabled real-time feedback on attempts to increase adherence, which were guided by the behavioural intervention.

I now consider where complexity was located using the domains of the NASSS framework. Please note, I am considering this based on the knowledge and evidence available during the time frame of the epoch (2012 to 2016). This epoch pre-dated the introduction of ETI (2020), therefore only a small proportion of the UK CF population would have had access to earlier generation CFTRm, such as ivacaftor.

Domain 1: The condition

In 2012, there were approximately 10,000 pwCF in the UK, with a median age of 18 years and life expectancy of 43 years (148). A younger demographic, who may be expected to more easily engage with technological innovations, helped mitigate some of the complexities that might arise with an older population, where implementing health technology can be more challenging (149).

Due to resource constraints, the CFHealthHub central team decided to focus on one particular aspect of CF care: adherence to inhaled medicines. The main cause of death in CF is respiratory failure resulting from a progressive decline in lung function due to chronic infection and inflammation alongside recurrent exacerbations (74). Use of inhaled medicines in CF improves outcomes and reduces unscheduled care use, yet real-world adherence to these was in the region of 30-40% (63, 74, 146, 150-152). This underpinned the decision to focus on lung health, through supporting adherence to inhaled medicines.

As a condition with multiple manifestations, such as lung disease, pancreatic insufficiency and CFRD, there were requests to add other elements of CF care, such as blood glucose monitoring to CFHealthHub. These requests were declined in order to maintain focus on adherence to inhaled medicines. Scope creep, where there are changes to the goals or features of a digital innovation, can introduce complexity and subsequently be a barrier to successful implementation (138). By focussing on adherence to inhaled medicines, CFHealthHub reduced the complexity of requiring users to pay attention multiple competing elements within the platform.

Taking inhaled medicines as prescribed requires a long-term daily commitment, as is the case with most medicines in long-term conditions. Incorporating multiple daily treatment sessions into one's life, taking account of all other competing pressures/priorities, is complex, and as such the development of a complex behavioural intervention which could be tailored to the individual was required. Socio-culturally, in the early 2010s, supporting adherence to inhaled medicines was considered high priority in CF, and related interventions were sought (145, 150).

Domain 2: Technology

Supporting adherence relies on accurate measurement. The absence of accurate methods of measuring adherence is a significant barrier to developing adherence interventions (153). Previous studies have shown that self-report and Medication Possession Ratio (MPR) overestimate adherence for both for inhaled and oral medicines, compared to electronic data capture, which therefore is considered the optimum

method for measuring adherence (146, 154). Electronic data capture also provides date and time-logged data, providing a richer insight into how medicines are being used at the individual level. From an intervention perspective, this can allow clinicians and pwCF to identify opportune timings to take medicines with the intention to help build a routine.

Thus, in terms of the technology, it was considered essential for CFHealthHub to have access to a digital platform capable of receiving and presenting adherence data from nebuliser devices with electronic data capture capability. The CFHealthHub digital platform being device agnostic, in that it was compatible with both I-nebs and eTracks, was intended to reduce complexity in that pwCF and clinicians could choose between either device based on preferences and local resource.

To reduce the complexity data collection within the digital platform, nebuliser usage data was uploaded via a cloud-based server without the need for user-initiated data input. In previous studies of digital health platforms, as few as 1% of people persistently engage with platforms requiring manual data input, and passive data capture has been more successful (155-157). Whilst the system was still complicated, requiring a functioning nebuliser device with an active network connection to the cloud-based server, the additional complexity of requiring user-initiated upload for each dose of treatment taken was removed.

The data transfer mechanisms from device to cloud-based server for the I-nebs and eTracks were different, which added complexity. The I-neb passively logs nebuliser usage data, but these data must then be manually uploaded to the CFHealthHub server. Fortunately, this can be done as a batched transfer (not individually for every logged dose) and was typically done by a clinician during a clinical encounter. The eTrack had a simpler data transfer method, where data would automatically be transferred to a mobile network hub, which would be connected to a mains power supply in the home of the person using the device. As long as the hub remained powered, then data transfer from the eTrack to the CFHealthHub server would be passive (every 5 minutes), allowing for real-time data to be presented on the CFHealthHub digital platform.

Digital platforms collecting and displaying health data are often abandoned, with 39% being abandoned after as few as 10 uses (158). One reason for this may be that there is an absence of underlying theory as to how these data would lead to behaviour change, and as such key mechanisms required to sustain engagement and change behaviour are not triggered by having access to a digital record alone (159, 160). Taking this into account, CFHealthHub offered not just a digital platform, but also an accompanying clinician-delivered, theory-informed behaviour change intervention, based on the (Capability Opportunity Motivation – Behaviour) COM-B model of behaviour change, which was supported by the objective, electronically captured adherence data on the digital platform (147, 161). This was consistent with recommendations from MRC for the development of complex interventions (25).

Complexity can also exist in the knowledge and skills required to generate, use, and interpret the output of the technology, in this case the CFHealthHub digital platform. To reduce this, the platform was co-designed with a diverse group of stakeholders including pwCF to ensure the data were captured and presented in an acceptable, trusted, and understandable way to all users.

Domain 3: Value Proposition

The value proposition can be considered as upstream supply-side (to the innovation developers) and downstream demand-side (to the innovation funders/users). For the companies who manufactured I-nebs and eTracks, collaborating on the development of the CFHealthHub platform which would optimally utilise their devices functionality was an attractive proposition. Technical and financial support was obtained from both companies, though this was not the main source of funding.

The value proposition to funders, such as NHS England, related to the benefits of higher medicines adherence. Pulmonary exacerbations were associated with accelerated decline in lung function, reduced survival, reduced quality of life and increased healthcare utilisation for pwCF (56, 162-173). PwCF with higher adherence to preventative inhaled medicines had fewer exacerbations and lower healthcare utilisation (145, 151, 174). CFHealthHub was designed to support a shift in treatment

paradigm from CF from expensive, inpatient rescue treatment for exacerbations to cheaper, outpatient preventative treatment, aligning with national priorities (175).

NHS funding of digital innovations is inherently complex. A health economic analysis was undertaken which demonstrate the potential cost effectiveness of CFHealthHub (176). These projections were modelled before the RCT and demonstrate the potential savings of up to £50million over 5 years, but this was contingent on the rate of exacerbations being reduced by 50% (176).

Additionally, at this time, there was an NHS Commissioning for Quality and Innovation (CQUIN) scheme specifically intending to fund interventions which aimed to improve patient activation (177). Recognising this opportunity, measurement of patient activation was incorporated into the CFHealthHub RCT, and funding for the technology was obtained from the CQUIN scheme.

For clinicians working in CF, the value proposition was understandably less concerned with economic considerations and more focussed on desirability, clinical efficacy, and usability (137). The value proposition to pwCF was more complicated. The prognostic benefits of higher adherence were clear, but it is well-recognised that knowledge, or providing knowledge through education, is often not sufficient to change/sustain healthy behaviours, such as adherence (178, 179). Sustained behaviour change may be better achieve through multi-faceted complex interventions, and as such should be underpinned by appropriate behaviour change theory (161).

The development of the CFHealthHub intervention was underpinned by the Theoretical Domains Framework, an integrative framework consisting of 14 domains representing a range of factors which may influence behaviour (180, 181). These domains each relate to aspects of capability (C), opportunity (O) and motivation (M) which influence behaviour (B). This described together by the heuristic COM-B model and the Behaviour Change Wheel: a method for designing behaviour change interventions (161). Use of the COM-B model was recommended for designing interventions which allowed additional funding to be obtained through the aforementioned patient activation CQUIN (177).

Previous work identified barriers and facilitators to adherence in CF, which were considered in the development of the CFHealthHub intervention (182-186). A key finding was that pwCF with higher adherence tend to report habit and automaticity around their treatment, therefore the CFHealthHub intervention was designed to helping pwCF develop habits of treatment-taking (147, 187, 188). Habit formation requires an initial investment of time and attention but offers the potential of sustained behaviour with reduced perceived burden through automaticity (189, 190). The offer made by CFHealthHub was that if pwCF are prepared to work with clinicians over a period of time (anticipated 6-8 weeks) to form habits of treatment-taking, then they may develop automaticity and stand to optimise their benefits from inhaled medicines with a reduction in perceived treatment burden (189).

Domain 4: Adopter System

The adopter system pertains to all users of an intervention, so complexity was considered as it related to both clinicians and PwCF using CFHealthHub. For clinicians, adopting CFHealthHub required a shift in the treatment paradigm of CF, from rescue treatment to preventative treatment. With the historic "invisibility" of adherence and reliance on self-report, it was difficult for clinicians to pay attention to adherence in a meaningful way (175). Providing clinicians with objective adherence data, similar to providing health information to pwCF, was considered unlikely to be enough to promote adoption of this new paradigm. Implementing objective adherence data risked threatening presumed two-way trust in information sharing between clinicians and pwCF, despite objective evidence that self-reported adherence is inaccurate (146). Furthermore, within each CF Centre, there may have been historic social norms in terms of the discipline within the MDT who took ownership of adherence, and challenging these norms through CFHealthHub may have risked adding complexity.

To promote the consideration of adherence as important and worthy of attention, CFHealthHub fostered the use of a new mantra in participatory Centres: "*FEV_1, body mass index (BMI), adherence*". Mantra, originating from Sanskrit, refers to a syllable or phrase which is repeated to powerful effect (191). FEV_1 and BMI were already being collected in every CF consultation, in line with the CF Trust Standards of Care (121).

Adding “adherence” to this mantra encouraged anchoring of the concept of adherence into every CF consultation, to make paying attention to adherence habitual for clinicians (192).

Combining environmental and cognitive restructuring can accelerate and sustain behaviour change (161). A key structure in the adult CF Centre where CFHealthHub was developed was the pre-clinic MDT meeting, in which all pwCF attending that day were discussed. The meeting was restructured to promote the sharing of information pertaining to FEV_1, BMI and adherence for each pwCF discussed. This environmental restructuring supported the mantra-induced cognitive restructuring and supported clinicians to pay attention to adherence.

The intention was for pwCF to adopt CFHealthHub to support habit formation around treatment-taking and receive real-time feedback in the form of objective adherence data on the digital platform. Ideally, once a habit was formed, pwCF would not need to routinely refer to their adherence data, and these would instead be monitored by the clinical team, thereby avoiding new demands, which risk inadvertently disempowering users (193). The requirement for active self-tracking would have added complexity for pwCF and is recognised as a barrier to sustained use of digital platforms (194-196).

Most pwCF are familiar with nebuliser devices, though the introduction of the two new data-logging devices was complex for some who were well-established on older devices without electronic data capture capability. Encouraging all newly starting people to use only I-nebs or eTracks prospectively reduced complexity related to unfamiliarity with the devices.

Domain 5: Healthcare organisation

The CFHealthHub programme was conceptualised and originally developed by clinicians from the Respiratory Medicine directorate in a single NHS Foundation Trust, with no prior operational experience of the development of digital innovation. The CFHealthHub programme was initially designed as a clinical trial, passing administration responsibilities to the Research & Development department and the local University Clinical Trials Unit, who were better resourced to deliver such projects than the clinical

directorate. Developing CFHealthHub as a clinical trial necessitated the acquisition of funding for treatment costs. By aligning CFHealthHub with the patient activation CQUIN, the complexity around funding was managed (177). Additionally, a National Institute for Health and care Research (NIHR) Programme Grant for Applied Research (PGfAR) provided over £2,000,000 of funding towards intervention development and the RCT.

The CFHealthHub digital platform was developed in collaboration with the Digital Health Software team at another University, who had expertise in delivering digital health projects. With their experience of relevant information governance policy, the NHS Trust sponsor was relieved of the complexity in managing this.

An additional aspect of complexity was the time required for clinicians to pay attention to adherence data and deliver the CFHealthHub behaviour change intervention. Recognising that the amount of organisation slack would vary between Centres, funding was provided for each Centre to have a dedicated clinician, known as the "CFHealthHub Interventionist", who was given protected time to deliver the CFHealthHub intervention and contribute to necessary RCT activities. This helped reduce the complexity of each Centre incorporating this work into already-stretched clinician work schedules, as organisational slack, or lack thereof, is a recognised barrier to implementation (197). Ultimately CFHealthHub activities would need to be incorporated into clinicians' standardised job plans, but at this early stage of intervention development and testing in the RCT, it was decided that the Interventionists' time required should be funded directly by the programme.

Domain 6: Wider system

In the national medical context, there was significant interest in patient activation as a strategy for optimising long-term condition care, leading to schemes such as the CQUIN (177). By aligning CFHealthHub with this priority, support was gained with policy- and decision-makers at a national level. Furthermore, the UK CF Trust were supporting digital transformation in CF care and provided additional funding for CFHealthHub Interventionists during the pilot study (134).

Whilst this had not been explored in the literature, there were anecdotal reports that doctors, as part of the CF MDT, were less involved in supporting medicines adherence than other MDT members. Acknowledging this, the CFHealthHub "Interventionist" posts were not required to be held by doctors. Interventionists were drawn from allied health professionals with an interest in adherence, such as nurses, physiotherapists, dieticians, psychologists, and a social worker. The need to develop an intervention that could be delivered by CF clinicians from a range of disciplines introduced some complexity, compared to designing it to be delivered by a more homogenous group of clinicians within a single discipline. However, this was balanced with a reduction in complexity when it came to recruiting Interventionists, as there was a larger pool of CF clinicians who could apply. This also led to the establishment of a community of practice within CFHealthHub which was more representative of the CF MDT. Historically, and in line with the CF Trust Standards of Care, physiotherapists would have more clinical involvement with nebulisers and adherence, so a training module was created to allow Interventionists from other disciplines who may have no prior direct experience of nebulisers to learn what was required to deliver CFHealthHub in their Centre (198).

Domain 7: Adaptations over time

The "potential for reinvention" is considered a key determinant of successful implementation (199). Medicine is endlessly evolving and following the inception of CFHealthHub there were several significant changes in context which have added complexity to the programme. I describe key changes in context, such as unanticipated RCT results, changes to NHS funding due to the COVID-19 pandemic and the introduction of ETI and describe how CFHealthHub adapted and reinvented, in the aim to achieve sustainability.

2.4.3 Epoch 2: Transition to learning health system (2017 to 2019)

The MRC Complex Intervention Framework suggests considering implementation at an early stage (25). As discussed, positioning CFHealthHub as a learning health system capable of delivering quality improvement was considered an important facilitator of implementation.

Quality in health care is challenging to define and measure. NICE use two processes, quality standards and quality indicators, to represent quality. Quality standards consist of a series of statements, linked to a clinical condition or care scenario. Each statement outlines what would comprise "good quality" in that specific case. For example, for CF, there are four quality statements (200):

- PwCF have the results of all assessments they have had during the past year reviewed annually by a specialist multidisciplinary team.
- PwCF have individual rooms with ensuite facilities when admitted to hospital as inpatients.
- PwCF who have chronic *Pseudomonas aeruginosa* infection have sustained treatment with an inhaled antibiotic.
- PwCF who have clinical evidence of lung disease are prescribed DNase as the first choice of mucoactive agent.

These standards were designed to support service providers, healthcare professionals, commissioners, and pwCF to focus their attention on evidence-based practices to improve quality. CF Centres could use these standards to review their "quality" and identify areas for improvement. Whilst meeting these standards was not mandatory, the Care Quality Commission (CQC), the independent regulator of health care in England, work in partnership with NICE in developing quality standards which align with the CQC inspection model for making judgements about care provided by organisations (201).

Quality indicators, however, are designed to specifically "*measure outcomes that reflect the quality of care, or processes linked by evidence to improved outcomes*" and are used to identify where improvements are needed, set priorities for and support quality improvement, create local performance dashboards, benchmark performance against national data, demonstrate progress that local health systems are making on outcomes (202).

With this in mind, whilst the RCT was ongoing, the CFHealthHub central team contemporaneously collaborated with NICE to develop the first CF quality indicators, using the median percent adherence to inhaled medicines for all pwCF at Centre-level

(203, 204). By developing the NICE quality indicators, which recognised CFHealthHub as the platform to provide these data, the value proposition to NHS Trusts, who would ultimately be required to fund CFHealthHub in routine care, was strengthened.

With the NICE quality indicators providing justification for CFHealthHub implementation at an organisational level, consideration was given to the clinician adopter system. A core strength of CFHealthHub was in developing a community of practice, where CF clinicians from across the UK could meet regularly to share ideas, collaborate, and learn. During the RCT, weekly meetings were held to deliver updates and provide a space for discussion. Recognising the value in regular meetings in establishing relationships to develop a community of practice, these meetings continued after the RCT and evolved to cover topics including local and national improvement work, technical updates, and research planning.

2.4.4 Epoch 3: Exacerbations not reduced in RCT (2019)

The value proposition of CFHealthHub from the pre-RCT economic analysis was predicated on a reduction in exacerbation rate of 50% (176). However, in the RCT, the reduction in exacerbation rate was only 8%, which was not considered clinically or statistically significant (34). This added complexity to the value proposition to NHS trusts and therefore a new work stream was designed, aiming to inform this proposition, focussing on reduction of medicines waste using objective adherence data.

Medicines waste costs the NHS £30million per annum, of which up to 50% is considered preventable (205). Using objective adherence data to understand how much medicine is actually being used can inform personalisation of the supply process, to prevent excess supply and stockpiling. Objective adherence data were used to optimise the medicines supply process by supporting the move from regular, uninterrupted medicines delivery to a “just-in-time” model. This project, Easy Medicine for Burden Reduction and Care Enhancement (EMBRACE) demonstrated a potential saving of £822 per person/per year (206). For a Centre with a caseload of 200 pwCF, this would equate to over £150,000 per annum, more than covering the annual CFHealthHub platform costs. This informed the value proposition to NHS trusts who would be required to contribute to CFHealthHub platform costs for the first time as part of post-RCT implementation.

2.4.5 Epoch 4: COVID-19 pandemic (March 2020)

In 2020, the COVID-19 pandemic drove rapid change in the way UK healthcare was delivered. On 17th March 2020, the NHS Chief Executive, Sir Simon Stevens, wrote to all trusts advising important actions for hasty implementation (207). Included in these actions, relevant to the implementation of CFHealthHub, was a change to the traditional funding model.

The cost of providing pwCF with inhaled medicines was historically covered by a "pass-through budget", where NHS England would directly reimburse the NHS trusts of individual adult CF Centres for their expenditure. The EMBRACE project was designed to demonstrate savings in medicines supply which could be passed back to the NHS Trusts and invested in sustaining access to CFHealthHub (206, 208). The financial sustainability plan for CFHealthHub following the RCT was for it to be funded at an NHS Trust level by savings made through using CFHealthHub to reduce medicines waste, improve adherence and improve outcomes. This was detailed and approved by the NHS England Specialised Commissioning Quality, Innovation, Productivity and Prevention (QIPP) scheme in 2021.

One of the initial COVID-19 response actions from NHS England was to suspend "pass-through" budgets to minimise administrative burden. Moving to block contract payments "on account" meant that the distribution of NHS England savings, from projects such as EMBRACE, back to individual NHS Trusts required additional negotiation at each Trust, rather than centrally agreed reimbursement, which annulled the impact of savings outlined in the QIPP scheme. This added complexity to funding decisions within all healthcare organisations.

Fortunately, there was residual resource from the original CQUIN funding, which had been held in reserve to mitigate such financial turbulence. This demonstrates the importance of anticipating complexity and setting aside appropriate resources to mitigate problems whilst definitive solutions are found.

Once the original NIHR and CQUIN funding had expired, individual CF Centres were required, for the first time, to pay for access to the CFHealthHub digital platform. These

platform costs were calculated based on the size of the Centre (classified as small, medium, or large, based on their caseload) but complexity lay within the process for raising the invoices. At this time, CFHealthHub had not been formally recommended by the NHS England Specialised Respiratory Clinical Reference Group, who provide national guidance on funding CF services. Therefore, the NHS Foundation Trust which sponsored CFHealthHub declined to invoice other trusts for CFHealthHub platform costs as they would be commissioning a platform without an NHS England recommendation, so may be accountable for refunds if CFHealthHub was unable to deliver what was promised. One mitigation was that the CFHealthHub invoices in any given tax year covered the cost of the following tax year. For example, payment for invoices sent in the 2021-22 tax year would cover access to CFHealthHub in 2022-23. As NHS trusts do not allow money to be carried over to the next financial year, this was considered the most appropriate invoicing strategy to ensure sustainability of CFHealthHub.

An alternate solution was to establish CFHealthHub as a community interest company, a special type of limited company which benefits the community, rather than shareholders, and to issue invoices from this company (209). The intellectual property for CFHealthHub was owned by the sponsoring NHS Foundation Trust. Unfortunately, technical challenges in transferring the intellectual property to a community interest company meant this solution was temporarily abandoned, leaving CFHealthHub unable to invoice for platform costs. As a temporary measure, the University who maintained the CFHealthHub digital platform agreed to invoice NHS Trusts for CFHealthHub platform costs.

The legal and financial complexity around digital innovations in healthcare could have led to the abandonment of CFHealthHub at this time, with no clear method to invoice for platform costs. Within CFHealthHub, there was a recognition that solving complexity required attention to be paid, despite attention being an incredibly precious resource, especially for those working in health care. Therefore, by recognising and paying attention to complexity, solutions which enabled sustainability of CFHealthHub were repeatedly found.

Whilst some of the financial changes resulting from the COVID-19 pandemic created new challenges for CFHealthHub, there were also opportunities. There was a new drive to leverage technology to provide remote care, both to free up inpatient capacity for people with COVID-19 but also for infection control to prevent social mixing, for example in waiting rooms. The fact that CFHealthHub supported remote monitoring added to the value proposition to NHS trusts and additional funding from a special £2,000,000 COVID-19 budget reduced complexity in the technology supply model, by supporting the purchase of additional eTracks for use with the CFHealthHub digital platform. Additionally, NICE issued a Medtech innovation briefing in July 2020, describing how CFHealthHub may contribute to the management of pwCF during the COVID-19 pandemic (210).

2.4.6 Epoch 5: The introduction of ETI (August 2020)

The care of pwCF was revolutionised by the introduction of CFTRm, in particular ETI, for which 80% of pwCF in the UK are eligible (104). In August 2020, ETI was licensed by the European Medicines Agency and made available to pwCF through the NHS. ETI offered pwCF substantial improvements in quality of life, lung function and weight, alongside reductions in cough and sputum production (105, 106, 114, 211, 212). ETI significantly changed nature of the condition of CF, which had implications on the role of inhaled medicines. Whilst the landmark clinical trials considered CFTRm as add-on therapies to established treatment regimens, including inhaled medicines, real-world data showed clear reductions in the prescription and use of inhaled medicines for those prescribed CFTRm (111, 112, 114, 213, 214).

A key driver of this decline in inhaled medicines usage may be the CF community's top priority since 2018: reducing treatment burden (215). Studies evaluating the impact of withdrawing certain preventative inhaled medicines, as a way of reducing burden, for those on ETI began to recruit shortly after it was made available (216-219). Whilst these studies were ongoing, the change in both the clinical and socio-cultural nature of CF meant that, until the role of inhaled medicines was clarified, implementation of CFHealthHub using NICE quality indicators reliant on adherence to inhaled medicines was no longer an appropriate implementation strategy. Graphical representation of how

ETI influenced the coherent conceptual framework for CFHealthHub are represented in Figure 1 and Figure 2.

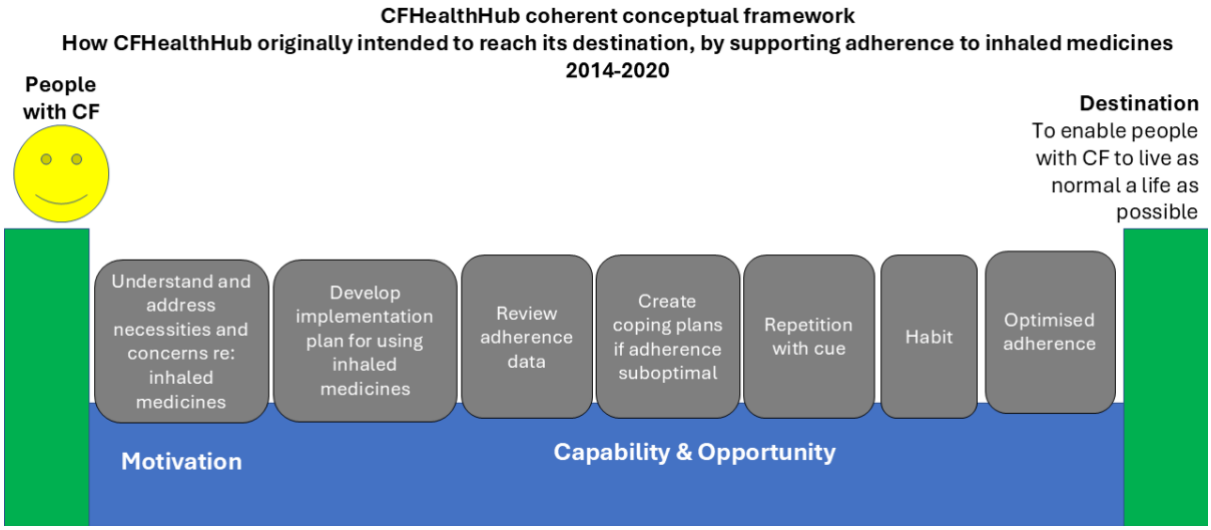

Figure 1: The original CFHealthHub coherent conceptual framework.
Supporting adherence to inhaled medicines was considered the mechanism for enabling pwCF to live as normal a life as possible, as this would reduce disruptive pulmonary exacerbations and preserve lung function, which is associated with better outcomes. The steppingstones outline how the COM-B model was used to provide a conceptual framework for optimising adherence through habit formation.

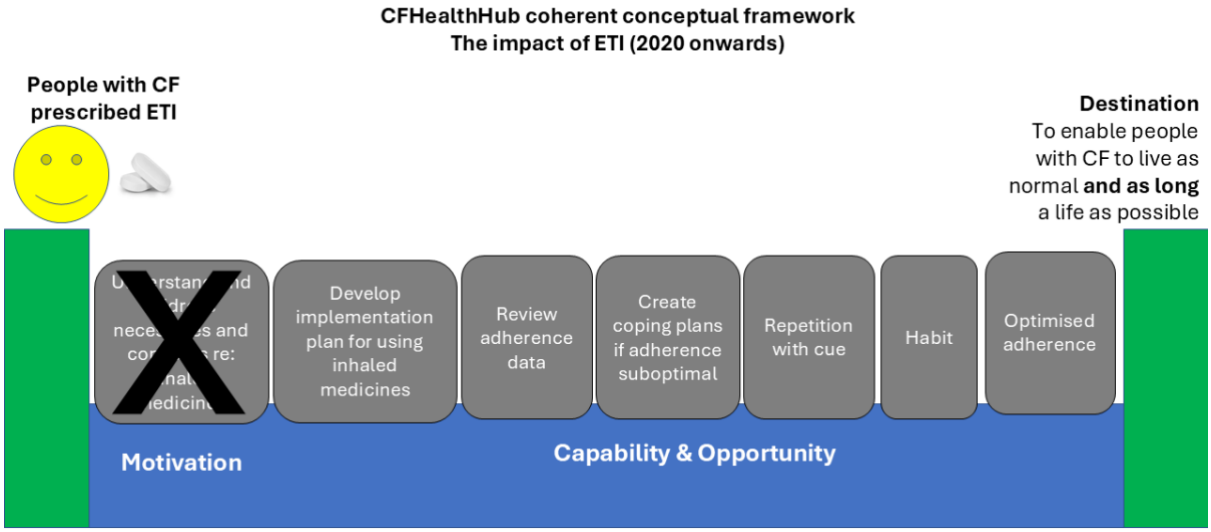

Figure 2: The impact of ETI on the CFHealthHub coherent conceptual framework.
ETI offers pwCF improvements in clinical outcomes and quality of life. The availability of ETI, along with a cultural drive to reduce treatment burden led pwCF and clinicians to question the necessity of inhaled medicines for those on ETI.

Therefore, in 2021, CFHealthHub launched the National Efficacy-Effectiveness CFTR Modulator Optimisation study (NEEMO), an observational study which aimed to explore the relationship between adherence to inhaled medicines and outcomes for pwCF prescribed ETI (218, 220). With 1400 pwCF enrolled across 14 adult CF Centres, CFHealthHub had a unique opportunity to use objective, electronically captured adherence data to determine the real-world impact of adherence to inhaled medicines on clinical outcomes. How NEEMO was incorporated into the CFHealthHub coherent conceptual framework is depicted in Figure 3.

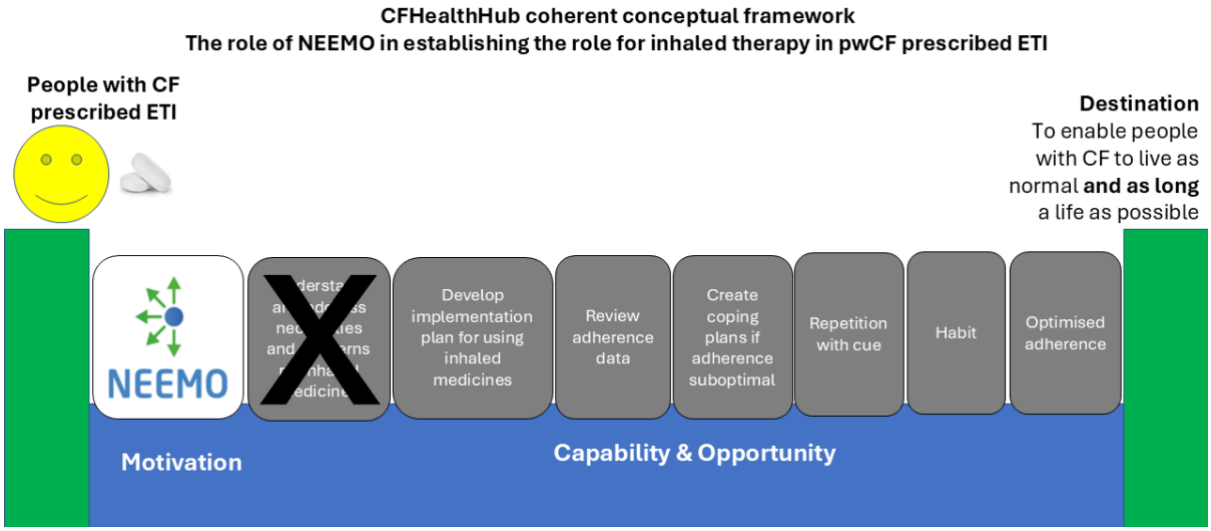

Figure 3: CFHealthHub designs NEEMO in response to the context change of ETI.
NEEMO was designed to determine the role of inhaled medicines for PwCF taking ETI. Should NEEMO robustly demonstrate that adherence to inhaled medicines remains necessary to support PwCF to reach the destination, then the coherent conceptual framework underpinning how CFHealthHub meets this aim by supporting adherence to inhaled medicines would be maintained.

Adequate data collection was essential for NEEMO to achieve its aim. Therefore, it was important to encourage sufficient pwCF to enrol in CFHealthHub and collect accurate adherence and clinical outcome data. Informal discussions within the CFHealthHub community highlighted uncertainty about CFHealthHub's role in the post-ETI era, given uncertainty as to the necessity of inhaled medicines for pwCF prescribed, resulting in a degree of disengagement with CFHealthHub recruitment and adherence data collection. These uncertainties demonstrate the significant complexity arising from the availability of ETI, which increased the risk of CFHealthHub's abandonment and implementation failure (138). These dependencies, as stepping stones to achieve the aims of NEEMO, are depicted in Figure 4.

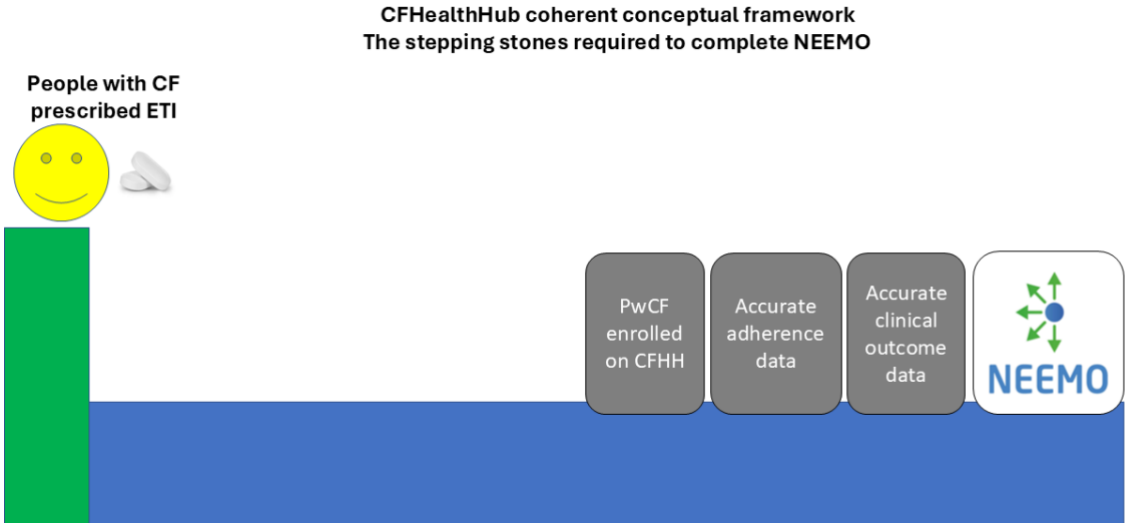

Figure 4: Data completeness requirements for successful completion of the NEEMO study. A magnified view of the CFHealthHub coherent conceptual framework, demonstrating the data completeness steppingstones required to enable NEEMO to achieve its aim of determining the necessity of inhaled medicines for PwCF taking ETI. The blank space between the person with CF and the NEEMO steppingstones represents that there are additional requirements before these steppingstones can be reached, due to the informal observation of potential disengagement with CFHealthHub by both clinicians and PwCF.

The studies aiming to provide population-level evidence as to the role of inhaled medicines in those taking CFTRm would not report until 2025 or beyond. There was, however, an urgent need to support the delivery of personalised and optimised care to pwCF in the real world, as less inhaled medicines were being used despite no evidence to support this. Therefore, in addition to NEEMO, CFHealthHub also developed a novel clinical framework, PLUTO (Personalised data-Linkage to Understand Treatment Optimisation), which was designed to be integrated into the routine assessment of PwCF in outpatient clinics. PLUTO intended to support clinicians and pwCF to use their own clinical outcome and adherence data to determine if their treatment was optimised. A detailed description of the PLUTO framework was published in January 2025 (221).

Within the PLUTO framework, FEV_1 and weight/BMI trends for each pwCF are assessed to determine if their health status could be considered optimised or not. Real-world modelling data suggests that, if FEV_1 decline can be limited to ≤1% per year, then pwCF prescribed ETI could have a life expectancy akin to that of the general population (222). Maintaining a BMI of at least 23 for males and 22 for females was associated with the best FEV_1 outcomes in adults with CF (78) and remained the recommended weight target as per the CF Foundation (223). Since the introduction of CFTRm, overweight and obesity

were increasingly recognised but their impact on outcomes was not certain (224). Where both FEV_1 and weight/BMI were considered satisfactory, then both clinicians and pwCF can be reassured that the current treatment regimen and adherence to it are "optimised".

Should FEV_1 and/or BMI be considered unsatisfactory, then PLUTO prompted clinicians to consider adherence to both ETI and inhaled medicines alongside considering whether the current prescribed regimen remains adequate or diagnostic tests for new pathology/complications would be indicated. The PLUTO framework flow chart is shown in Figure 5.

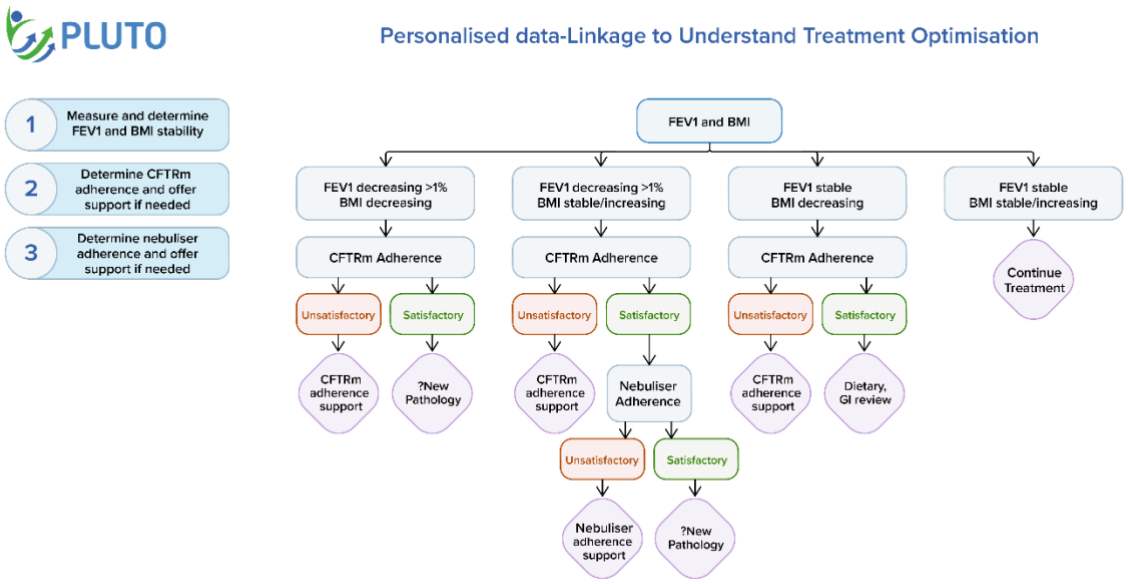

Figure 5: The PLUTO framework.

Not only could PLUTO support personalised decision-making, but it could also support data collection for the NEEMO study. The steppingstones required to deliver PLUTO and subsequently NEEMO are shown in Figure 6. How PLUTO and NEEMO fit into the overall conceptual framework of CFHealthHub is shown in Figure 7.

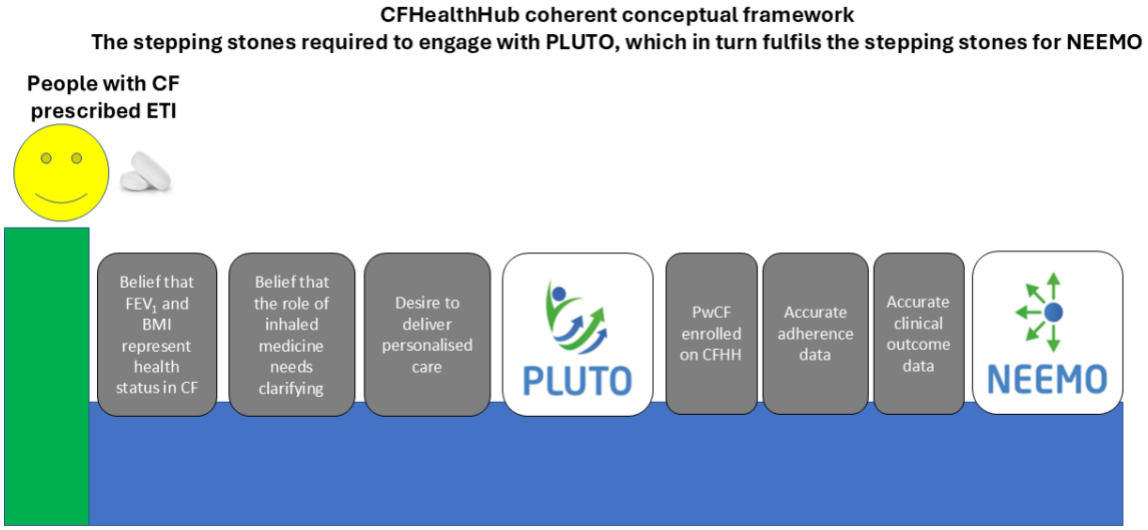

Figure 6: Conditions required for acceptance of PLUTO and completion of NEEMO
In order for clinicians to consider PLUTO as an acceptable clinical framework, the three preceding steppingstones were thought to be required. Should PLUTO be implemented, then it should encourage the collection of data which will contribute to NEEMO and simultaneously allow clinicians to deliver personalised care.

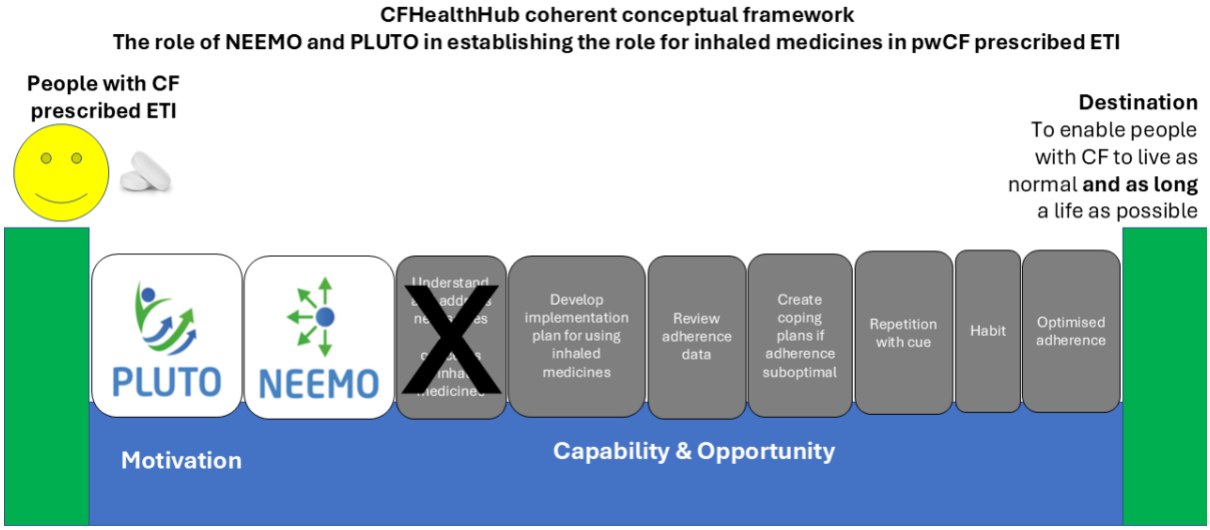

Figure 7: How PLUTO and NEEMO fit into the CFHealthHub coherent conceptual framework
Both PLUTO and NEEMO are steppingstones to determining the role of inhaled medicines and if that will allow CFHealthHub to continue to meet its aim.

A tabulated summary of the different complexities and considerations across the five epochs is displayed in Table 3.

Table 3: Tabulated summary of considerations in different domains of the NASSS framework related to CFHealthHub.

NASSS Domain	Epoch 1 (inception to RCT)	Epoch 2 (establishing learning health system)	Epoch 3 (RCT failing to meet primary endpoint)	Epoch 4 (COVID-19 pandemic)	Epoch 5 (introduction of ETI)
Condition	**Nature of condition** Young demographic. Adherence to inhaled medicines is low. CF is a multi-morbid condition, with respiratory failure as main cause of death, so focussed on inhaled medicines as these reduce exacerbations and improve lung function. **Sociocultural factors** Treatment burden important in CF, and inhaled medicines considered particularly burdensome.		**Nature of condition** Created some doubt as to the importance of adherence to inhaled medicines in improving outcomes	**Nature of condition** PwCF advised to shield, increasing uptake of remote monitoring.	**Nature of condition** Many pwCF experienced fewer symptoms and better lung function post-ETI, leading to re-evaluation of the role of inhaled medicines.
Technology	**Material features** CFHealthHub digital platform co-produced with pwCF and compatible with both available data-logging nebulisers. Passive data capture reduces need for user engagement. Complex intervention incorporated alongside digital platform, as platform alone unlikely to change behaviour **Technology supply model** Aligned CFHealthHub with NHS England priorities regarding patient activation to obtain funding for devices				
Value Proposition	**Supply side (to manufacturer)** Data-logging nebulisers brought to market through CFHealthHub. **Supply side (to NHS England)** NHS England supported interventions to increase patient activation, improve health outcomes, and reduce unscheduled care. Pre-RCT economic analysis suggested cost savings if CFHealthHub improved adherence and decreased exacerbations. **Demand-side (clinicians)**	**Supply side (to NHS Trusts)** Co-developed NICE Quality Indicator for national benchmarking using CFHealthHub data.	**Supply side (to NHS Trusts)** RCT showed a no significant effect on exacerbations, invalidating the economic analysis. Therefore, EMBRACE medicines optimisation workstream required	**Supply side (to NHS Trusts)** Remote monitoring aligned with NHS Trusts' goal of minimising hospital footfall.	

	CFHealthHub provided clinicians with accurate adherence data (self-report was inaccurate) **Demand-side (pwCF)** Habit formation to reduce perceived burden and optimise health through higher adherence.				
Adopter System	**Clinicians** Clinicians engaged using "FEV_1, BMI, and adherence" mantra. Electronic data capture made adherence "visible." **PwCF** Required initial motivation to increase adherence, but habit formation aimed for sustained adherence with reduced perceived treatment burden	**Clinicians** NICE Quality Indicator to stimulate improvement work. Weekly CFHealthHub Interventionist meetings fostered a community of practice.		**Clinicians** Interest in digital transformation and remote monitoring accelerated.	**Clinicians and pwCF** The value of supporting adherence to inhaled medicines through CFHealthHub was less clear. PLUTO designed to demonstrate how adherence data could be used to optimise outcomes
Healthcare organisation	**Readiness for technology/change** Collaboration with academic and digital health partners to support information governance and research procedures. **Nature of funding decision** Funding via NHS England CQUIN (~£6m) and NIHR PGfAR (~£2m) **Work needed to implement change.** Dedicated, trained CFHealthHub Interventionists at each Centre.		**Nature of funding decision** EMBRACE programme designed to fund CFHealthHub by reducing medicines waste (via NHS England specialised commissioning QIPP scheme).	**Readiness for technology/change** Partnered with University to invoice CF Centres using CFHealthHub after NIHR/NHS England funding ended. **Nature of funding decision** Change to reimbursement mechanisms for NHS trusts meant QIPP was no longer valid. COVID budget offered £2m to support remote monitoring.	**Nature of funding decision** CF Centres were required to pay for access to CFHealthHub, despite new uncertainties around the role of inhaled medicines
Wider System	**Political** CFHealthHub aligned with NHS-wide focus on patient activation. **Professional** CFHealthHub Interventionist training appropriate for those from all clinical MDT disciplines. **Socio-cultural** CF Trust funded digital transformation projects	**Professional** Growing interest in learning health systems to drive quality improvement		**Professional** NHS digital transformation accelerated.	**Socio-cultural** Interest grew in inhaled medicines withdrawal studies for pwCF on ETI. Developed NEEMO observational study of the impact of adherence on outcomes in those taking ETI using real-world CFHealthHub data

2.5 Rationale for the study

Optimisation of the care of people with long-term conditions is important, and significant progress had been made through development of the CFHealthHub learning health system. Implementing CFHealthHub in routine care, at a time of significant external context change due to the availability of ETI and an unprecedented global pandemic introduced additional complexity. This presented an opportunity to further understand the effect of external context changes on complex adaptive systems, such as UK CF care provision and implementation of complex interventions, such as CFHealthHub.

2.6 Research questions

1) How have ETI and the COVID-19 pandemic shaped perspectives of CF clinicians on inhaled medicines and the demands on their services?
2) How have ETI and the COVID-19 pandemic shaped the experiences and care needs/preferences of pwCF?
3) What factors are associated with adherence to inhaled medicines for pwCF in the post-ETI era?

2.7 Study objectives

The objectives of the work presented in Chapters 4 to 6 were to qualitatively answer the first research question by exploring the impact of ETI and the COVID-19 pandemic on specialist CF clinicians across the UK, with a particular focus on decision-making regarding inhaled medicines for pwCF prescribed ETI, and the implications for implementing adherence support programmes such as CFHealthHub.

The work in Chapters 7 and 8 aimed to answer the second and third research questions, by using both qualitative and quantitative methods, to understand how lived experiences of CF had changed and to inform service development, from the perspectives of pwCF.

The work in Chapter 9 sought to contribute further to the third research questions through a purely quantitative analysis, identifying factors associated with adherence to inhaled medicines, using a unique dataset comprising an entire CF Centre cohort with objective, electronically captured adherence data.

3. Methodology

3.1 Introduction

In this chapter I outline the methodology underpinning this study alongside an overview and rationale for the methods used to answer the three research questions. Further detail is described in the methods section for each subsequent chapter.

3.2 Selection of research paradigm

The study of real-world situations in inherently complex environments brings limitations when taking polar, mono-paradigmatically orientated research approaches, such as positivism or constructionism. Therefore, this study was designed using principles of realism, to support the ability to answer the research questions regarding the changes in both outcomes and the relative importance of different mechanisms, which arise when a complex system (living with and caring for pwCF) is confronted with a large external context change (a revolutionary new medicine).

3.2.1 Positivism

Positivism is an epistemological stance that advocates the application of natural science methods to the study of social reality, based on the principle that only knowledge derived from sensory experience and empirical observation is valid (225). What can be observed in experiments is considered as “true”. It maintains that research should be conducted objectively, with findings considered as proof of reality, independent of the researcher, in order to ensure validity and minimise the influence of bias. However, the assumption that valid knowledge can only be derived from observable phenomena limits the applicability of positivism in complex real-world settings, where outcomes are shaped by individuals’ behaviours and their interpretations of events within a given context.

3.2.2 Constructionism

An alternate ontological position, constructionism (also known as constructivism), holds that reality is socially constructed, and meaning is continuously made and revised by social actors (225). Therefore, in contrast to positivism, what is observed does not always represent reality and reality is constantly changing. Whilst this philosophical position

can offer rich descriptions, there are limitations in generating causal explanations for outcomes in complex settings, where contexts are continually changing.

In this study, the aim was to move beyond surface-level description to explore how and why different outcomes emerge within a complex, real-world health system where individual behaviours (e.g. preferences and perceptions) interact with structural factors (e.g. funded care models) to shape service delivery and experience. To generate meaningful causal explanations and provide evidence-based recommendations for service design, a research philosophy was required that could accommodate both observable outcomes and the underlying mechanisms driving them.

Realism offered this potential by recognising a layered understanding of reality, where empirical data are used alongside theory to uncover causal mechanisms within their contextual settings. In contrast, the limitations of positivism, in that it is too narrowly focussed on observable, measurable phenomena, and constructionism, in that it is centred primarily on local meaning-making without explanatory depth, make them less suitable for addressing the aims of this study. Therefore, a realist approach was adopted to support the development of transferable insights that can inform health delivery and practice.

3.2.3 Realism

Realism is characterised by ontological depth, retroductive theorising and the recognition that hidden mechanisms generate an experienced and observed reality (226). A key principle of realism is its stratified ontology, where reality exists at three distinct but inter-related layers, though only parts of it can be experienced or observed. The three layers of reality are (227):

1) The Empirical: the level where events are experienced and observed, which can be detected through human senses and empirical study.
2) The Actual: the level experiences happen regardless of whether they are observed.
3) The Real: the deepest level, containing unobservable generative mechanisms which have the potential to produce events in the actual and empirical layers.

To explore mechanisms operating within the real domain, realism employs retroductive theorising, where researchers work backwards from what is observed to theorise the plausible generative mechanisms that may have given rise to them (228). Unlike induction or deduction alone, retroduction allows researchers to infer causal explanations by reconstructing the conditions for certain outcomes to occur, paying attention to the interplay between contextual features and mechanisms, even when those mechanisms are not directly observable (228).

Mechanisms are inherently latent, in that they may exist without observable effects unless activated by sufficiently conducive contextual conditions. Recognising these enabling contexts is therefore essential, as in their absence, mechanisms remain latent and are empirically undetectable. This limitation underscores the importance of retroductive theorising in realist research, where the aim is not only to describe patterns but to explain the deeper structures and mechanisms which generate them.

The "basic realist formula" states that *context* + *mechanism* = *outcome* (131). The acceptance that mechanisms are hidden yet may be theorised through retroduction is the epistemological stance that empowers realist research. The pursuit of generative mechanisms allows generalisability of findings from a rich understanding in a specific setting, where different contexts and mechanisms interact to produce outcomes. In particular, a realist approach encourages specific attention to be paid to the impact of context and is recommended for evaluation of complex systems (229).

3.3 Realist Evaluation

Realist Evaluation is a pragmatic approach to understanding how programmes work, with a focus on the complexity of real-world settings, such as the delivery and utilisation of care within UK adult CF services (131). Whilst reporting guidelines outline the processes expected in a Realist Evaluation (230), the process recognises that methodological flexibility and diversity, drawing on a range of data sources and methods, are required to develop a comprehensive understanding of the programme under study. This includes integrating primary data from stakeholders, practitioners, and recipients with existing literature, while employing retroductive theorising to generate and refine hypotheses which comprise Programme Theory, describing how, why, and in what

contexts the programme works (231, 232). The findings of this Realist Evaluation are intended to provide members of the CF community, including clinicians, service managers, policymakers and pwCF, a deeper understanding of the key contexts and mechanisms which are shaping outcomes, to inform recommendations for care delivery in the post-ETI era.

3.3.1 Programme Theory

Programme theory explains how and why different outcomes are generated in different contexts (233). These causal insights may be programme-specific or more related to the broader context within which the programme sits. This is advantageous when it comes to generalising findings outside of the specific programme being evaluated to help support development of programmes in other settings. To further support generalisability, Programme Theory is typically presented in the middle range (234). The basic framework used to describe causal insights in Programme Theory are the Context (C), Mechanism (M), Outcome (O) configurations (CMOC).

3.3.2 Context Mechanism Outcome Configurations

CMOCs serve as a heuristic tool to support the development and organisation of Programme Theory, helping to distinguish between elements of context, mechanisms, and outcomes, and to identify gaps in theoretical understanding (131, 235). Given the variation in how these terms are defined across realist studies, it is recommended that researchers provide explicit definitions of context, mechanisms, and outcomes within the specific parameters of their evaluation (236).

In this study, contexts were generally understood as relational and dynamic structures, encompassing both physical elements (e.g. adoption of virtual appointments for routine care) and non-physical constructs (e.g. the holding of a certain belief) (236). At the same time, some contexts may be more rigid and observable (e.g. reduced collection of sputum samples in the post-ETI era). Crucially, rather than viewing contexts and mechanisms as merely co-existing, this study emphasised the importance of examining the relationships between them to generate meaningful causal insights. This perspective guided the development, testing, and refinement of Programme Theory throughout the Realist Evaluation.

Mechanisms have been described in various ways within the Realist Evaluation literature. As described in section 3.2.3, mechanisms can be broadly conceptualised as hidden or unobservable generative forces that may be triggered, or remain dormant, depending on the surrounding context, ultimately leading to different outcomes (237). Determining whether specific elements within an intervention function as contexts or mechanisms is a challenge in Realist Evaluation (238, 239). An early definition of a realist mechanism was the ideas, opportunities, or resources that a programme introduces to its target group (234). Mechanisms may also be defined as the reasoning and responses of participants to programme components (131). In keeping with published recommendations, when describing mechanisms throughout this thesis, reference is made to whether each mechanisms is considered a resource, response or reasoning (238).

Outcomes describe "*the intended or unintended consequences of the programmes, resulting from the activation of different mechanisms in different contexts*"(131). Realist Evaluation does not consider whether a programme was successful or not, but more what were the outcome patterns and how might divergence result from the interaction between contexts and mechanisms. For example, in this work, an outcome pattern would be that some pwCF maintain adherence to inhaled medicines post-ETI, whereas other decrease adherence. The realist approach would seek to explain in what specific circumstances certain mechanisms are triggered, leading to people to experience different outcomes.

The iterative refinement of CMOCs typically follows a 4-step process (240):

1) formulation of initial programme theory (IPT) in CMOC form
2) collection of data relating to the CMOCs
3) data analysis to test CMOCs and
4) formulation of a final set of refined CMOCs

In this study, the structure of the 4-step process was used to help focus data collection though I remained open to the generation of new Programme Theory statements throughout the entire project.

3.3.3 Sources of data collection and analysis

In this study, different methods of data collection and analysis were employed at various stages, unified by a consistent focus on generating causal insights into the underlying mechanisms shaping CF care in the post-ETI era. Realist Evaluation is characterised by methodological flexibility, drawing on a range of tools and techniques suited to theory generation, testing and refinement, which can vary depending on the nature and context of the study (231, 241). In line with this, multiple data sources were utilised, including published literature, interviews, surveys, focus groups and electronic health records, and analysis combined both descriptive and hypothesis-testing approaches for quantitative data, alongside thematic and realist analysis of qualitative data. A summary of how each piece of work described in this thesis contributed to answering the three research questions is provided in Table 4.

Table 4: Summary of methods used to answer each research questions and the corresponding chapter(s) of the thesis

Methods used	Chapter(s)
Research Question 1: How have ETI and the COVID-19 pandemic shaped perspectives of CF clinicians on inhaled medicines and the demands on their services?	
Semi-structured individual and group interviews with CF clinicians.	4 to 6
Research Question 2: How have ETI and the COVID-19 pandemic shaped the experiences and care needs/preferences of pwCF?	
Survey and focus groups with pwCF.	7 to 8
Research Question 3: What factors are associated with adherence to inhaled medicines for pwCF in the post-ETI era?	
Qualitative insights from aforementioned interviews, survey and focus groups.	7 to 8
Quantitative exploration through cross-sectional study using objective adherence data including a whole Centre population of pwCF, through multivariable regression modelling.	9

ETI = elexacaftor/tezacaftor/ivacaftor. COVID-19 = Coronavirus disease 2019. CF = cystic fibrosis. pwCF = people with CF.

3.3.4 Strengths and limitations of Realist Evaluation

Realist Evaluation focusses on developing an understanding of how and why variation in outcomes occurs within complex systems, such as the care of pwCF. The approach's strengths lie in its ability to generate explanatory insights which account for critical yet nuanced interactions between features of context and the mechanisms which are subsequently triggered, or not, or to what extent. This offers a deeper understanding and explanation of the dynamics underpinning variation in outcomes and inform recommendations for care provision. This is particularly beneficial for understanding the complexities of healthcare systems, where outcomes are often influenced by multiple factors, which interact in unpredictable ways. Realist Evaluation is also methods-neutral, prioritising depth of insight over strict limitations on what is considered a source of data, which strengthens its applicability to pragmatic, real-world research.

A key limitation of Realist Evaluation is the technical language which surrounds its methodology, such as programme theory, CMOC and retroduction. While these terms are integral to the process, they can be difficult to interpret for those unfamiliar with the approach, particularly healthcare professionals who may not have methodological training or experience. Balancing the need to retain the complexity of the findings while making them accessible to a clinical audience was challenging. Throughout this study, I addressed this by considering how the presentation of findings would align with the practical realities of CF care provision, leveraging my clinical background and drawing on the expertise of a supervisor with clinical experience in CF but no methodological experience in Realist Evaluation. This helped ensure that the outputs remained meaningful and actionable without oversimplifying the insights.

Additionally, it is unclear where Realist Evaluation is positioned within the hierarchy of evidence-based medicine. RCTs, which are considered as one of the most valuable sources of evidence are characterised by homogeneity, generalisability and a researcher-independent epistemology, as described in section 3.2.1 (Positivism). Realist Evaluation directly contrasts this philosophy, recognising the active role of the researcher in generating evidence, not least through the process of retroduction. Where outcomes depend on human reasoning and action, the expected outcomes of an RCT

may not be seen when the intervention is delivered in a real-world setting, particularly when that intervention is complex. Realist Evaluation has the potential to generate causal insights into "what works, for whom, in what circumstances and why", but this depends on a detailed evaluation of intervention delivery, which would equate to a case report or series, which occupy the lowest levels of the evidence-based medicine hierarchy (242).

Another limitation is the process of setting boundaries for the evaluation. The care of pwCF encompasses a wide range of factors, as outlined in section 2.3 (Cystic fibrosis), necessitating prioritisation. This decision-making process is shaped not only by the data collected in the study but also by the researcher's own interpretations, thoughts and beliefs. This also introduces another critique of Realist Evaluation, which is the potential influence of researcher bias in shaping the scope and direction of the work. This is considered in detail in section 3.5 (Reflexivity).

3.4 Ethical approval

The work was carried out between two host organisations, The University of Sheffield (TUoS) and Sheffield Teaching Hospitals NHS Foundation Trust (STH). I was employed as a Clinical Research Fellow in the Sheffield adult CF Centre at STH, meaning I was responsible for both supporting clinical care for adults with CF and research activities within the Centre.

Ethical approval covering collection of primary data through interviews, the national survey and focus groups (Chapters 4, 6, 7 and 8) was granted by TUoS Research Ethics Committee (Reference Number 055012). As the direction of the Realist Evaluation was shaped by its findings at each stage, a total of five amendments were made throughout the course of the study to cover additional activities. These are described in more detail as each piece of work is discussed in this thesis.

The work described in Chapter 9 involved a secondary analysis of routinely collected data. As a clinical member of the MDT, I had existing legitimate research access to the EMR for all pwCF on the Sheffield adult CF Centre caseload. Data were extracted from the EMR and stored on the STH secure server, compliant with existing regulatory approval

obtained from NHS Health Research Authority (Integrated Research Application System [IRAS] Reference Number 210313). This approval covered research involving routinely collected data relating to adherence, or factors associated with adherence, in the Sheffield adult CF Centre.

With existing NHS ethical approval, this piece of work was then approved through self-declaration by the TUOS Research Ethics Committee (Reference Number 052033). Pseudo-anonymised data files were transferred via secure NHS email to the University of Sheffield password-protected secure drive prior to statistical analysis, in line with the Data Management Plan and approvals from STH as data controllers. The pseudo-anonymisation key was stored exclusively on the secure STH NHS server and never transferred between locations.

3.5 Reflexivity

Reflexivity involves recognising how the researcher's position, experiences, and perspectives interact with the research process, and how these interactions may shape both data collection and interpretation (243). A recent call to action underscores the importance of transparent documentation of reflexivity within Realist Evaluation, recognising the intrinsic influence of personal experiences, education, and beliefs on the theorisation process, particularly retroduction is used (244).

3.5.1 My role as a researcher and clinician

I am a cisgender, heterosexual, married, university-educated male physician, and have worked as an NHS doctor for over a decade. I approached this PhD as someone with a professional interest in optimising care delivery for people with long-term conditions within the NHS. During this study, I was employed as a Clinical Fellow at STH, in the adult CF Centre, where I delivered clinical care on a once-weekly basis, dedicating the remaining four days to research activities. Given that I was working within a programme I was simultaneously evaluating as part of a national evaluation initiative, I considered myself as a partially embedded researcher (245). This dual role allowed for close engagement with the clinical setting and stakeholders, while also necessitating a continuous awareness of how my involvement might influence both data collection and

interpretation. Practicing reflexivity throughout the research process is a recommended way of mitigating some of the challenges associated with dual-role research (246). Immersion within an adult CF MDT and the CFHealthHub programme allowed me to gain insights which would otherwise have been difficult to obtain (140).

3.5.2 My epistemological perspective

As a physician trained and practising in the era of evidence-based medicine, my default epistemological stance has been shaped by the principles of positivism, where truth is understood as that which can be observed and verified through appropriately designed and conducted studies (247). This orientation influenced how I initially approached research, valuing objectivity, measurement, and causal inference primarily through empirical observation.

However, exposure to alternative research philosophies, particularly critical realism, broadened my perspective. Engaging with critical realism enabled a deeper, more nuanced scientific inquiry into the complexities of care for people with long-term conditions in this study. Embracing this approach required a conscious reorientation of my epistemological stance, allowing for a more layered understanding of causality that goes beyond what was immediately observable.

3.5.3 My perspectives on inhaled medicines

Prior to this appointment, I did not have clinical experience in the care of pwCF. My clinical specialty is Rheumatology, where I am familiar with the care of people with long-term conditions. As such, my understanding of CF care was shaped through engagement with colleagues in the adult CF MDT and through my involvement with the CFHealthHub learning health system. Similarly, my initial knowledge of inhaled medicines and CFTRm was limited and influenced by existing work conducted within the CFHealthHub programme and the perspectives of experienced colleagues. At the outset of the study, I held several preconceptions regarding inhaled medicines in the post-ETI era, which are outlined below.

Based on evidence from the literature, my experience as a practising clinician, and discussions with colleagues in the CF MDT and within the CFHealthHub learning health

system, I understood that ETI had resulted in substantial health improvements for many pwCF. However, it is important to acknowledge that my exposure to CF care was shaped predominantly through the lens of the CFHealthHub programme. As a result, I became very familiar with the expression of caution surrounding the reduction or withdrawal of inhaled medicines following the introduction of ETI.

This perspective is supported by existing evidence: inhaled medicines were continued alongside ETI in the pivotal RCT (105) and in the case of the first-generation CFTRm, ivacaftor, real-world data indicated that reduced adherence to inhaled medicines was seen alongside a decline to pre-ivacaftor lung function over a five-year period (110, 111).

Within the Sheffield adult CF Centre, clinicians did not routinely seek to withdraw or reduce inhaled medicines for pwCF prescribed ETI. Consequently, I was primed to question, and perhaps doubt, the rationale behind such approaches if disclosed by clinicians from other Centres during interviews or informal discussions. This also influenced my decision to focus on how ETI may have led to changes in thoughts and behaviours around inhaled medicines, as a specific facet of CF care explored in the work of this thesis. Whilst I remained open to exploring other emergent areas of importance, such as longevity and virtual care, I maintained a keen interest in exploring the role of inhaled medicines throughout this study.

3.5.4 My perspectives on CFHealthHub

Being part of the CFHealthHub central team brought with it an implicit expectation, both personally and from within the team, that I would view the programme as valuable and support its wider implementation. Given that CFHealthHub was developed and deeply embedded within the Centre where I worked, I was predisposed to regard this as a model exemplar of effective implementation. As such, I entered the study with a strong assumption that CFHealthHub represented best practice in the post-ETI context.

However, upon critically revisiting the results of the CFHealthHub RCT, I appreciated why others may question this assumption. The headline finding, a 10% increase in adherence in the intervention arm, was not accompanied by improvements in the primary outcome of pulmonary exacerbation rate (34). The results of the study were internally framed as

positive: "*it was the largest study in CF conducted in the UK, and the first to demonstrate an approach which significantly improved adherence to inhaled medicines and reduced perceived treatment burden*."

Despite this, at the time of my study CFHealthHub was active in <50% of UK adult CF Centres (248). No new Centres had joined the programme since the RCT completed and in fact a number had withdrawn. An editorial acknowledged that, whilst the RCT results were encouraging, the CFHealthHub behaviour change intervention was considered too complex for most settings and the challenge would lie in tailoring and streamlining it for broader adoption (249).

This prompted me to reflect on the extent to which others may consider CFHealthHub "effective," particularly in clinical terms. While these questions about the programme's effectiveness or value were not openly discussed within the central team, this personal reassessment allowed me to approach the data with a more balanced and critical view.

Clinicians interviewed over the course of the study were aware of my affiliation with CFHealthHub and, as a result, likely perceived me to be strongly aligned with the programme's aims and values. This perception may have influenced how they expressed their views or the extent to which they felt comfortable sharing critical reflections on the programme or its implementation in their Centre.

Research interviews between professional peers, as conducted in this study, present unique methodological challenges and benefits. One such challenge is that, despite reassurances, interviewees may perceive the interview as a test of knowledge and, as a result, provide factually correct responses which they believed that I, as the interviewer, was seeking (250). Conversely, and advantage of an interview between two peers is the ability for the researcher to harness prior subject matter understanding and professional culture, which improved my ability to engage in meaningful questioning and seek necessary clarification during the interviews (250). Additionally, my involvement in the CFHealthHub learning health system facilitated relationship-building with clinicians across the collaborative, which in turn supported recruitment for the semi-structured interviews detailed in Chapters 4 and 6.

3.5.5 My perspectives on virtual care

In the adult CF Centre where I worked clinically, virtual care and remote spirometry monitoring had not been adopted as local experience found them to be unreliable and of limited clinical utility. Consequently, I had no direct experience of delivering CF care using these modalities, which meant I brought less experiential insight to the interpretation of data related to virtual care. This limited exposure may have influenced how I engaged with findings in this area though I consider this one aspect where my views were mostly shaped by the data, rather than personal experience.

3.6 Conclusions

Realist Evaluation was chosen as the methodology for this study due to its foundational emphasis on depth ontology and its focus on uncovering generative mechanisms within complex settings, whether or not these mechanisms are empirically observable. This enabled me to focus on the effects of changing contexts and offer valuable insights for a community in transition, as UK CF services adapt to such significant changes in the therapeutic landscape. Realist Evaluation embraces data collection through a range of methods whilst maintaining focus on identifying plausible generative mechanisms. Reflexivity played a role throughout the study, as my perspectives, decisions, and responses to emergent findings were shaped by my own professional experiences and exposures.

4. Clinician interviews

4.1 Introduction

The community of practice within the CFHealthHub programme consisted of clinicians working across 14 UK specialist adult CF Centres. As described in Chapter 2, an initial theory emerged from discussions with the CFHealthHub programme director, that the perceived necessity of inhaled medicines had been called into question following the introduction of ETI. This perception introduced new complexity into the implementation of the CFHealthHub learning health system, which was designed to support adherence to inhaled medicines. Aspects of this theory were partially supported by evidence that the use of inhaled medicine has decreased for people prescribed ETI, or earlier generation CFTRm (111-114, 213, 251-255) and by tacit knowledge gained in my role as both a member of the CFHealthHub central team and a practicing physician in a specialist adult CF Centre.

As CFHealthHub was intended to be implemented within routine care delivery at specialist adult CF Centres, it was important to gain a broader perspective on the impact of ETI from clinicians across the network. This aimed to explore whether the initial theoretical proposition was sustained, to deepen understanding of clinicians' perspectives, and to support the development of a formal IPT, an essential early step in Realist Evaluation.

Additionally, whilst the impact of ETI on clinical outcomes was well described, less was generally known about clinician perspectives regarding how ETI has affected CF care provision. Qualitative study helps contextualise quantitative findings which predominately used health indicators such as FEV_1, BMI and quality of life measures to indicate post-ETI outcomes.

This phase of the study was designed to answer the first research question ("*How have ETI and the COVID-19 pandemic shaped perspectives of CF clinicians on inhaled medicines and the demands on their services?"*) by building on insights gained from the CFHealthHub programme director, as described in section 2.4 (CFHealthHub), and my own experiences as a CF clinician. The objectives were as follows.

1) Understand the impact of ETI on the health and care of pwCF, from the perspectives of adult CF clinicians.
2) Understand participants thoughts on current complexities of caring for pwCF, in particular the role of inhaled medicines.
3) Understand the perceived role of CFHealthHub and how it is being used as part of routine care in CF Centres
4) Discuss the PLUTO framework and understand barriers and facilitators of implementation in CF Centres

4.2 Methods

4.2.1 Recruitment

Consultant physicians and CFHealthHub Interventionists (n=55) across all CFHealthHub Centres were approached via email on 7th September 2023. Interventionists included clinicians from physiotherapy, nursing, dietician, pharmacy, and psychology disciplines. No reminders were sent to non-responders. All participants provided written informed consent prior to the interview.

4.2.2 Interview schedule development

Each interview was broadly separated into three sections, with the intention to apportion a similar amount of time (approximately 15 minutes) to each. Section 1 was designed to explore the changes to the context of CF as a condition, from the perspective of the interviewee. Section 2 explored the current complexities in optimising the care of pwCF, in particular relating to inhaled medicines. Section 3 more specifically examined the interviewee's perspectives of CFHealthHub, how it was being used in their Centre, followed by a specific discussion around the PLUTO framework. The initial interview schedule was drafted and revised in collaboration with the supervisory team.

Starting the interviews with open, "easy" questions. asking participants for recall of observed phenomena and then moving to more detailed questioning allowed participants to become comfortable and provided space to reflect on their own practice. Designing section 3 using a more realist line of enquiry, for example a teacher-learner cycle around the PLUTO framework and probing participants on whether or how far the

framework may work in their Centre, allowed participants to consider their current working practices and how these may align with or oppose those suggested in the PLUTO framework (256). By taking a realist approach, a two-way dialogue between the participant and myself resulted in shared learning, rather than the transfer of information, overcoming a constraint of a constructionist-oriented research interview.

4.2.3 Data collection

Interviews took place via Microsoft Teams (Microsoft Corporation, Redmond, WA, USA) between 11th September 2023 and 10th November 2023. Each interview involved one participant and me as the sole interviewer. Audio-visual recordings were made and used to produce verbatim, naturalised transcripts of each interview, with only identifiable data being redacted. A transcript was automatically generated through Microsoft Teams, which I then reviewed and edited for accuracy through line-by-line comparison with the complete audio-visual interview recording. Final transcripts were sent via secure NHS email to participants, providing an opportunity for them to check the content for accuracy and provide validation of the transcript as an accurate record of the interview.

I kept a reflexive journal during data collection, capturing my thoughts on each interview and how my positionality may influence the interpretation. Interviews followed a pre-defined topic guide, shown in Appendix 1. There was no formal piloting, and the topics discussed did not significantly differ between interviews.

4.2.4 Data analysis

The data for the analysis were interview transcripts. The analysis intended to identify patterns but also highlight and explore variation. The interview schedule was designed to allow the collection of data that could be analysed using, first, thematic analysis and, later, realist methods. Thematic analysis allowed to identification of patterns in experiences and informed a broader understanding of CF care in the post-ETI era, beyond that which I had gained from own experience as a clinician in a single Centre and member of the CFHealthHub central team. This also allowed me to consider, broadly, elements of context, mechanism, and outcome, which could be subsequently explicated using realist analytic methods. Data were read at a combination of literal, interpretive and reflexive levels (257).

Each audio-visual recording was reviewed and used to validate the transcript, ensuring verbatim transcription and data immersion. Line-by-line transcript proofing alongside an audio-visual recording gave a second opportunity, after the interview, to identify potentially relevant cues and behaviours demonstrated by participants through intonation and expression, rather than relying solely on the words transcribed. Transcripts were first analysed using a reflexive thematic approach (258). This approach enabled focus on participants' experience and allowed themes to be inductively generated from the data.

After the first three interviews, an initial code structure was generated and then refined after discussion with the supervisory team. The first three interview transcripts were then reviewed again, with direct coding in NVivo (Version 14, QSR international Pty Ltd., Burlington, MA, USA) using the refined code structure which linked to the research objectives of the interviews (259). During the coding phase, some themes were generated and codes grouped within the NVivo code structure where it was considered appropriate.

The final code structure was exported to Microsoft Excel (v2408, Microsoft Corporation, Redwood, WA, USA) and is shown in Appendix 2. All codes were individually reviewed and grouped into generated themes, which were then defined and named. Themes were then ordered to be consistent with the story produced from the data, to aid description of the intersection of themes and the shaping of perspectives. Themes were evidenced by direct quotations from interview transcripts. Some quotations presented in this thesis were edited to improve readability without altering their meaning. Ellipses (…) were used to indicate omitted sections, while square brackets, [ ], denoted clarifying words which were manually added.

Questions exploring objectives 3 and 4 related to the CFHealthHub programme and the PLUTO clinical framework, described in Chapter 2. Therefore, to describe and understand the ways CFHealthHub was being used across different Centres, separate summary notes for each Centre were kept in a document using Microsoft Word (Version 2408, Microsoft Corporation). Additionally, codes and themes related to perceptions of the PLUTO framework were categorised into barriers, facilitators, changes needed for

implementation and general thoughts on the framework, to allow an initial consideration of how PLUTO may be implemented across a range of sites.

Semi-structured interviews are a valid and commonly used source of data in Realist Evaluation, as they allow a rich exploration of the phenomena under investigation and lend themselves to the dyadic conversation that is crucial to realist questioning (256). Accordingly, interviews enabled exploration of both CFHealthHub programme-specific topics as well as those related to the context of CF care in the post-ETI era more broadly.

Both reflexive thematic analysis and Realist Evaluation do not consider data saturation as a key aspect of determining sampling strategies or making decisions on when to stop data collection (256, 260). Reflective thematic analysis holds that meaning is generated through interpretation of data rather than what can be extracted from a critical quantity of data (such as the quantity of interviews required for saturation of themes) whilst Realist Evaluation recognises that understanding of complex systems is never complete and the process of developing theory is unpredictable and uncertain. In keeping with these perspectives within these methods, saturation was not used to inform recruitment throughout this study.

4.3 Results

4.3.1 Participant characteristics

Of the 55 clinicians invited, 11 participated in interviews lasting a mean of 54 minutes, standard deviation (SD) was 12 minutes, with a range of 40 minutes to 1hour:17 minutes. The 11 participants included five Consultant physicians, five physiotherapists and one nurse representing nine separate UK adult CF Centres. Three Consultant physicians and one physiotherapist represented “large” adult CF Centres (>300 pwCF on caseload) with all but one other participant being from “small” Centres (caseload <150). The sole participant from a nursing background represented a medium-sized CF Centre (caseload 150 to 300). Aside from one participant (PT_07), all had over a decade of experience in CF (median 18 years, range 3 to 31 years). Participant characteristics are shown in Table 5.

Table 5: Characteristics of interview participants

ID	Professional group	Sex	Years of experience in CF	Size of CF Centre (caseload of pwCF)	Centre ID
DR_01	Consultant	F	19	>300	A
PT_01	Physiotherapist	F	26	<150	B
N_01	Nurse	F	17	150 to 300	C
DR_02	Consultant	M	31	>300	D
PT_02	Physiotherapist	F	23	<150	E
DR_03	Consultant	M	17	<150	F
PT_03	Physiotherapist	F	3	<150	G
DR_04	Consultant	M	13	>300	D
PT_04	Physiotherapist	F	18	>300	H
PT_05	Physiotherapist	F	17	<150	G
DR_05	Consultant	F	19	<150	I

CF = cystic fibrosis. PwCF = people with CF. M = male. F = female.

4.3.2 Themes generated

Five key themes were generated using reflexive thematic analysis:

1) Many PwCF are enjoying better health since the introduction of ETI.
2) Healthcare delivery preferences have changed because of improved health post-ETI and the COVID-19 pandemic.
3) There are new challenges associated with improved health.
4) The relationships between clinicians and pwCF have changed.
5) There is uncertainty and variation relating to the role of inhaled medicines for pwCF prescribed ETI.

The first objective was to understand participant's thoughts on CF care in the post-ETI era. In particular, participants spoke about the changes in health outcomes that pwCF have experienced.

Theme 1: Many PwCF are enjoying better health since the introduction of ETI.

All participants recognised positive changes in the health of pwCF, such as increased general wellness, increases in lung function, improvement in glycaemic control and gastrointestinal symptoms, positive increases in weight and improvements in quality of life alongside reductions in symptoms, pulmonary exacerbation rates and need for lung transplantation.

> *"I think there has been a significant improvement in health of patients with cystic fibrosis in the Kaftrio era. Generally, most patients who have been started on CFTR*

modulators, Kaftrio, have shown substantial benefit, so they are much better." (DR_02).

Theme 2: Healthcare delivery preferences have changed because of improved health post-ETI and the COVID-19 pandemic.

Most participants spoke about how they incorporated virtual consultations and remote monitoring into their care delivery processes during the COVID-19 pandemic, and that some of these changes had been sustained. There was variation among participants in how virtual consultations were implemented. For example, some Centres offered an equal split for all pwCF between virtual and in-person appointments, while others selectively scheduled virtual consultations for pwCF who were clinically stable, advising in-person consultations for others. One participant remarked that a key condition for a virtual appointment was engagement with home monitoring practices and microbiological sample delivery, highlighting the perceived importance of objective clinical information in the adequate provision of care and how virtual care can interfere with the collection of these data.

"Essentially if they're not doing their monitoring and I'm not getting the samples then they are coming to face to face only. They have no option. Because if I don't get the information, how on Earth can I..." (DR_05).

Aforementioned improvements in health and well-being have influenced how pwCF engage with healthcare services. Additionally, all participants also recognised the concurrent impact of the COVID-19 pandemic on the way that care continues to be delivered.

"it's difficult to untangle between how much of that [change] has been because of the introduction of Kaftrio and how much has been because there was a massive impetus to change during the COVID response as well." (PT_02).

Perceived advantages to virtual consultations seemed centred around the reduction in burden to pwCF associated with attending a hospital clinic.

"And because virtual was never an option before, but now it is, it's a lot easier to do a virtual clinic for many people than it is to try and find a parking space and get to clinic." (N_01).

Despite this advantage, there were concerns about the quality of care and monitoring that can realistically be achieved remotely.

> *"We just need to try and make sure that we're providing the best quality of care in those virtual appointments, because I think there's a few things that are lacking. We obviously can't do sputum samples. A lot of them aren't doing the spirometry. We can't do bloods. And the eyeball test is a bit dodgy on Teams. Yeah, they can hide a lot." (PT_04).*

Specifically, regarding home spirometry, most participants reported suboptimal experiences, with one expressing specific regret, due to lack of engagement with monitoring requests from pwCF.

> *"we're regretting that [offering home spirometry]) now because we don't get much [data] back from them [pwCF]." (DR_03).*

Theme 3: There are new challenges associated with improved health.

Whilst there have clearly been many positive changes associated with ETI, there have also been emergent challenges. The potential for increased longevity is considered a key positive outcome, however with that comes challenges associated with age-related co-morbidities (e.g. cardiovascular and cancer risk). Furthermore, several participants have noted some pwCF have adverse health outcomes following ETI initiation, such as liver dysfunction, worsening mental health and excessive weight gain. The improvement in respiratory health has also led to the emergence of non-respiratory issues, such a gastro-intestinal and psychological problems, with which CF clinicians are less familiar.

> *"There seems to be a lot more of everything else and it's almost as if everything else has been given a chance to come to the forefront." (PT_01).*

Theme 4: The relationships between clinicians and pwCF have changed.

Several participants explained how their roles and responsibilities within the adult CF MDT appeared to have changed. For example, roles appear to have expanded with pwCF approaching CF clinicians with issues that were not historically considered CF-specific, such as mental health issues and cardiovascular risk monitoring. As described above, the non-respiratory needs of pwCF have become more salient. For one participant, their role has changed to involve more outpatient care and administrative tasks due to fewer acute admissions and exacerbations.

> *"I think I almost feel 'what am I gonna be today?' Am I a psychologist, am I an exercise therapist... am I MSK [musculoskeletal], what is the patient going to present with today." (PT_01).*

> *"My role is massively different. As a nurse in the team now it's much more about replenishing homecare prescriptions for the modulators. I've noticed that there's less overall urgent reviews for patients who are unwell." (N_01).*

For another participant, the changing health demands for pwCF conflicted with their perceived areas of specialism.

> *"Spending ... a higher proportion of our time, dealing with psychological or gastrointestinal symptoms rather than respiratory symptoms. And they are things that I am less good at, so there's a slight degree of discomfort with that." (DR_03).*

Several participants remarked that they do not feel they know the pwCF for whom they care for as well as they used to, particularly those who have recently transitioned from paediatric to adult care. This seemed to be driven by the reduction in care requirements as a result of improved health.

> *"I feel like I don't know the patients who are transitioning through from paediatric into adult care as well as I would have done pre-modulator, because they're so much better. I don't feel like we see them as often, so I don't feel like I know the families as well ... we're seeing less people admitted to hospital with exacerbations...we're giving out less courses of home IV antibiotics as well." (N_01).*

There was also a recognition that, whilst it may be clinically appropriate to reduce the frequency of outpatient appointments for pwCF who are clinically stable, this could lead to a deterioration in the therapeutic relationship, which could lead to suboptimal care in the future.

> *"If they're well and stable, we're essentially wanting to encourage them and solidify or continue the trust, the therapeutic relationship, so that when they have a problem, they feel safe talking to us." (DR_03).*

Theme 5: There is uncertainty as to the role of inhaled medicines for those on ETI.

Several participants commented on the reduction in use of inhaled medicines by pwCF taking ETI, though this was not always consistent with their clinical recommendations.

There was also concern from multiple participants that withdrawal of inhaled medicines was happening autonomously, without clinician approval.

> *"We whinge a lot if patients do it of their own accord, which some of them have, they've done their own thing like having a month holiday of antibiotics every three months." (DR_03).*

> *"I could advise whatever you like but if a patients decided they're going to stop the treatment they're going to stop the treatment anyway... I think or I suspect a load of them have just stopped their treatment." (DR_01).*

Participants reported uncertainty and varying perspectives on the role of inhaled medicines for pwCF taking ETI. Reducing or discontinuing mucolytics, particularly in individuals with CF with minimal sputum burden post-ETI, was generally viewed as more acceptable than reducing antibiotics. This perspective was rationalised by the fact that ETI has mucolytic properties but not antibiotic properties.

> *"I'm not sure that I really quite know what the right advice (to give pwCF about inhaled medicines) is." (DR_01).*

> *"I'm not clear there's still an active role for regular use of mucoactive agents in somebody who's not producing sputum on a day-to-day basis and are clinically stable." (DR_04).*

> *"As far as we're aware at the minute, as far as the evidence shows, we're really keen for you to keep going with your antibiotics because we don't think that the Kaftrio has any kind of antibiotic benefits. So, if you're going to do one, we'd really like you to carry on with that one'." (PT_05).*

One participant also offered the perspectives of pwCF, again related to the perceived necessity of nebulised mucolytics and chest physiotherapy when sputum burden is low.

> *"And there's definitely uncertainty on the patient side... 'why is this physio asking me to clear my chest three times a day when I rarely get any sputum up anymore.'" (DR_04).*

Beyond uncertainty related to inhaled medicines in post-ETI era, several participants explained more broadly about the uncertainties they had experienced.

> *"We felt like we knew what we ought to advise people to do, whereas now it feels like maybe we don't really know... We don't know anything anymore. We're no longer experts." (DR_01).*

Furthermore, given the prospect of pwCF discontinuing treatment, there is an acceptance of lower levels of treatment or adherence. For example, accepting that medicine which is prescribed as twice daily being taken just once daily, when this would have been considered less acceptable pre-ETI.

> *"Maybe we feel more comfortable accepting someone taking an antibiotic once a day, whether that's the right thing to do or not, I don't think we know from the from the evidence." (PT_05).*

The role of CFHealthHub and current implementation across Centres

Participants identified several ways in which CFHealthHub has had an impact across Centres. These included supporting creation of an open culture where adherence can be discussed between clinicians and pwCF, the utility of objective adherence data and how it can support clinical recommendations, and the ability to contribute to ongoing research agendas to build the evidence base around inhaled medicines in CF post-ETI.

> *"I think one of the things that CFHealthHub has been very good for within our department is to move away from a bunch of health professionals assuming that adherence is easy and being a bit kind of "finger-waggy" to a bunch of health professionals who realise that adherence is difficult and therefore speak to patients about it in a different way." (DR_01).*

> *"I'm ever bound to the fact that electronic data capture is the most powerful tool any of us have, to have conversations about treatment taking." (PT_02).*

> *"It's only by having that objective data over a number of Centres that we can start to really look at what is happening to people who carry on their treatment, what is happening to people who don't?" (PT_02).*

Interestingly, one participant remarked how the culture of discussing adherence to inhaled medicines appeared to have influenced the quality of discussions around adherence to other medicines, such as ETI.

> *"I think having CFHealthHub and adherence just being a normal part of our conversation has had impacts on people being open about their modulator adherence." (DR_01).*

Participants also commented on some of the challenges and frustrations related to CFHealthHub including technical issues, lack of data availability for many pwCF and variable engagement with CFHealthHub across MDT members.

> *"Lots of patients turn the hub off so even if you go to the bother of looking quite often you don't really get any data out." (DR_01).*

> *"So, the physios have certainly embraced it. We have struggled to get the nurses to join in those type of conversations." (PT_05).*

Regarding the use of CFHealthHub in their Centre, most participants reported that CFHealthHub data for individual pwCF were reviewed in a targeted way in advance of scheduled appointments. There were generally certain MDT members who assumed responsibility for accessing CFHealthHub data and shared it with the wider team either in scheduled MDT meetings or by sending summaries/spreadsheets. Most Centres considered the responsibility for reviewing CFHealthHub data to lie with the Physiotherapists in the MDT.

PT_04 reported having a specific, twice-weekly adherence clinic, where all pwCF in their Centre who were on CFHealthHub were reviewed on a rolling schedule. However, this was a virtual clinic and PT_04 reported that the intervention did not work as well in this setting compared to in-person.

> *"We have half-hour slots [in the adherence clinic] virtually, which isn't ideal because I think face to face works a lot better for the CFHealthHub interventions." (PT_04).*

Several participants reported that, whilst the CFHealthHub adherence data were reviewed, the delivery of the CFHealthHub Intervention was suboptimal. Reasons for this included a lack of staff resource, opportunity, training, confidence, and familiarity with delivering the intervention for clinicians and a lack of pwCF engagement with key structures of the Intervention, such as writing action and coping plans.

> *"I think the bit that everyone recognises doesn't happen, which we're all a bit sad about, is the interventions... I think if people don't have the time and space to specifically think about interventions and the background theory and to feel competent in doing them frequently enough, then they don't happen." (PT_02).*

Thoughts on the PLUTO Clinical Framework

The general sentiment towards the PLUTO framework was positive, with it being considered logical, able to support discussions between pwCF and clinicians and able to mitigate some challenges associated with frequent staff turnover and standardisation of clinical assessments.

> *"we've got two newer Consultants who might find it a useful way of framing how they go about their clinics, and also perhaps for more junior medical staff who probably need a little bit more of a framework with less sort of experience." (PT_03).*

> *"I think it gives it a structure and it would maybe standardise it a bit more with staff changes." (PT_01).*

In both of the above quotes, the respondents appeared to suggest that PLUTO was not necessarily considered useful for their own practice but may help to address the challenges associated with lack of experience and to help standardise processes for new staff. This may explain why several respondents considered the steps of PLUTO framework to represent what they were already doing, rather than requiring them to do anything new.

> *"We definitely use the principles from it, but just in a more informal way." (PT_04).*

> *"I think when we talked before our Consultant was like "well, I do this any anyway." They didn't feel that it necessarily added or changed anything." (PT_05).*

Facilitators for implementation of PLUTO include a culture of valuing adherence, its similarity to existing processes and its contribution to the aspiration of delivering personalised care.

> *"Actually, do people with CF care about population-level data? Some do, but most probably don't. What they care about is what works for me. So, you know, having this personalised approach where we can show what's happening for them rather than a population, I think will remain really powerful, as a clinician." (PT_02).*

> *"I suppose that a supporting factor here that this is an easy-to-understand framework. I think it is on one page it reads easily, it reads well." (PT_02).*

> *"'are you on enough treatment to keep you stable.' I think that's a really nice way to frame it and patients seem a bit more engaged with that." (PT_05).*

Despite the positive sentiment towards the framework, all participants reported local barriers to implementation including competing priorities, resource constraints, quality/availability of CFHealthHub data and the fact that the PLUTO framework was not considered innovative and omitted symptom burden.

> *"I think the biggest barrier, as with nearly everything we do is it's kind of the pressure on everybody's time and that the resource available." (DR_04).*

> *"there's a bit of a mismatch at the moment in how perhaps our Consultants perceive how much we should worry about these patients, particularly ones with quite high lung function." (PT_05).*

> *"And symptoms don't disappear. They have to be alongside this. And I don't think you can separate out only to have objective FEV_1 and BMI data." (DR_05).*

A specific issue with the detail of the framework was uncertainty about the relevance and application of using a >1% per annum decline in FEV_1 as the definition of suboptimal lung health.

> *"I'm not sure if I did my FEV_1 8 times a year when I came to clinic, it would always be within 1% of the... at the same number." (DR_04).*

> *"And falling by less than 1% over a year, umm, that seems a very small margin and that's quite a difficult one." (DR_02).*

One of the final questions "*Has this conversation led to any changes in the way you think about this topic?*" revealed the thinking that had been done during the interview by several participants. For example, in discussing how PLUTO may be implemented in her Centre, N_01 reflected that they don't have enough spirometry readings to really identify FEV_1 decline which led her to consider that her role should perhaps change to do more home visits for spirometry recording.

For PT_02, a large portion of the discussion was based around the concept of an "FEV_1 reset", in that the numerical values of lung function which were considered "good" or represented a "significant change" for pwCF in the pre-ETI era have not been re-established despite many pwCF having substantial improvements in lung function since being prescribed ETI.

> *"I think that we all struggle to reset, so I and I've heard this a lot in MDT's, I think we struggled to reset in that if you've got someone who was blowing a litre [FEV_1 = 1L], then post-modulators they're regularly blowing, let's say 1.8[L], and then they come in and they're blowing 1.2[L]…but in everyone's mind they're comparing that 1.2[L] with the [1] Litre. They're kind of going "oh well, it's down, but it's still not bad compared with how they were". But it's still 600mL down from their best…there's a really fascinating thing going on there… I see it over and over with amazing, excellent clinicians and patients who previously would have been absolutely on it. It's almost like their brain can't reset the new number." (PT_02).*

PT_02 explained how, even though certain volumes of FEV_1 decline (e.g. 600mL) would have been very concerning in the pre-ETI era, when the post-decline FEV_1 is still higher than the pre-ETI baseline, clinicians are seemingly less concerned. At the end of the interview, PT_02 reflected more on this observation and identified that this was something they needed to discuss as an MDT and agree an approach.

DR_03 noted that their team might benefit from a pre-clinic MDT meeting, a structure I described from my own Centre, to better prioritise the allocation of resources. PT_04 recognised the need to monitor ETI delivery data as a proxy for adherence, which her MDT had not considered. PT_05 saw value in introducing the PLUTO framework to her team, while DR_05 highlighted the need for more rigorous FEV_1 monitoring to identify decline. Beyond generating research data, these examples illustrate how realist interviewing may stimulate improvement initiatives, though assessing this impact was beyond the scope of this study.

4.4 Discussion

4.4.1 Main findings

In this chapter, I developed a broader understanding of clinicians' perspectives on the impact of ETI on the health and care of pwCF using reflexive thematic analysis. Clinicians universally acknowledged the substantial health improvements associated with ETI. However, changes in care delivery preferences and uncertainty regarding the optimal role of well-established treatment regimens alongside ETI have introduced new challenges, which has led to variation in practice.

These findings align with those reported in a US survey of CF clinicians, which similarly highlighted the health benefits observed in pwCF prescribed ETI (261). However, these interviews offered a richer exploration of the broader implications of improved health outcomes, addressing a limitation inherent to survey-based research. Other qualitative studies have focussed on specific areas such as weight management and nutrition in the post-ETI era, whereas I sought to understand the perspectives of health care providers more broadly (262).

The COVID-19 pandemic led to a well-documented acceleration in the worldwide uptake of virtual and remote care in CF (263) and coincided with the introduction of ETI in the UK in August 2020. Participants reported varied implementation of virtual and remote care, with both positive and negative outcomes. This will be explored further throughout this thesis.

Regarding the variation in attitudes towards the role for inhaled medicines for pwCF, the findings align with those of the TEMPO study in the paediatric CF population (264). Through semi-structured interviews, they identified that paediatric CF clinicians were reducing inhaled medicines regimens after witnessing ETI-driven improvements in the health of the children with CF under their care.

Consistent with my findings, clinicians also described a notable discomfort with the uncertainty surrounding whether these decisions might compromise sustained long-term health improvements offered by ETI. However, reducing treatment burden is

considered a high priority for the CF community and pwCF are prepared to trade-off health improvements to achieve burden reduction (265).

Of particular interest was how the participants seemed to feel about the changes to their roles. For example, DR_03 explained that they felt some "*discomfort*" in being presented with non-respiratory issues, in whose management they were less clinically confident. The discomfort may represent shame. Within healthcare, there is a professional culture of perfectionism which can lead to guilt and shame when errors are made or standards not met (266, 267). Objective measures of perfectionism appear to be increasing amongst those in higher education, such a trainee clinicians, over the past three decades (268). It is plausible that CF clinicians, who identify as experts in the care of pwCF, may experience shame if they feel they are not able to meet the needs of the pwCF for whom they care, as their needs have changed rapidly over the past few years. Whilst this was beyond the scope of this study, it may represent an important area for future work.

There was variation in how CFHealthHub was implemented across sites. All participants incorporated CFHealthHub adherence data into routine care but there was variation in who took responsibility for this. In most Centres represented in this phase of the study, there were named CFHealthHub Interventionists who assumed the responsibility for reviewing CFHealthHub adherence data and delivering adherence support. This Lone Champion model is recognised as a common feature of CFHealthHub implementation efforts (269). Whilst champions are often cited as facilitators of implementation, the empiric evidence to support this as an implementation mechanism is mixed (270). Other Centres had chosen to embed the responsibility for CFHealthHub data sharing within the MDT, usually amongst all members of one discipline, most commonly physiotherapy.

Whilst all participants were clear about the importance of discussing adherence, the actual delivery of the intervention was delegated to specific team members, typically the CFHealthHub Interventionist. A recognised challenge to the implementation of CFHealthHub is the resource-intensive nature of the intervention (249). In Centre E, PT_02 reported that they explicitly avoided this strategy in an attempt to embed adherence support in the whole team; however, the outcome of that was that the intervention was not being delivered. PT_02 suggested that an underpinning reason for

this was that, in order to deliver the CFHealthHub Intervention with fidelity, a clinician needed to be doing it regularly. Each Centre has a different set of contextual factors, which have influenced their implementation strategy.

4.4.2 Strengths

Validity, reliability, and trustworthiness are important concepts in determining the quality of qualitative studies. Validity refers to the "appropriateness" of the tools, processes and data (271). Thematic analysis was a valid method of meeting research objectives 1 and 2 as it allowed identification and organisation of themes in a structured manner to describe patterns in the data. Additionally, interviewing 11 clinicians allowed both dominant collective opinions and variation to be unearthed.

Reliability was ensured by following a standard topic guide across all interviews. Whilst there were slight changes to the questioning as my understanding of the area developed during the interview process, the same topics were covered in each interview. Constant data comparison was achieved with a living codebook within NVIVO, where new insights were either coded into an existing code or required generation of a new code. Manually editing transcripts, reviewing audiovisual recordings, and conducting sequential transcript analysis enabled revisiting of earlier transcripts when new findings emerged in later ones. Additionally, offering all interviewees the opportunity to review the final transcript prior to analysis increased the reliability of the data.

Trustworthiness was established using the following steps. The findings themselves are credible, as the experiences that the participants reported in terms of health outcomes post-ETI are consistent with those reported in the trial and real-world literature. All participants were known to the researcher, as an embedded member of the CFHealthHub Central team, and as such had valid experiences of CF care. One participant did not have experience of CF care in the pre-ETI era, having a background in non-respiratory physiotherapy; therefore, the interview focussed less on what has "changed," as for this participant there was no pre-ETI experience against which to judge "change".

4.4.3 Limitations

Recruitment for this phase of the study was opportunistic rather than theoretical or purposive. All Consultant physicians and Interventionists in CFHealthHub Centres were invited, which meant that insights were not gleaned from other members of CF MDTs. Using opportunistic rather than theoretical/purposive sampling limited the scope for the subsequent realist analysis, described in Chapter 5, in that some important outcomes or contexts may have not been explored if they were not relevant for those who participated. For example, to purposively sample clinicians who reported specific (and opposing) beliefs and practices with relation to inhaled medicines for pwCF prescribed ETI may have allowed direct comparison of the contexts and mechanism driving opposed outcomes. However, as this was the earliest phase of data collection for the study, the priority was getting a broad overview.

Additionally, as the setting for this study was within the CFHealthHub learning health system, and section 3 of the interview related specifically to CFHealthHub, recruitment was restricted to clinicians who worked in adult CF Centres which were part of CFHealthHub. Therefore, the findings may not generalise to other CF Centres, such as non-UK Centres, paediatric CF Centres, or CF Centres where CFHealthHub had not been adopted. This may be particularly relevant when asking about the current role and perceived necessity of inhaled medicines, as those who work in CFHealthHub Centres are likely to have been exposed to the general philosophy that adherence is important and that CFHealthHub is a way of supporting adherence.

CFHealthHub Interventionists, who comprised five of the 11 participants, are specifically trained and expected to deliver the CFHealthHub Intervention. This will inevitably shape their opinions on inhaled medicines, and one would expect the direction of influence to be in favour of maintaining all inhaled medicine regimens post-ETI. However, despite this expectation, there was clear variation between participants regarding their attitudes towards therapeutic rationalisation via treatment withdrawal.

Furthermore, the five largest UK adult CF Centres by caseload (Cambridge, Leeds, Liverpool, London South West and Manchester) are not part of CFHealthHub and as such, clinicians at these Centres were not eligible for inclusion (38). Most participants

were from small (caseload <150) or medium (caseload 150-300) UK adult CF Centres. Relationships between clinicians and pwCF may be influenced by the caseload or staff-patient ratios and therefore future work exploring the perspectives of clinicians in larger Centres may provide an important insight into the impact of caseload on experiences and relationships (272).

Whilst my professional background as a clinician helped me establish rapport and engage in a meaningful conversation with fellow clinicians in the interviews, my known role as a member of the CFHealthHub team had the potential to introduce response bias. Whilst not asked directly, participants may have assumed I hold certain pre-conceptions regarding the optimal management of CF, in particularly with regards to the sustained importance of inhaled medicines and commitment to the use of CFHealthHub data and adherence support in routine care. Additionally, all participants were aware that I was first author on a manuscript outlining the PLUTO framework, and as such they may have been reluctant to share negative thoughts due to the risk of causing offence. Consequently, some participants may have tailored their responses to align with what they assumed to be my beliefs, aiming to provide socially desirable answers.

There was some evidence of this, with DR_01 referring to PLUTO as "*mine*", though reassuringly this was as part of a more negative perspective on the potential of the framework for adoption.

> *"So, PLUTO, your PLUTO is lovely Rob, but it's not gonna cut the mustard if we end up having to spend £4000 on nebulisers". (DR_01)*

Additionally, when asked how CFHealthHub was being used in her Centre, N_01 initially sighed and mentioned how her colleagues seemed less engaged with the programme since the introduction of ETI. She looked uncomfortable and it was immediately followed by a string of positive comments, potentially intended to mitigate the initial negative sentiment. Similarly, I recognised PT_04 she seemed quite reluctant, and almost embarrassed, to give some answers that did not fully align with the CFHealthHub philosophy. The fact that she still shared this information despite potential embarrassment provided some reassurance that the rapport we had built meant she felt she could be honest with me, rather than opt for concealment of important information.

4.5 Conclusions

In this chapter, semi-structured interviews with adult CF Clinicians in CFHealthHub Centres revealed the impact of ETI and the COVID-19 pandemic on CF care provision. The data helped develop the answer to the first research question (*"How have ETI and the COVID-19 pandemic shaped perspectives of CF clinicians on inhaled medicines and the demands on their services?"*). Widespread improvements in health for pwCF, alongside digital acceleration has led to a reduced need for acute rescue treatment and increased adoption of remote monitoring and virtual appointments. Whilst these changes are generally regarded as positive, it has introduced some challenges for clinicians in terms of uncertainty regarding optimal use of established treatments, such as inhaled medicines, and emergence of non-respiratory issues in which CF clinicians may feel they have less expertise. With this broad understanding, interview transcripts were reviewed for a second time, this time using a realist approach to analysis, in order to develop an initial programme theory (IPT) for the delivery of CF care in the post-ETI era.

5. Development of Initial Programme Theory

5.1 Introduction

This chapter outlines the development of Initial Programme Theory (IPT) from the interview transcripts, collected as described in Chapter 4. IPT serves as the foundational framework for a Realist Evaluation, enabling the evaluator to hypothesise about the mechanisms of change and the conditions under which these mechanisms are expected to operate (131, 237). By exploring these elements, IPT provides insights into how a programme might bring about its outcomes and under what circumstances, which is critical for understanding why certain outcomes emerge in some contexts and not others (230). The development of IPT, particularly relating to the perspectives of clinicians helped to develop my answer to the first research question *("How have ETI and the COVID-19 pandemic shaped perspectives of CF clinicians on inhaled medicines and the demands on their services?")*.

From my discussions with the CFHealthHub programme director, which informed Chapter 2, and my role as a member of the CFHealthHub central team, I developed initial insights, particularly around general improvements in wellbeing and reduced use of inhaled medicines post-ETI. The emerging uncertainty regarding the necessity of inhaled medicines seemed to disrupt the implementation of CFHealthHub, as a programme designed to support adherence to inhaled medicines specifically. This suggested that the programme's effectiveness might depend on how such uncertainty influences how clinicians and pwCF engage with the CFHealthHub digital platform and behaviour change intervention.

The thematic analysis in Chapter 4 revealed two key ideas that are central to the Realist Evaluation: first, the prevalent uncertainty surrounding multiple aspects of CF care post-ETI, and second, the resulting variation in practice and preference between clinicians and pwCF. These findings laid the groundwork for identifying the contextual conditions that shape how CF care is delivered, as well as the mechanisms through which these uncertainties and variations lead to different outcomes.

The Realist analysis described in this chapter enabled me to reach a deeper ontological understanding by focussing on the underlying mechanisms that are triggered by changes in the context of CF care. In contrast to surface-level patterns, this ontological depth sought to identify not just the outcomes, but the causal processes and conditions that explain how and

why aspects of CF care, including CFHealthHub, work (or don't) in specific situations, offering a richer understanding of outcome variation.

5.2 Methods

5.2.1 Theory development process outline

Interview transcripts were reviewed and annotated using Microsoft Word. A coding approach was used where key pieces of information in textual data were categorised into contexts (C), mechanisms (M) and outcomes (O), to support the generation of initial CMOCs either as CO, MO or CM dyads, or CMOC triads (273). This allowed insights to be articulated directly from the words of the participants and revealed the interactions of contexts, mechanisms and outcomes. Additionally, where mechanisms in particular were not explicated in the textual data, retroductive theorising was used, in order to offer plausible mechanisms or outcomes related to emergent dyads (228).

IPT statements were structured using the CMOC heuristic (131). This approach not only facilitated the articulation of early theoretical propositions but also highlighted partial theory fragments, where elements of context, mechanism, or outcome were missing or uncertain. These gaps were then explored through existing data or used to guide future data collection. Realist Evaluation embraces retroductive theorising, whereby researchers draw on theoretical knowledge and intuition to hypothesise and refine causal explanations, particularly in relation to the generative mechanisms driving observed outcomes (228). An example of a CMOC is:

When pwCF notice a deterioration in their health state (Context, C), this may increase the perceived health threat of CF (Mechanism, M1: reasoning) or be an internal cue (Mechanism, M2: response) leading them to increasing their used of inhaled medicines (Outcome, O).

Evidence for this statement may include quotes, such as

> *"In the last year to six months we're getting more patients that are returning with symptoms. They're being more open to perhaps starting or upping treatments again" (PT_05).*

In this quote, there is clear reference to an outcome ("*upping treatments again*") and a potential contextual factor that appears related to this outcome ("*patients that are returning with symptoms*"). This statement does not provide information related to the behavioural

mechanism that leads to pwCF who return with symptoms to “up treatments again” but retroductive theorising allows hypothesis on the causative mechanism which may link the context to outcome. In this case, an increase in symptoms may increase the perceived health threat, or be perceived as an internal cue for the action of taking treatment (compared to times of no or lesser symptoms), which is derived from the Health Belief Model (274). This hypothesis, about perceived necessity was then explored later in the study to build empiric evidence for this theory statement.

CMOC development was tracked in a text document using Microsoft Word. After reviewing the first six transcripts and generating CMOCs, these were refined, consolidated, and indexed. The remaining five transcripts were reviewed with a focus on how they informed the development of the CMOC index. CMOCs were grouped into topic areas, to help sort and consolidate the data. A graphical summary of the theory development process is shown in Figure 8.

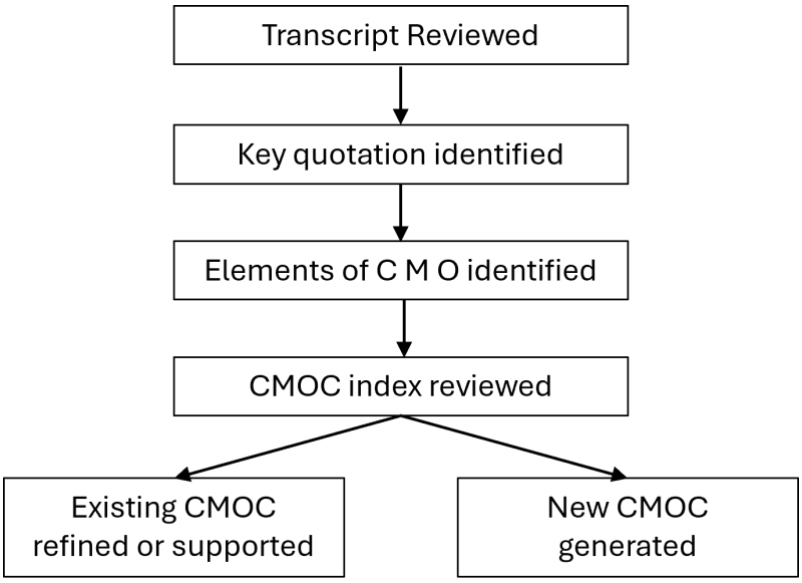

Figure 8: Flow chart representing the process of theory development and CMOC index generation.

5.2.2 Theory development examples

The following examples demonstrate how difference pieces of evidence, including interview transcripts and published literature contributed theory fragments, related to contexts, mechanisms and outcomes. Where possible, fragments were configured into CMOCs from the primary data, however retroductive reasoning was used when necessary to offer causal insights. CMOCs were then further refined through identification of supporting, advancing or contrasting evidence in subsequent data collection and analysis.

Example 1 – The transformative impact of ETI

CMOC Code: ETI_01_v01:

CMOC Title: The transformative effects of ETI leading to reduced emphasis on non-ETI treatments.

CMOC: The introduction of ETI during the emotionally intense period of the COVID-19 pandemic, coupled with its widespread availability and significant clinical benefits (C) meant that both clinicians and pwCF perceive ETI as a transformative solution (M1: reasoning) and are optimistic that it may "*fix*" the problems associated with CF (M2: reasoning) resulting in pwCF leading lives more akin to that of the general population (O1) with a reduced emphasis on adherence to non-ETI treatments such as inhaled medicines (O2).

Theory development process

Initially, two interview quotations contributed to the identification of contextual factors and, through retroductive reasoning, informed hypotheses about the mechanisms that may be activated to produce the observed outcomes.

> *"So one is that you know ivacaftor was just literally a handful of patients. so suddenly it's gone from being like most people don't have a modulator to most people do…. It's just you know that have been more patients where it's made like a really huge difference." (DR_01).*

> *"it's the fact that it [ETI] covers a lot of people and has a dramatic impact. So, the fact that some people or a lot of people now wake up and don't have to spend hours clearing their chests, as there's very little sputum there. It's such a dramatic improvement in quality of life and equally sometimes, you know, seeing some people's FEV_1's gone up by 20% is really gratifying as well. And you got people who cycle a lot, who are now at the front of the group of lots of people without CF, who would have been OK, but at the back. So that's gratifying to see." (DR_01).*

A key contextual insight emerging from these quotes is that ETI has widespread eligibility across the UK CF population, resulting in the majority of pwCF at any given Centre being prescribed it. These accounts also highlight substantial reductions in sputum production and improvements in quality of life which have, in turn, reduced the perceived necessity for time-intensive chest clearance, a daily practice historically central to CF care. Reference to "*huge*" differences, "*hours*" of the day no longer being required for chest clearance, and "*dramatic*" improvements in physical function all suggest that ETI is perceived as transformative for the

health and daily lives of pwCF. These quotes supported formulation of the following theory fragments:

Context (C1) – Most pwCF are eligible for and prescribed ETI.

Context (C2) – Many pwCF have improved health and quality of life as a result. *(NB: whilst this could be considered an outcome of widespread eligibility and prescription of ETI, in this theory statement, I considered it a contextual factor which triggers the mechanism described next)*

Mechanism (M1: reasoning) – ETI is perceived as transformative.

This CM dyad offers insight into the changing contextual landscape of the post-ETI era and the ways in which these changes are being perceived. Whilst this quote itself does not articulate a specific outcome, retroductive theorising, drawing on the quote from DR_03 "*you got people who cycle a lot, who are now at the front of the group of lots of people without CF, who would have been OK, but at the back"* supports the hypothesis that pwCF are now experiencing a degree of physical functioning akin to that of the non-CF population. This is captured in the outcome fragment:

Outcome (O1**) –** pwCF are living lives more akin to that of the general public.

An additional quote contributed to the development of this theory fragment, particularly by offering insight into to the mechanisms that may be triggered in the contexts described in C1 and C2.

> *"And I think the problem is now because there's this kind of feeling that, you know, well CF is all fixed now and people's lung functions much better and all the rest of it. That argument of you know well, this long-term adherence stuffs like really, really important is just not washing in quite the same way, I don't think." (DR_01).*

The perceived effectiveness of ETI may create the impression that CF is "*fixed*," thereby diminishing the perceived importance and influence of clinician recommendations regarding long-term adherence to other (non-ETI) treatments. This quote supported formulation of the following theory fragments:

Mechanism (M2: reasoning) – some people consider that CF is now "*fixed*".

Mechanism (M3: response) – pwCF do not find clinician's arguments in favour of maintaining long-term adherence to non-ETI treatments impactful.

An additional quote provided further insights, related to the CM dyad, but not the outcome of living lives akin to that of the general public (O1).

> *"I think there was something really interesting about the timing that Kaftrio was commissioned, in that it was in the midst of shielding for people with CF and a really difficult emotional time for lots of clinicians who were uncertain about what things might look like. Were uncertain whether they should be shielding from their own families at home and lots of emotional triggering things going on. And then...Kaftrio. So of course everyone's gonna have a warm, glowy feeling about it and see it as a silver bullet and going to conference during the clinical trials and seeing those clinical trials was like nothing else. It was a very special kind of thing to hold on to. So, I think there is the risk as clinicians that we lose that science bit of our heads, and we end up being very human about it and kind of going "this is brilliant. All our problems are solved, and we don't need to really think about it [CF] anymore. They take the tablets [ETI] and we're all good." (DR_02).*

This quote introduced another element of context, which deepens the understanding of why ETI is perceived as transformative. It was introduced to pwCF in the UK as part of routine care during the COVID-19 pandemic, a period marked by heightened emotional intensity. I retroductively theorised that this convergence of events may have contributed to another outcome: reduced adherence to inhaled medicines among those prescribed ETI, which is a well-established in the CF literature (111-114, 213, 251-255). This was captured in the following theory fragments:

Context (C3) – ETI introduced during the COVID-19 pandemic.

Mechanism (M4: reasoning) – this was a period of high emotional intensity, meaning the positive emotional impact of the ETI was amplified.

Outcome (O1) – resulting in reduced adherence to inhaled medicines.

These theory fragments were subsequently consolidated and articulated as a CMOC, described at the start of this sub-section, offering a causal insight into this aspect of CF care post-ETI.

Example 2 – The changing nature of pulmonary exacerbations

CMOC Code: PEX_01_v02:

CMOC Title: Pulmonary exacerbations present differently post-ETI, meaning they risk being unrecognised and there are delays to treatment.

CMOC: PwCF who are prescribed ETI and experience fewer or no symptoms, even when there is an acute decline in lung function (C) are less likely to recognise when they are having an exacerbation (O1) because the symptoms they had associated with exacerbations have changed (M1: reasoning). Therefore, clinicians cannot rely on pwCF recognising and reporting exacerbations (M2: reasoning) increasing the reliance on objective measures such as lung function (M3: response), increasing the risk of delayed intervention, such as deterioration to more severe, acute clinical conditions, such as pneumonia (O2).

Theory development process

> *"Patients don't recognise symptoms in the same way. So, I think some of the changes are a bit more subtle with people and then we'd notice it more in the in the lung function and then that would spark a conversation about "oh, how are you feeling in yourself?" And I just feel like patients have said it's like there was a pre Kaftrio way that I used to feel... I think for people who've recognised the symptoms of their condition and when they need a certain intervention before, that's now different. So, there are people who perhaps wouldn't notice things at all." (N_01).*

This quotation provided the initial fragments of a theory regarding pulmonary exacerbations in the post-ETI era. In the pre-ETI era, an exacerbation typically involved an increase in subjective symptoms, such as cough, alongside a decline in objective health indicators, such as lung function (275) . However, in the post-ETI era, subjective symptoms now appear more subtle or may be entirely absent, even in the presence of a decline in lung function (276). This observation gave rise to the following CO dyad.

Context (C1) - PwCF who are prescribed ETI and experience fewer or no symptoms, even when there is an acute decline in lung function.

Outcome (O1) – PwCF do not recognise when they are having an exacerbation.

A second quote from the same participant later in the transcript offered further insights that helped develop and refine these theory fragments.

> *"I think before [pre-ETI] when someone was getting unwell, some people would sort of notice it quite quickly and they'd be in touched quite quickly. Where are they've reported that it's more of a slow burner these days. The symptoms are less severe, so sometimes by the time they think "Oh yeah, I'm actually not feeling very well" they're really not feeling very well, but because things come on more gradually." (N_01).*

The same CO dyad was referenced in the quote but more information about the consequential outcomes of delayed recognition was provided and captured in this second outcome fragment.

Outcome (O2) – resulting in more severe clinical manifestations due to delayed intervention.

A third quote, from a different participant, referenced same CO dyad as both previous quotes.

> *"They often haven't recognised that exacerbation straight away. It's presented differently." (PT_02).*

In recognising the repeated reference to this CO dyad, I considered potential mechanisms that may explain the outcome, using retroduction. It is plausible that, for pwCF who have become accustomed to recognising the symptoms which indicate pulmonary exacerbations over a lifetime of lived experience in the pre-ETI era, the transformative changes in their day-to-day symptoms post-ETI extend to those experienced during an exacerbation. The Health Belief Model considers that people respond to "cues to action" and for pwCF the cue (an increase in symptoms indicative of exacerbation) that previously triggered the action of contacting care providers to inform of an exacerbation and discuss treatment, such as inpatient admission for IV antibiotics, had now been disrupted. Whilst the quotes do not directly identify this mechanism, Realist Evaluation acknowledges that mechanisms are often hidden, generative forces that require retroductive theorising to uncover. This mechanism is captured as follows:

Mechanism (M1: response) – pwCF relied upon specific changes symptoms to indicate exacerbation as a cue to contact care providers.

A fourth quote provided further insights into how clinicians may respond to this outcome, and its influence on treatment decisions.

> *"They're not as unwell, so the number of bed days is dramatically lower but we're still getting people who get productive with an exacerbation as well as a drop in spirometry. I think we have had people we've given IVs to just because of a drop in FEV_1 without becoming productive [of sputum], but I think the majority have become productive" (DR_03)*

Mechanism: (M2: reasoning) – Clinicians are not relying exclusively on symptoms (such as increased sputum production) but instead on objective markers of lung function when making treatment recommendations for exacerbation.

These theory fragments were subsequently consolidated and articulated as a CMOC, offering causal insight into the changing nature of pulmonary exacerbations in the post-ETI era and its impact on care.

CMOC code: CMOC PEX_01_v01.

CMOC title: The symptoms of pulmonary exacerbations for pwCF have changed post-ETI, resulting in reduced recognition and delayed treatment.

CMOC: PwCF who are prescribed ETI and experience fewer or no symptoms, even when there is an acute decline in lung function (C) are less likely to recognise when they are having an exacerbation (O1) because the symptoms they had associated with exacerbations have changed (M1: reasoning). Therefore, clinicians cannot rely on pwCF recognising and reporting exacerbations (M2: reasoning) increasing the reliance on objective measures such as lung function (M3: response), increasing the risk of delayed intervention (O2).

As more interview transcripts were reviewed, additional evidence emerged that supported this CMOC.

> *"I think identifying exacerbations on Kaftrio is a lot different to pre-Kaftrio. They're not getting that really awful cough and huge amounts of sputum. It might just be that they're a little bit more breathless or they're a little bit more fatigued and they've lost their appetite. It might not necessarily be those horrible chest symptoms that they got before. That's what they're looking out for, so it might be a little bit more subtle, and I think it's important for us to look at those things." (PT_04).*

This quote supported the following aspects of the CMOC: C; O1; M1; M2 and M3. The statement "*That's what they're looking out for, so it might be a little bit more subtle"* also provides evidence in support of my retroductive theorising for M1. The following quote also supported C, O1, M1 and M2.

> *"people who had always been producing phlegm and knew that they were brewing an infection because they got more of it and feeling short of breath and feeling a bit wheezy and would come to you. 1) now produce very little phlegm. The phlegm that they produce is much lighter and thinner. And when they get a cold and they've still got a cough, but it's so much less than it ever was before, even though they're now coughing up quarter of a pot when they were coughing nothing, [they] ignore it. They don't come to you straight away. They just [stay] on that bit where if they had a viral infection before modifiers*

> *[modulators], they'd have sat it out to say "is it going to get better or is it going to stay? Do I need antibiotics or not?" And now they're almost applying that principle because they feel that the sputum load is so low in comparison to anything they had pre-modifiers [modulators] that they are not getting into their head that they don't have a cough normally and that this has gone on for more than a viral infection should and I should do something about it...I just think they are not being prompted by their symptoms both to do their nebulised therapies and to come and see us about things." (DR_05).*

A further quote again supported the retroductive theorising of M1.

> *"I think the other thing that they're struggling with on feedback in the past, if you are more symptomatic and you came to clinic, your lung function was down. So, the two bits of information went side by side. You've got your head around it and it came back up. Now they can come in. Feeling very symptomatic may be triggered by our viral infection but feeling symptomatic and then FEV_1 not gone down. And then that's totally unpicking all the information that's in their head about it, and I think it's hard enough for us and it's certainly hard for them and there's certainly, the other bit that's very hard is that we would use a lot of sputum colour, tenacity and now it's just volume, often, because it doesn't get thick in the same way. Because CFTR, the modulator's working, so it stays thin. So again, that it's difficult. All those bits that were their reinforcement mechanisms that I need to do something about it aren't there and they're having to relearn them slightly differently, but they are putting previous experience in in place." (DR_05).*

Finally, another quote from the DR_05 expanded the consequences of delayed intervention, which was incorporated into the O2 fragment.

> *"I think actually the bit that everybody else has observed and we've only had in a couple of patients, but we're much smaller group, is that they don't necessarily always present with an airway infection, and then they get the pneumonias, whereas always, they'd almost always, invariably there would be a symptomatic airway infection and you'd head it off very early so you didn't get to the pneumonias on the whole, unless there were loads of other things going on." (DR_05).*

This led to a revised iteration of the CMOC, developed in response to the emerging evidence.

CMOC PEX_01_v02: PwCF who are prescribed ETI and experience fewer or no symptoms, even when there is an acute decline in lung function (C) are less likely to recognise when they are having an exacerbation (O1) because the symptoms they had associated with exacerbations have changed (M1: reasoning). Therefore, clinicians cannot rely on pwCF recognising and reporting exacerbations (M2: reasoning) increasing the reliance on objective measures such as lung function (M3: response), increasing the risk of delayed intervention, such as deterioration to more severe, acute clinical conditions, such as pneumonia (O2).

Example 3 – Reduced symptoms post-ETI results in uncertainty around the role of inhaled medicines

CMOC ID: PBM_05a_v02

CMOC Title: PwCF who have less severe, or no symptoms have reduced adherence to inhaled medicines.

CMOC: When pwCF experience significant improvements in health from ETI (C) they may perceive ETI as a solution (or cure) to CF (M1: reasoning) and feel that CF poses a lower health risk (M2: reasoning). This belief may also make them more receptive to questionable sources of information which reinforce this perspective (M3: reasoning), leading them to reduce the use of other treatments, such as inhaled medicines (O).

CMOC ID: PBM_05b_v01

CMOC Title: PwCF who have less, or no symptoms have reduced adherence to inhaled medicines.

CMOC: When pwCF experience significant health improvements from ETI (C), they may perceive ETI as a realisation of the long-established hope for an effective treatment reduces which burden (M1: response). This feeling empowers PwCF to exercise autonomy (M2: response) and reduce or stop other treatments (such as inhaled medicines) without waiting for clinical evidence or support from their healthcare providers (O).

A prominent finding across the interviews was that the reduction in symptoms, particularly sputum production, following initiation of ETI emerged as important contextual factor contributing to the observed decline in adherence to inhaled medicines.

> *"I feel a lot of patients were really keen to stop other treatments, not just nebuliser treatments, but everything else really as soon as they got Kaftrio, which they'd perceived as the answer to CF." (PT_02).*

> *"So, I think we've seen some patients who feel really well since modulator. The ones that have had the biggest increase in FEV_1, the biggest quality of life improvements, the biggest changes in terms of not needing so many courses of IV antibiotics for example, and some patients now feel like they don't need to have as much [other treatment" (N_01).*

> *"A lot of patients don't cough up sputum [post-ETI]. That's been their main troubling symptom. And so, because they don't cough up sputum, they stop a lot of their*

> *medication, and they come to clinic a lot less often. They're much more reluctant to take on new treatments." (DR_03).*

These three quotes provide support for the CO dyad of reduced symptoms post-ETI (context) lead to reduced use of inhaled medicines (outcome). The first quote, from PT_02, also alluded to a potential mechanism, namely the perception of ETI as a cure for CF. Together, these fragments were articulated as a simple, evidence-informed CMOC.

CMOC ID: PBM_05a_v01

CMOC Title: PwCF who have less, or no symptoms have reduced adherence to inhaled medicines.

CMOC: When pwCF experience significant improvements in health from ETI (C) they may perceive ETI as a solution (or cure) to CF (M1: reasoning), leading them to reduce the use of other treatments, such as inhaled medicines (O).

This CMOC did not fully explain the mechanism which led the feeling of being "cured" to the reduction in use of other medicines and was therefore considered provisional, being marked for refinement through the analysis of further data and/or retroduction. A quote from DR_02 contributed to the development of the proposed, missing mechanism, suggesting that pwCF are now less concerned about maintaining adherence to non-ETI medicines. This may be reinforced by informal sources of information, such as peer discussions or social media (e.g. "*I've read something somewhere*") which I theorised to reflect information primacy as a manifestation of confirmation bias.

> *"I think more people at the start going on to modulators or certainly by the end of the first year were of the "well everything's good now on Kaftrio. I'm not worrying about any of the other treatments, maybe some Creon, that's it". Even to the point of their diabetic treatment, it's kind of like "you know I've read something somewhere that I should still be better it's all fine" kind of thing." (DR_02).*

This mechanistic insight was captured within a revised iteration of the CMOC.

CMOC ID: PBM_05a_v02

CMOC: When pwCF experience significant improvements in health from ETI (C) they may perceive ETI as a solution (or cure) to CF (M1: reasoning) and feel that CF poses a lower health risk (M2: reasoning). This belief may also make them more receptive to questionable sources

of information which reinforce this perspective (M3: reasoning), leading them to reduce the use of other treatments, such as inhaled medicines (O).

A third quote also provided additional mechanistic insight into the CO dyad.

> *"Often when asked, CF patients will say what they want is something that will make them feel better but reduce the treatment burden. They don't just want extra treatment to make them better, the taking the treatment is part of the thing they struggle with CF, so I think they've got what they asked for in a treatment that's useful and might enable them to stop other treatments. And so, without waiting for the proof of whether you can, they're just voting with their feet." (DR_03).*

This quote was used alongside retroductive theorising to propose that considering ETI as the realisation of a long-standing hope for a treatment which would allow pwCF to reduce treatment burden, may generate a sense of autonomy among pwCF, empowering them to discontinue non-ETI treatments without waiting for clinician approval or published trial data to support such treatment rationalisation. This theorised mechanism was articulated in a new CMOC (PBM_05b), related to the one described above (PBM_05a).

CMOC ID: PBM_05b_v01

CMOC: When pwCF experience significant health improvements from ETI (C), they may perceive ETI as a realisation of the long-established hope for an effective treatment which reduces burden (M1: response). This feeling empowers PwCF to exercise autonomy (M2: response) and reduce or stop other treatments (such as inhaled medicines) without waiting for clinical evidence or support from their healthcare providers (O).

As these examples demonstrate, theory development is complex and relies on multiple sources of evidence alongside retroductive theorising. Whilst CMOCs are a heuristic used to help organise theory statements in Realist Evaluation, the objective is to develop and present a context-sensitive understanding of the system under investigation, rich with mechanistic insights, to help stakeholders make sense of why certain outcomes are occurring and what may be required to deliver intended outcomes.

5.3 Results

5.3.1 Key areas of theory development

Reviewing the interview transcripts using the aforementioned approach yielded the following insights, building on the results of the thematic analysis reported in Chapter 4. ETI has had a transformative impact on CF care, driven by widespread eligibility and significant improvements in symptoms. This has led clinicians and pwCF to re-evaluate the role of other, long-established medicines for pwCF who have responded well to ETI. Given the high treatment burden associated with CF over the life course, pwCF in particular seem motivated to leverage the benefits of ETI to autonomously reduce their overall treatment burden, despite a lack of clinical trial evidence or clinician support in taking this approach.

In the case of inhaled medicines, especially mucolytics, which act by reducing sputum viscosity and volume, the marked reduction in sputum production reported by many pwCF following initiation of ETI has directly challenged the underlying rationale for adhering to daily treatment regimens. Clinicians are navigating uncertainties around the role for inhaled medicines, which is reflected in inconsistent clinical recommendations. At times they advocate strongly for the use of inhaled medicines, particularly when there are objective markers of deterioration such as lung function decline. At other times, clinicians deal with uncertainty by adopting a shared decision-making approach and supporting careful monitoring when treatments are discontinued.

Clinicians consistently emphasise the value of robust, published evidence to guide these decisions, but in its absence, thoughts and behaviours vary. Some experience feelings of disempowerment whereas others describe a positive shift towards learning, embracing, and sharing uncertainty with pwCF and engaging more fully with shared decision-making practices.

Both clinicians and pwCF are re-evaluating the role of established models of care, such as routine 6 to 12-weekly in-person appointments, especially in those who are much improved post-ETI. This re-evaluation of care models has been accelerated by the widespread adoption of virtual appointments and remote monitoring, driven by the COVID-19 pandemic. Whilst virtual consultations hold advantages in terms of equity of access to care and convenience, clinicians are mindful of the limitations of virtual care, including reduced ability to leverage in-person interaction to build strong therapeutic relationships and access to sufficient, accurate

health indicator data to make thorough assessments of health and guide clinical recommendations. In addition to the model of care, clinicians also recognise changes in the demands on their service, with non-respiratory issues, with which they perceive less expertise and familiarity, coming to the forefront of the lived experience of many pwCF prescribed ETI.

Finally, clinicians described current efforts to implement adherence support through the CFHealthHub programme, using a range of workforce and workflow structures to keep adherence on the agenda. There were positive sentiments towards implementation of the PLUTO framework, though there was a broad recognition that, despite being perceived as a in keeping with current practice and priorities, implementation would require changes to workflow and workforce structures that act as barriers to implementation. Initial theories related to the PLUTO framework were developed, including topics such as perceived value of the framework and changes required to enable implementation. However, as no Centres responded to the offer to implement the framework, these theories were not explored further.

5.3.2 Development of CMOC index

After review of the first six transcripts, 76 CMOCs were generated across 15 topic areas, including changes in the way pwCF engage with inhaled medicines and care, clinician uncertainty around the role of inhaled medicines and roles and challenges associated with virtual and remote care. After review and consolidation, the CMOC index was reduced to 59 CMOCs across 13 topic areas. After analysis of the remaining five interview transcripts, 57 CMOCs, across 12 topic areas constituted the formal IPT of this Realist Evaluation, which is presented in Appendix 3.

5.4 Discussion

5.4.1 Main findings

The CMOC index contained 57 theory statement, which comprised the IPT and helped inform the subsequent stages of data collection and analysis in this study. Therefore, a concise summary of the key topics within the IPT is presented here, with a more detailed interrogation of the final, refined Programme Theory presented later in the thesis.

The IPT described how improvements in health from ETI has resulted in uncertainty in how best to continue to promote optimal health for pwCF. There is uncertainty, disagreement, and variation between both clinicians and pwCF which manifests in range of ways, which can range from a lack of confidence in clinical recommendations, variable reliance on discordant objective and subjective measures of health and the adoption of shared decision-making approaches. Some challenges have been exacerbated by adoption of hybrid care models, which involve combination of virtual and in-person appointments. Whilst the adoption of these models was initially driven by the COVID-19 pandemic, they have been sustained in many Centres. Generally, virtual appointments seem to be favoured by pwCF, in terms of convenience, whereas clinicians are more sceptical, who recognise that there are risks of important clinical information being unavailable or missed during virtual appointments.

5.4.2 Strengths

As described in section 4.4.2, a strength of the clinician interviews was the representation of clinicians across eight UK adult CF Centres, ensuring a range of contextual factors could be incorporated into the IPT. Linked coding of aspects of context, mechanism and outcome strengthened the internal logic of CMOC and transparent documentation of retroduction reflected fidelity to realist methods. Additionally, retroduction permitted inference of generative mechanisms, rather than simply describing patterns in the data. CMOCs were grounded in the language and lived experience of participants, ensuring the theoretical insights were empirically anchored to enhance the face validity of the IPT.

5.4.3 Limitations

As described in section 4.4.3, the primary limitation was related to opportunistic sampling from a pool of Consultant physicians and CFHealthHub Interventionists. Therefore, contextual factors which may be found in non-CFHealthHub Centres were not incorporated in the IPT. However, identifying where adoption of CFHealthHub was a contextual factor, for example in CMOCs SUP_01, SUP_03, SUP_05 and IMP_01-03, one can theorise how the counterfactual position of not having access to CFHealthHub may lead to mechanisms not being triggered, resulting in opposing adherence-related outcomes. Additionally, there was the potential for social desirability bias to influence responses, with my position as a member of the CFHealthHub central team being known to all participants, though, reassuringly, critical viewpoints were shared, suggesting the impact of this bias was limited.

5.5 Conclusions

This chapter presented the IPT for the Realist Evaluation in the form of 57 empirically grounded CMOCs, which were tested and refined throughout the subsequent work of this thesis. The IPT primarily developed my answer to the first two research questions ("*How have ETI and the COVID-19 pandemic shaped perspectives of CF clinicians on inhaled medicines and the demands on their services?*" and "*How have ETI and the COVID-19 pandemic shaped the experiences and care needs/preferences of pwCF?*").

At this point, I offered to evaluate implementation efforts of the PLUTO framework across Centres within the CFHealthHub learning health system, but no Centres responded to this offer. Therefore, theories directly related to the PLUTO framework were not explored further.

The challenge posed by a rapidly evolving therapeutic landscape, clinician uncertainty and the autonomy of PwCF has significant implications for both CF care delivery as a whole and also for the implementation of CFHealthHub, as an adherence support programme for a treatment (inhaled medicines) where there is a new, fundamental question of its role and necessity. Whilst the constant comparative method allowed consistent theory development by updating CMOCs as relevant evidence was obtained,

the next phase of the study involved a focussed interview with a CF physiotherapy team and a CFHealthHub Interventionist at a single site, in order to directly test and develop CMOCs related to the delivery of adherence support in the post-ETI era (Chapter 6) before moving to further theory testing and refinement directly with pwCF (Chapters 7 and 8).

6. Physiotherapy team and CFHealthHub Interventionist interviews

6.1 Introduction

In this chapter, I describe semi-structured, realist interviews conducted with key stakeholders at a single CF Centre to test and refine the IPT developed in Chapter 5. In the post-ETI era, the implementation of CFHealthHub and adherence support has been directly influenced by a range of contextual factors, mechanisms, and outcomes as identified in IPT statements SUP_01 to SUP_05 and IMP_01 to IMP_03.

It was evident that clinicians delivering adherence support valued aspects of the CFHealthHub intervention, such as regular in-person contact and home visits. However, resource constraints, technical challenges, and variable engagement from pwCF have limited the uptake of adherence support. Engagement has been further affected by the positive health effects of ETI, which have introduced uncertainty around the ongoing necessity of inhaled medicines. As a result, adaptations to intervention delivery are common. These include the use of virtual clinics, recording action and coping plans outside of the platform (if at all), and the introduction of tiered adherence support. Consequently, the intervention is being delivered with varying fidelity by clinicians across the wider MDT, often with little or no additional training.

These interviews aimed to explore how the mechanisms and contextual factors identified in the IPT manifest in practice, specifically in the provision of adherence support to pwCF in the post-ETI era. This helped to continue developing my answer to the first research question ("*How have ETI and the COVID-19 pandemic shaped perspectives of CF clinicians on inhaled medicines and the demands on their services?*"), though narrowed the focus on the practical delivery of adherence support, which had emerged as a key part of service provision which had been disrupted by ETI and the COVID-19 pandemic. This Centre was selected for this phase of the study due to my established role as an embedded member of the clinical team. This positioning enabled access to CF clinicians and facilitated the development of collegiate relationships, which were instrumental in supporting in-depth qualitative enquiry.

At this Centre, CFHealthHub was well-integrated into routine clinical practice, with responsibility for adherence support distributed across both the physiotherapy team and the designated CFHealthHub Interventionist. Importantly, none of the clinicians interviewed in Chapter 4 were based at this Centre, allowing for comparative insight by considering the perspectives of those delivering adherence support in this context alongside the views of clinicians operating in other settings, which had already been captured.

6.2 Methods

6.2.1 Data collection

The lead physiotherapist was approached via email to arrange a group interview with all members of the physiotherapy team at a mutually agreeable time. Group interviews, particularly between health care professionals and researchers, can uncover implementation strategies from real-world implementation efforts (277). Group interviews also capture peer-to-peer discussions, where agreement can identify patterns, and inherent variation prompts questioning, probing, and justification, providing the potential for deeper mechanistic insight.

The group interview took place in-person and was audio-recorded using Microsoft Teams. The recording was used to produce a verbatim, naturalised transcript, with identifiable data being redacted. The interview followed a structured topic guide, shown in Appendix 4.

The CFHealthHub Interventionist was then invited for a virtual interview, using Microsoft Teams. An audio-visual recording of the interview was taken and used to produce a transcript, similar to as described for the group interview. The topic guide was similar to that used in the physiotherapy group interview but was refined based on insights gained during that discussion. It is shown in Appendix 5. All interviews incorporated the use of realist interviewing techniques to contribute to the collection of data which would allow generation of new theory statements but also refinement and testing of the IPT (256).

6.2.2 Data analysis

Transcripts from both interviews were reviewed line-by-line and analysed using a realist approach in Microsoft Excel. When important data were identified in transcripts, they were compared with the existing IPT CMOC index to either provide evidence in support of existing CMOCs or generate a new CMOC, as demonstrated in Figure 8 in section 5.2.1. This Constant Comparative Method is considered most appropriate for testing and refining CMOCs, though it also supported recognition of when a new CMOC was required to capture the insight (241).

6.3 Results

The physiotherapy group interview lasted 38 minutes and took place in the private meeting room on the CF ward. Six members of the physiotherapy team attended, consisting of two permanent CF physiotherapists (CPT_02, CPT_03), two physiotherapy assistants (CPT_06, CPT_08), who are permanently attached to the CF MDT, and two more junior, rotational physiotherapists (CPT_04 and CPT_05) who were midway through a 6-month rotation in the CF Centre.

Each participant made at least one contribution, however the most junior members of the team (CPT_04 and CPT_05) made less contribution than the more senior members of the team. The participants identified pwCF's own levels of engagement, their understanding of clinician recommendations regarding optimal treatment, the regularity of contact between clinicians and pwCF and maintaining the reliable collection of adherence data through CFHealthHub as particular topics to explore during the interview. The majority of the interview covered the interactions between the clinicians and pwCF regarding inhaled medicines.

The interview with the CFHealthHub Interventionist lasted 1 hour and five minutes. They also spoke about the importance of intrinsic motivation from pwCF in the adherence support process, the value they ascribe to objective health and research data in explaining the importance of inhaled medicines to pwCF, and how the team dynamics lead to variations in the provision of adherence support across the Centre.

6.3.1 Key areas of theory development

These interviews supported previous theory development from Chapter 5 around the fact that pwCF who have fewer symptoms post-ETI are questioning the role of inhaled medicines, as it is no longer clear for them what benefits they confer.

> *"...since patients have been on...Kaftrio their...appreciation of why they're taking their nebulisers has changed because a lot of them...feel a lot better in themselves...whereas before maybe they could see more of the necessity to take their DNase because they knew it loosen their sputum because now...it's like, 'well, I've not got sputum, so why do I need to do this nebuliser?'." (CPT_02).*

When questioned about this necessity, clinicians relied on published evidence as proof of the validity of their recommendations, though pwCF do not always accept this rationale.

> *"There is obviously research that's shown that there can be the decline in the FEV_1, we want to maintain that....a lot of the conversation I feel I have with patients. "Well, I don't see why I need to do it anymore because I don't have that"...that's sometimes been the most challenging part." (CPT_02).*

> *"[I] talk about the ivacaftor 5-year study and how lung function's back to baseline after five years and...a 1% annual decline in FEV_1 could help to promote your normal life expectancy...I do talk about the NEEMO 2-year data now as well, which is really nice to have." (INT_01).*

Hospital admissions are perceived as valuable opportunities to initiate adherence discussions and support. Acute illness, particularly when preceded by periods of low adherence, can help pwCF make the connection between adherence and health outcomes. Additionally, demonstrating how adherence levels relate to objective health measures, such as lung function, is considered a valuable and effective tool for clinicians when supporting adherence.

> *"it's normally more they are becoming unwell [CPT_03 agrees] or they need to come into hospital [CPT_03 agrees] then that's when...they start doing their nebs because they feel unwell [hums of agreement]." (CPT_06).*

> *"If patients have got, for example, lowered lung function compared with what it has been previously, then that can be a nice door in as well... you can sort of say "oh, you know, and why do you think you might have lower lung function" and that can*

sometimes bring about a realisation that it might be related to lower adherence to nebs." (INT_01).

Participants emphasised the importance of open and honest conversations about adherence, underscoring the need to invest time in uncovering barriers when adherence is low. Attributing low adherence solely to subjective reports of improved health post-ETI may obscure deeper challenges that pwCF feel less able to disclose.

"it's not like patients were 70-80% adherent to their nebs before. Adherence has always been low...I feel like it's...sometimes just another excuse for a certain cohort. They would have had reasons and barriers before [ETI]...some of these patients... really managed anyway. I think sometimes patients feel better about saying "I'm not doing it because I feel well" rather than "I'm not doing it because of other reasons." [broad agreement from the group]." (CPT_06).

Adherence support was clearly embedded in the culture of this Centre. When adherence monitoring and support are viewed as integral to professional roles and identities, adherence support programmes such as CFHealthHub are more likely to be sustained as part of routine care at the local level.

"I don't think I [would] particularly have a job as such if we didn't have like the adherence work that we do...that's kind of the majority of what I'm doing." (CPT_06).

"It's like our bread and butter, it's part of our every day, every contact that we have with a patient, adherence will be discussed." (CPT_02).

The intrinsic motivation for pwCF to engage with adherence support emerged as a key mediator in terms of whether clinicians feel persisting with adherence support would be successful and/or valuable. Clinicians respond to this by prioritising adherence support on those who demonstrate more motivation and avoiding it in those who are openly dismissive, where persisting with unwelcome adherence support risks damaging the therapeutic relationship. Another contextual factor used to prioritise the delivery of adherence support is the severity of the overall clinical picture, with pwCF with more severe disease (usually defined by lower lung function) being prioritised over those with relatively preserved lung function.

> *"I…make a…more…conscious effort of [supporting adherence], if I know it's someone that really wants to focus on it…If I know…they're going to be really dismissive…I know that sometimes no point, you've got that barrier already there… people who've got low lung function or they're deteriorating, we might … encourage them to participate … but I think the biggest thing is listening to kind of language and how people are speaking to you, are they open?" (CPT_06).*

> *"[persisting with adherence support when there is a clear aversion from the pwCF] would potentially cause…a breakdown in relationship and you don't want to do that because hopefully in the future when perhaps a person is in a better place, you then want to be able to… have that conversation again… and they might be obviously more, you know, willing to discuss it." (INT_01).*

Participants described how the CFHealthHub adherence support intervention had been adapted to better align with the preferences of pwCF, favouring brief check-ins over the more detailed, structured schedule originally outlined. This adaptation was viewed as a way of respecting individual preferences and autonomy but there were concerns that it may be less effective in bringing about behaviour change.

> *"I don't think people want as in-depth support as…when they were unwell…pre-modulator…I don't feel like people wanted to sit with me and write an action or coping plan…they'll be happy to chat about routine…but they're wanting more quick snips, quick conversations rather than sitting down for an hour and to talk about things really in depth" (CPT_06).*

> *"…since joining the team is it's not really in-depth work… but fairly snapshot." (CPT_02).*

> *"…it's a good thing…to have a conversation with the patient about how their plans are going but patients don't always want that. They want…a reminder text….I've got someone… they've just started the journey, but they said, "can you just text me every week…for a bit…just to say, how are things going?" … which I don't think is as helpful in leading to long term change…I want people to have the inherent, erm, motivation to do their nebs and you know, rather than it just being like a "Oh are you doing your nebs?" (INT_01).*

Data from the interview transcripts informed the development of five new CMOCs which were incorporated into the Programme Theory CMOC index in the topic areas of: changes in the ways pwCF now engage with non-ETI treatments; clinician engagement with the CFHealthHub programme; the delivery of adherence support for inhaled medicines to

pwCF and Implementing CFHealthHub into routine care. Seventeen existing CMOCs from the IPT were supported or developed using data from these interviews.

Example 1 – Development of a new CMOC related to intervention adaptation

> *"I don't see CFHealthHub as a tool that has to be patient led. I think it's absolutely fine for the MDT to be using it more than the patients. if they want to log in, they can, but we won't pressure them to do that. So, it's picking out which bits of it are useful, and I do think there's a lot of potential that's not used within it, but I do think that's because I think adherence support has changed. People are wanting more, just a bit of a check in, a catch up with the feedback. But I don't think people want as in-depth support as what they did when they were unwell kind of pre-modulator, so things like the coping plans, the action plans, I feel like I rarely use now. I'll be interested to see what [CFHealthHub Interventionist] is using at the moment, but I don't feel like people wanted to sit with me and write an action or coping plan and have it written out. I feel like, kind of, they'll be happy to chat about routine and how they're going to tie it in and kind of cues and things like that. But they're wanting more quick snips, quick conversations rather than sitting down for an hour and to talk about things really in depth. Small check-ins. I feel people are wanting them like really in-depth intense work." (CPT_06).*
>
> *"I think it is more that they want the feedback, they want the check in, you know, quite often they might, you might say "well, we can give you a call" and they might well actually "I prefer just have a text" you know and with that feedback, a lot prefer the texts to calls." (CPT_02).*
>
> *"A lot prefer text. A lot of patients will say they don't want a phone call." (CPT_06).*
>
> *"I think it is that certainly my experience since joining the team is it's not really in-depth work. It is those discussions but fairly snapshot probably discussions." (CPT_02).*
>
> *"I think the conversations [regarding adherence to inhaled medicines] are different [to pre-ETI]. We're still obviously trying to offer ... how we work practically has probably not changed. How we try and get in touch with people and how we try and tap into things in clinic or any you know any appointment people come to. It's been like the biggest changes in conversations." (CPT_06).*

These quotes demonstrate how pwCF are expressing preferences for omitting certain elements of the CFHealthHub adherence support intervention, such as the formal documentation of action plans for treatment taking. The physiotherapists are obliging these requests and considering this a normalisation of adherence support process. The following theory fragments were produced from these quotations:

Context (C1): PwCF expressing a preference for adherence support via quick check-ins.

Mechanism (M1: Reasoning): Clinicians are uncertain whether detailed adherence support, as per the CFHealthHub Intervention, is required in the post-ETI era.

Outcome (O1): The CFHealthHub Intervention is adapted to align with these preferences.

Retroductive theorising allowed hypothesis of another mechanism which was not directly referenced in the quotation.

Mechanism (M2: reasoning): Clinicians feel obliged to respect this request to maintain the therapeutic relationship.

This led to the formation of a CMOC.

CMOC Code: SUP_08_v01:

CMOC Title: Adaptation of CFHealthHub adherence support intervention to comprise of quick check-ins.

CMOC: When pwCF express a preference for quick check-ins and less in-depth adherence support (C1), clinicians feel obliged to respect these preferences (M1: response, retroduction). Clinicians are also uncertain whether full fidelity to the CFHealthHub intervention is required in the post-ETI era (M2: reasoning). As a result, adherence support through is not delivered with fidelity to the CFHealthHub intervention, and clinicians engage in shorter, less detailed methods of support (e.g. text-based feedback or brief check-in conversations), rather than engaging in more intensive, in-depth planning (O).

Although not yet incorporated into the CMOC, I retroductively theorised that quick check-ins may be perceived as less intrusive by pwCF, particularly those with low adherence who may be struggling to increase it. Drawing on a mechanism in another CMOC (PBM_02), the avoidance of judgment or shame related to clinician disappointment during periods of low adherence may lead to disengagement with care. Choosing brief, virtual check-ins over frequent, scheduled face-to-face appointments (as recommended in the CFHealthHub intervention) could reflect this broader

disengagement. As CPT_06 alluded to in the first quotation above, they were interested in whether the CFHealthHub Interventionist had this same experience. Therefore, this theory was directly tested with the Interventionist in the subsequent interview. The following quotations highlighted their thoughts and experience.

> *"So, I feel as if it's a good thing if I'm able to have a conversation with the patient about how their plans are going but patients don't always want that. They want, sometimes, a reminder text to like to check in with them like I've got someone at the moment who has just, they've just started the journey, but they said, "can you just text me every week for a few, for a bit of time just to say, how are things going?" I feel like that is probably more of a, erm, it's that kind of external reminder, which I don't think is as helpful in leading to long term change cause of you know, do you know what I mean? I want people to have the inherent, erm, motivation to do their nebs and you know, rather than it just being like a "Oh are you doing your nebs?" I don't know." (INT_01).*

> *"Interviewer: one thing which I've been thinking about is patients preferring a quick check in not wanting to have frequent conversations. Do you find that...so if we take the case of someone who, say, hasn't been able to meet their targets for adherence, do you find that people like in that group are more likely to just want a text rather than a phone call? Almost because you know, you can't get told off over the text, you can just ignore it, but you know, if you were, if you felt you were gonna be, if you felt that you hadn't achieved your target, there was some shame attached to that you wouldn't necessarily want to speak to someone. Do you ever find that seems to influence people's behaviour? So those who are struggling to meet the target, not wanting as much face to face.*

> *INT_01: I think people who probably are perhaps a little bit less certain about their plans and whether they're going to achieve them might opt more for a sort of a distanced, perhaps a distanced text... But I think, yeah, your reflection is probably fair in a in a general sense."*

These quotations provided evidence in support of the C1, M1, O1 configuration and supported my theorised mechanism (M1) that quick check-ins may be preferred by those looking to avoid negative judgement for low adherence. Additionally, the Interventionist expanded on the perceived consequence of this adaptation, in that adherence support was less effective. This was then incorporated into an updated version of the CMOC.

CMOC Code: SUP_08_v02:

CMOC: When pwCF express a preference for quick check-ins and less in-depth adherence support (C1), clinicians feel obliged to respect these preferences (M1:

response). **PwCF who are struggling to increase their adherence (C2) may opt for quick, remote check-ins (O2) as a way of avoiding the shame or guilt associated with not meeting expectations or targets (M2: reasoning, retroduction).** Clinicians are also uncertain whether full fidelity to the CFHealthHub intervention is required in the post-ETI era (M2: reasoning). As a result, adherence support through is not delivered with fidelity to the CFHealthHub intervention, and clinicians engage in shorter, less detailed methods of support (e.g. text-based feedback or brief check-in conversations), rather than engaging in more intensive, in-depth planning (O). **This may result in less effective adherence support (O2)**."

Example 2 – "Testing" an existing CMOC

Programme theory development is an iterative process. Therefore, existing CMOCs were tested by applying them to data collected after their generation.

CMOC ID: IMP_01

CMOC Title: Incorporating CFHealthHub data review into existing workflows improves adoption and adherence support delivery.

CMOC: When CFHealthHub is embedded into routine workflows (C1), such as standardised pre-clinic preparation or weekly meetings (M1: resource), adherence data are used more consistently (O1), enabling clinicians to assess risk (O2) and prioritise adherence support for pwCF who are likely to benefit from it (O3). Regular discussions within the MDT about adherence (M2: resource) ensure a coordinated approach (O4), preventing pwCF feeling overwhelmed (M3: reasoning) and promoting efficient use of resources (M4: resource), which results in more streamlined and targeted adherence support (O5)."

Different quotations from the interviews described in this chapter supported different aspects of this CMOC as described in Table 6.

Table 6: Exemplar quotations supporting existing fragments of CMOC IMP_01.

Quotation	Aspects of CMOC supported
"Obviously people who've got low lung function or they're deteriorating, we might try and not necessarily push it [adherence support] on them, but we try to encourage them to participate a little bit more". (CPT_06)	O2, O3, M4, O5
***"**...routinely before each clinic CFHealthHub is opened up... we look at the last three months of adherence... also be looking back at sort of historical data to see whether adherence has changed ...if there's been a drop in adherence, then obviously those are the kind of people who would be wanting to target speaking with. I also always look at... so, the physios will look at it in our team, and I as the Interventionist will look at it as well." (INT_01).*	C1, M1, O3
"[if] the Consultants come out..[and] said "...they're really struggling with their mental health at the moment ..." Obviously, that is not the right time to broach that...we have a very communicative team which is really, really helpful...you can tell if you're broaching these things and people start to put up a bit of a wall." (INT_01).	M2, M3, M4, O4, O5

6.4 Discussion

6.4.1 Main findings

Adherence support was considered an important part of the roles of both physiotherapists and the CFHealthHub Interventionist at this Centre, where CFHealthHub was well-embedded into routine care. There was agreement across key aspects of the adherence support intervention, in that the inherent motivation of a pwCF to engage with support was a key determinant of whether that support would be offered and subsequently successful.

There was recognition that the preferences of pwCF seemed to be for short contacts, rather than deeper intervention, as is advocated in the evidence-based CFHealthHub Intervention, though there are concerns as to whether this method of adherence support is as effective. Clinicians were adapting the intervention to meet those needs, recognising the importance of tailoring to maintain engagement.

6.4.2 Strengths

A group interview convened all members of the physiotherapy team, which allowed individual viewpoints to be explored whilst stimulating discussion and reflection. Whilst there was broad agreement with some points, enhancing content validity, there were also disagreements, which encouraged interviewees to expand and justify their

positions, providing empirical data which was analysed to provide deeper insights into generative mechanisms. Interviewing the physiotherapists and Interventionist separately provided insights into their perceptions of each other's roles, which may not have surfaced if they were interviewed at the same time.

Allowing the participants to identify key topics for the discussion at the start of the interviews, which aligned with my intended topic guide, again ensured that insights were empirically grounded in their experiences. As a member of the adult CF MDT at this Centre, the interviewees were my direct colleagues, which helped with recruitment and scheduling. They appeared at ease and willing to talk openly in my presence. This meant only brief introductions to the topic guide and ground rules were required at the start of the interview, meaning more time could be dedicated to discussion.

6.4.3 Limitations

The majority of contributions in the group interview came from the most experienced team members. This was an expected inevitability of group interviewing in a clinical team with an inherent hierarchy. Specific questions were directed to the more junior physiotherapists, yielding insights into the department culture and the impact of structured workflows on the experience of team members on rotational placements. The more junior members of the team may have held back some contributions elsewhere in the interview.

Additionally, the theoretical insights gained here were from clinicians at a Centre where CFHealthHub was fully embedded in routine care. As identified in previous interviews, implementation strategies for CFHealthHub vary across Centres and, as such, key contextual elements in other Centres would not have been captured in these interviews, limiting the generalisability of some elements of Programme Theory.

6.5 Conclusions

Interviews with the physiotherapy team and CFHealthHub Interventionist at a single CF Centre, where CFHealthHub was well-embedded, contributed to the generation, testing, and refinement of the IPT outlined in Chapter 5. These interviews focussed on the delivery of adherence support in the post-ETI era, particularly within the context of the

CFHealthHub programme and helped develop my answer to the second research question (*"How have ETI and the COVID-19 pandemic shaped the experiences and care needs/preferences of pwCF?"*). While the CFHealthHub Intervention was theoretically informed and evidence-based, resource limitations and the preferences of pwCF led to adaptations in how adherence support was delivered, resulting in a deviation from the original intervention structure.

The data gathered so far offered valuable causal insights from the clinicians' perspectives, however, many of these insights related to the thoughts and behaviours of pwCF. As a result, the next phase of the study involved testing the Programme Theory directly with pwCF through a national survey (Chapter 7) and realist focus groups (Chapter 8).

As I conducted the work of this Chapter, it was announced that the CFHealthHub programme would close in late 2024 due to funding constraints. Consequently, aspects of the Programme Theory specifically related to CFHealthHub were explored no further. Instead, the priority for the final stage of the study was gathering insights from pwCF around CF care in the post-ETI era, to inform recommendations for the wider CF community beyond the CFHealthHub learning health system.

7. National survey of pwCF

7.1 Introduction

This chapter outlines the development, conduct and analysis of a national survey, informed by the Programme Theory and existing knowledge about factors which are associated with adherence to inhaled medicines in CF. A key CM dyad captured within several CMOCs in the Programme Theory was that that many pwCF had improved health post-ETI (Context) question the necessity, or importance, of inhaled medicines for them (Mechanism: reasoning). Clinicians generally feel this has led to reduced adherence to inhaled medicines (Outcome). The survey focussed on thoughts and behaviours around inhaled medicines, rather than exploring other aspects of the Programme Theory, such as virtual care and clinician thoughts and behaviours. This helped me to develop my answer to the second research question ("*How have ETI and the COVID-19 pandemic shaped the experiences and care needs/preferences of pwCF?*"). Additionally, this phase of the study also developed my answer to the third research question: "*What factors are associated with adherence to inhaled medicines for pwCF in the post-ETI era?*". The objectives of the national survey were:

- To determine how pwCF rate the importance of inhaled medicines in the context of ETI.
- To assess whether the perceived importance of inhaled medicines has changed for those prescribed ETI (or alternate CFTRm) and understand the reasons behind any changes.
- To evaluate the relative importance of specific factors influencing adherence to inhaled medicines, informed by Programme Theory statements to date.
- To identify any additional factors that pwCF consider when deciding whether to take their inhaled medications.

7.2 Methods

7.2.1 Survey design

An online survey was created using Qualtrics (Qualtrics LLC, Provo, UT, USA). The first draft was revised in response to supervisor feedback. The survey was further refined with input from academic colleagues, including one with both lived experience of CF and experience of academic surveys for pwCF. Further review was undertaken by members of the CF Trust (pwCF and public) Involvement group using a dummy version of the online survey. The feedback from all reviewers was used to improve readability and accessibility.

The final version of the survey consisted of four sections:

1) Eligibility screening and consent.
2) Demographics.
    a. Gender identity.
    b. Age group.
    c. UK specialist CF Centre at which they receive care.
        i. Drop down list of all CFHealthHub Centres with an extra option for "other UK CF Centre."
    d. Are they currently prescribed a CFTRm.
    e. Are they currently prescribed inhaled medicines.
    f. Method of recruitment, e.g. email invitation or social media.
3) Perceived importance of inhaled medicines.
    a. Asked to rate the perceived importance of inhaled medicines on a scale of 0-100 and indicate if this had changed (less important, equally as important, or more important) since they were prescribed a CFTRm, if relevant.
    b. Two free text boxes inviting them to provide an explanation for their perceptions.
4) Factors that may influence adherence to inhaled medicines.

a. asked to rate the important of seven factors which may be influential on their adherence to inhaled medicines on a scale of 1 (not important) to 5 (very important):
    i. Other life pressures (e.g. at work or home).
    ii. How well they are feeling at the time.
    iii. The relationship with their clinical team.
    iv. How taking the medicine makes them feel
    v. How important they think the medicine is for them.
    vi. If they have a routine for taking the medicine
    vii. The effort required to take the medicine.
b. An additional free text box where respondents were invited to list any further factors, which they considered missing from this list.

Section 3 captured a simple, quantified measure of the perceived importance of inhaled medicines but also provide the opportunity for respondents to provide more detailed free-text responses to provide textual data from which insights could be gleaned, to inform Programme Theory development. Section 4 was designed to help prioritise areas for discussion in the subsequent realist focus groups, based on the Programme Theory and the extant literature on factors associated with adherence in CF. The rationale behind selecting these seven areas for inclusion is described in Table 7Table 7.

Table 7: Factors rated in national survey with rationale for inclusion.

Factor	Rationale	Relevant existing CMOCs
Other life pressures (e.g. work/home)	Clinician interviews identified that many pwCF, who have improved health post-ETI, now have additional responsibilities, such as parenthood, full-time work & increased social opportunities, which compete with time required for health-related activities, such as taking inhaled medicines as prescribed. This is captured in CMOCs ETI_01 and PBM_09b	ETI_01 PBM_09b
How well they feel	A key insight generated from the findings of Chapters 4-6 is that when pwCF are feeling well, they seem less engaged with inhaled medicines and adherence is lower.	ETI_02b PBM_01, 03, 05, 06, 10, INH_02, 04, 05,
Relationship with clinical team	Clinicians reported that they feel they do not know the pwCF for whom they care, which can reduce the rapport they feel they have, which is a key component of the therapeutic relationship. Additionally, some clinicians suspect that some pwCF conceal true adherence when it is discussed in consultations. Clinicians also identified open and honest conversations, which would both be a product and facilitator of better therapeutic relationships, as essential for effective adherence support.	PBM_01, 02, 04, 11 INH_06, ROL_03, 04 VRT_02 SUP_01, 06
How taking the medicine makes you feel	This factor encompasses unintended side-effects, which may be a barrier to adherence, but also if there is a noticeable impact on following administration of inhaled medicines. The relationship between this noticeable impact and adherence aligns with the "perceived benefit" construct from the Health Belief Model (274)	PBM_05, 06, 07,
Perceived effectiveness of the medicine	This factor considers both unintended side effects, which can serve as barriers to adherence, and the noticeable impact of inhaled medicines on subjective health or symptom burden. The relationship between these felt effects and adherence is distinct but likely influenced by the previous factor (how taking the medicine makes you feel) and therefore also aligns with "perceived benefit" (274)	PBM_07
Routine	Previous work in CF has demonstrated that habit and adherence to inhaled medicines are strongly related (187, 278, 279). On these grounds, the CFHealthHub behaviour change intervention was centred on habit formation (147).	SUP_01, 02, 03, 05, 08
Burden	Previous work in CF has demonstrated that perceived treatment burden is a key barrier to inhaled medicines adherence (182, 280-282). Prior to ETI, reducing treatment burden was the top research priority for the CF community (115). Clinician interviews revealed that it appeared that pwCF saw reduction in adherence to inhaled medicines as a way to reduce treatment burden in the post-ETI era.	ETI_03 PBM_07, 08

On completion of the survey, respondents were automatically directed to a separate webpage (a Qualtrics survey with a single question) allowing them to declare their interest in participating in subsequent focus groups by sharing their preferred email address. This allowed email addresses to be collected without linking them to the previous survey responses, ensuring anonymity.

7.2.2 Survey distribution

The survey was distributed via email to the CFHealthHub "Consent to Future Research" mailing list (N=1535) and the CF Trust research mailing list (N=364). Key CF Facebook pages and X accounts were identified and contacted to ask for permission and support in distributing the survey, in order to maximise the opportunity for participation across the UK CF community.

7.2.3 Data analysis

When the survey was only partially completed, all provided data were retained for analysis. There was no imputation for missing data. Appropriate descriptive statistics were used for analysing demographic and quantitative data. The perceived importance of inhaled medicines was compared between those who reported being prescribed CFTRm with those who were not. The Type I error rate for all hypothesis tests was set at 0.05, and the null hypothesis stated that there was no difference in perceived importance between groups. No power or sample size calculations were performed.

Free-text responses were reviewed line-by-line and organised using Microsoft Excel. Related data were first categorised to generate insights, inspired by the reflexive thematic analysis approach (258). These data were then reviewed again with a realist lens to inform Programme Theory development using the Constant Comparison Method described earlier in Figure 8. Free-text responses were used to inform additional factors which may influence adherence that had not been captured. Some illustrative quotes were explicitly abridged with ellipses for readability without any intention to change the meaning. Additionally, potentially identifiable information was redacted (notation XXX).

7.2.4 Ethical approval

The CFHealthHub "Consent to Future Research" mailing list was comprised of email addresses for pwCF who had consented to be part of the CFHealthHub learning health system and had specifically indicated their consent to be approached for involvement in future research projects. Approval to use this mailing list was provided by Sheffield Teaching Hospitals, as the CFHealthHub learning health system data controller. Amendments covering this work were approved by the University of Sheffield Research Ethics Committee (Reference: 005012 - Amendments 4 and 5) prior to distribution of the survey.

7.3 Results

7.3.1 Response rate

The survey was open from 12th July 2024 until 15th August 2024 (34 days). Invitations were successfully sent to 1467 pwCF via the CFHealthHub mailing list on 12th July with a single reminder sent on 22nd July. A single email invitation was sent to 364 pwCF via the CF Trust research mailing list in the week commencing 15th July. This gave a maximum of 1831 email approaches, assuming no overlap between lists.

In addition to email recruitment, invitations to participate were posted on X and in permitted Facebook groups throughout July and August. Whilst viewing metrics provided some insight into how many times these posts were viewed or clicked, it was not possible to derive meaningful response rates from social media approaches.

A total of 439 responses were received, giving an estimated response rate of 24% to 30%, based on the assumed degree of overlap between mailing lists. Of these, 414 respondents (94.3%) were eligible to complete the survey based on a positive response to the screening item "*I confirm that I am a person with Cystic Fibrosis in the UK, and I am 16 years old or above*".

Of the 414 eligible respondents, the survey was fully completed by 340 (82.1%) and partially completed by 74 (17.9%). The majority of respondents (372, 89.9%) reported hearing about the survey via email, with only 4 (1.0%) citing social media platforms. The

median survey completion time was 4 minutes: 46 seconds (interquartile range [IQR] 3:13 to 8:45).

7.3.2 Data completeness

Data completeness at an individual item level ranged from 80.1% to 100% for those items with a quantitative response (e.g. demographics, rating, and ranking). Data completeness for each of these items is summarised in Table 8.

Table 8: Description of missingness across quantifiable survey items

Item	Number of cases with missing data: N (%)
Gender	30 (7.2)
Age group	36 (8.7)
Specialist CF Centre	36 (8.7)
Prescribed CFTRm	30 (7.2)
Prescribed inhaled medicines	30 (7.2)
Recruitment platform	30 (7.2)
Perceived importance of inhaled medicine	70 (16.9)
Has perceived importance of inhaled medicines changed post-ETI	61 (14.7)
Rating importance of following factors in determining adherence to inhaled medicines	
Life pressures	79 (19.8)
How well you are feeling	77 (18.6)
Relationship with CF team	79 (19.8)
How taking the medicine makes you feel	77 (18.6)
How important you think the effect of the medicine is	76 (18.4)
If you have a routine for taking medicine	79 (19.8)
Effort required to take the medicine	79 (19.8)

CF = cystic fibrosis. CFTRm = CF transmembrane regulatory protein modulator. ETI = elexacaftor/tezacaftor/ivacaftor.

7.3.3 Respondent characteristics

Of those who reported their demographics, the majority were female and in the younger age groups (16-25, 26-34 and 35-44 years). The majority were prescribed a CFTRm (n =

344, 83.1%) and/or inhaled medicines (n = 321, 77.5%). Characteristics of the 414 eligible respondents are shown in Table 9.

Table 9: Self-reported characteristics of survey respondents

Item	N (%)
Gender	
Male	170 (41.1)
Female	208 (50.2)
Non-Binary	3 (0.7)
Prefer not to say	3 (0.7)
Age group	
16-25 years	69 (16.7)
26-34 years	104 (25.1)
35-44 years	87 (21.0)
45-55 years	78 (18.8)
Over 55 years	46 (11.1)
Prescribed CFTRm	
Yes	344 (83.1)
No	40 (9.7)
Prescribed inhaled medicines	
Yes	321 (77.5)
No	63 (15.2)

CFTRm = Cystic fibrosis transmembrane regulatory protein modulator.

Respondents included those receiving specialist CF care at both CFHealthHub (n=386, 83.6%) and non-CFHealthHub Centres (n=30, 7.2%). The full geographic distribution of respondents is shown in Figure 9.

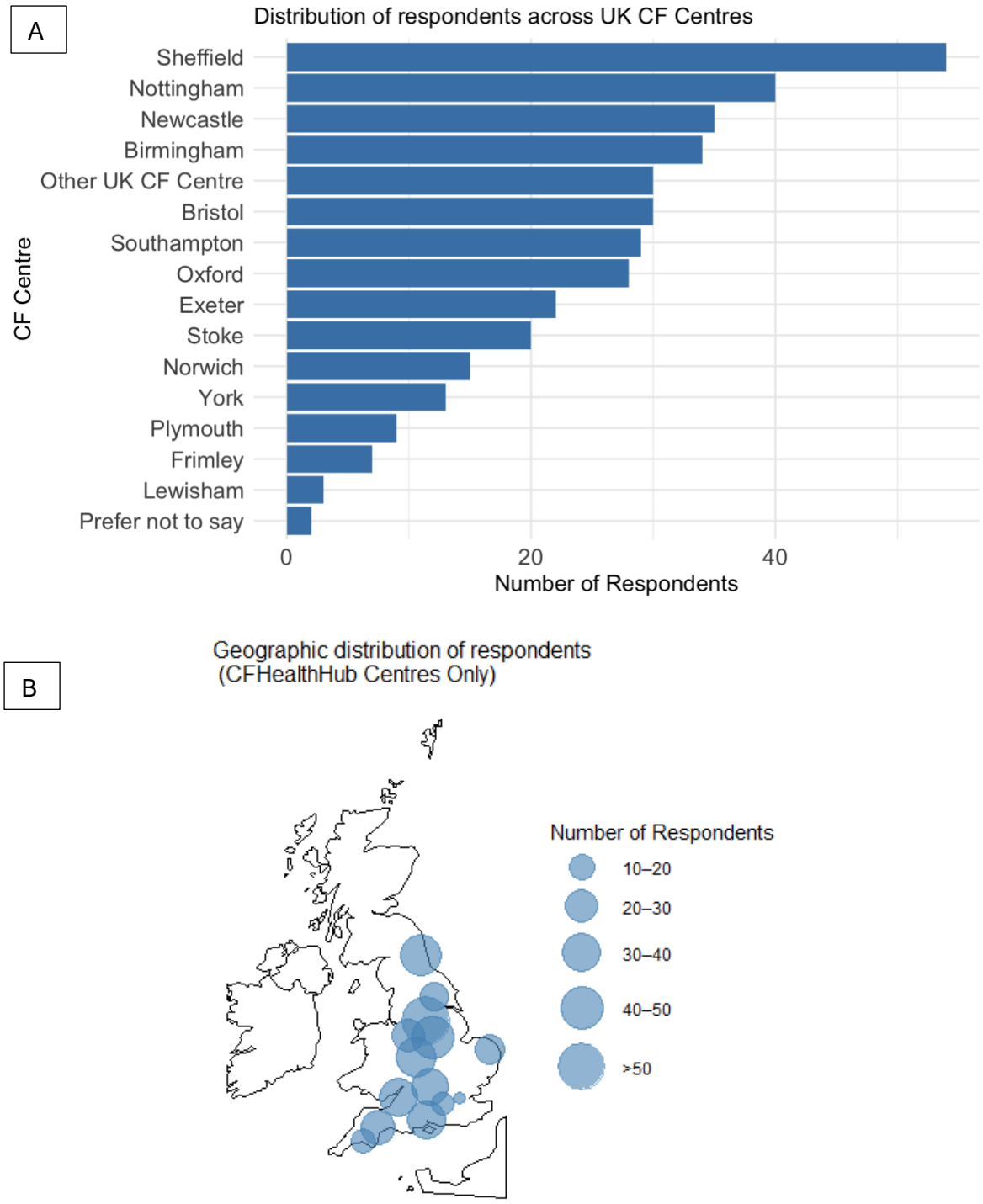

Figure 9: Geographic distribution of respondents. A) Frequency counts, B) Geographic distribution and density

A comparison of the age distribution of respondents with the UK CF population is shown in Table 10. Direct comparison is limited by difference in methods of categorisation, but the closest possible comparison is reported. While the UK adult CF population has a different biological sex ratio (53.9% male, 46.1% female) compared to the cohort of respondents (41.4% male, 50.2% female), I am confident that neither group is

disadvantaged by under-representation (38). This cohort also represented all age ranges, though contained proportionally higher representation of those aged over 26 years compared to the general UK CF population.

Table 10: Distribution of age for respondents compared to the UK adult CF population.

Respondent age group	Proportion of respondents	Most similar age group in CF Registry annual data report	Proportion of UK CF population
16-25 years	16.7%	16-27 years	24.9%
26-34 years	25.1%	28-35 years	15.9%
35-44 years	21.0%	36-43 years	11.2%
45-55 years	18.8%	44-55 years	7.9%
Over 55 years	11.1%	Over 55 years	3.6%

CF = Cystic fibrosis. UK = United Kingdom.

7.3.4 Perceived importance of inhaled medicines

Of 414 respondents, 344 (83.1%) rated their perceived importance of inhaled medicines from 0 to 100. Ratings were negatively skewed, with a modal value of 100, indicating highest possible importance, given by 79 respondents (19.1%). The median rating was 74/100 (IQR 50.0 to 96.3). The distribution of responses is shown in Figure 10.

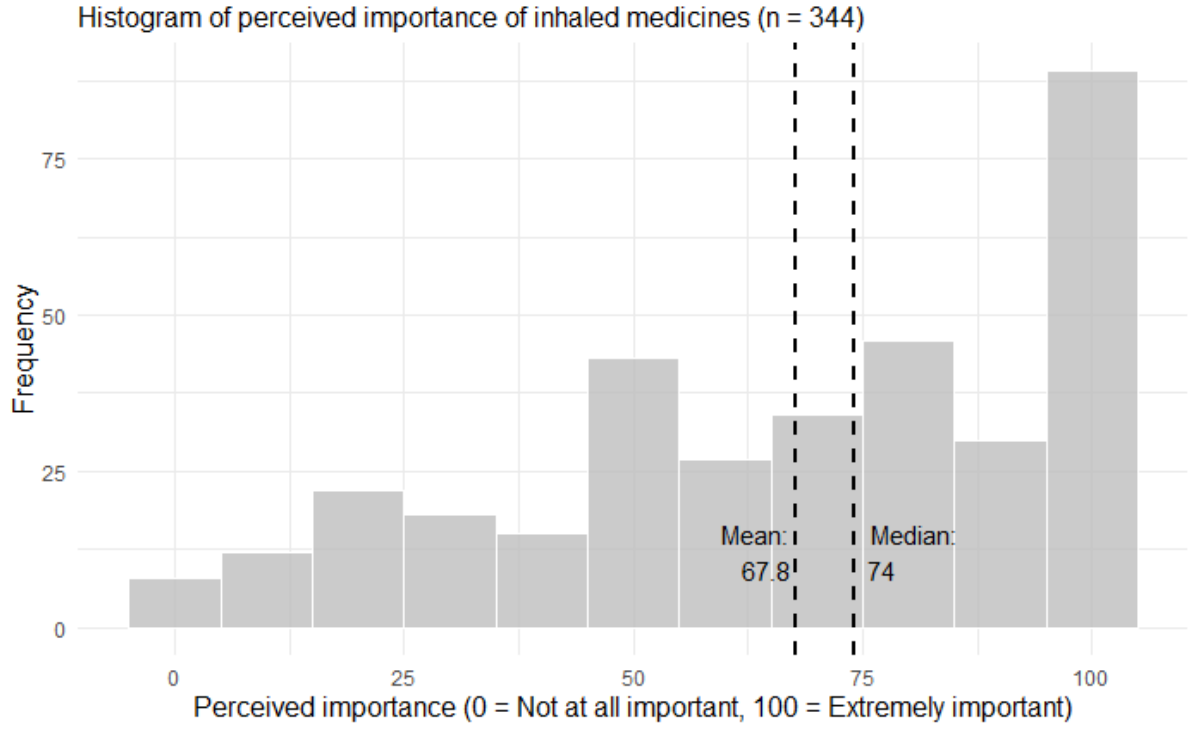

Figure 10: Histogram of perceived importance of inhaled medicines.

Of the 384 respondents who reported their CFTRm prescription status, 344 (89.6%) reported being prescribed one, while 40 (10.4%) reported they were not. Of the 344

prescribed a CFTRm, 138 (40.1%) indicated that they felt inhaled medicines were less important than before, 166 (48.3%) considered them equally as important and 8 (2.3%) considered them more important.

The median importance rating of inhaled medicines for those prescribed a CFTRm was 72/100 (IQR 49 to 92), which was significantly lower than for those not prescribed one (median 88, IQR 52 to 100, p = 0.03). The distributions of importance ratings between these groups are shown in Figure 11.

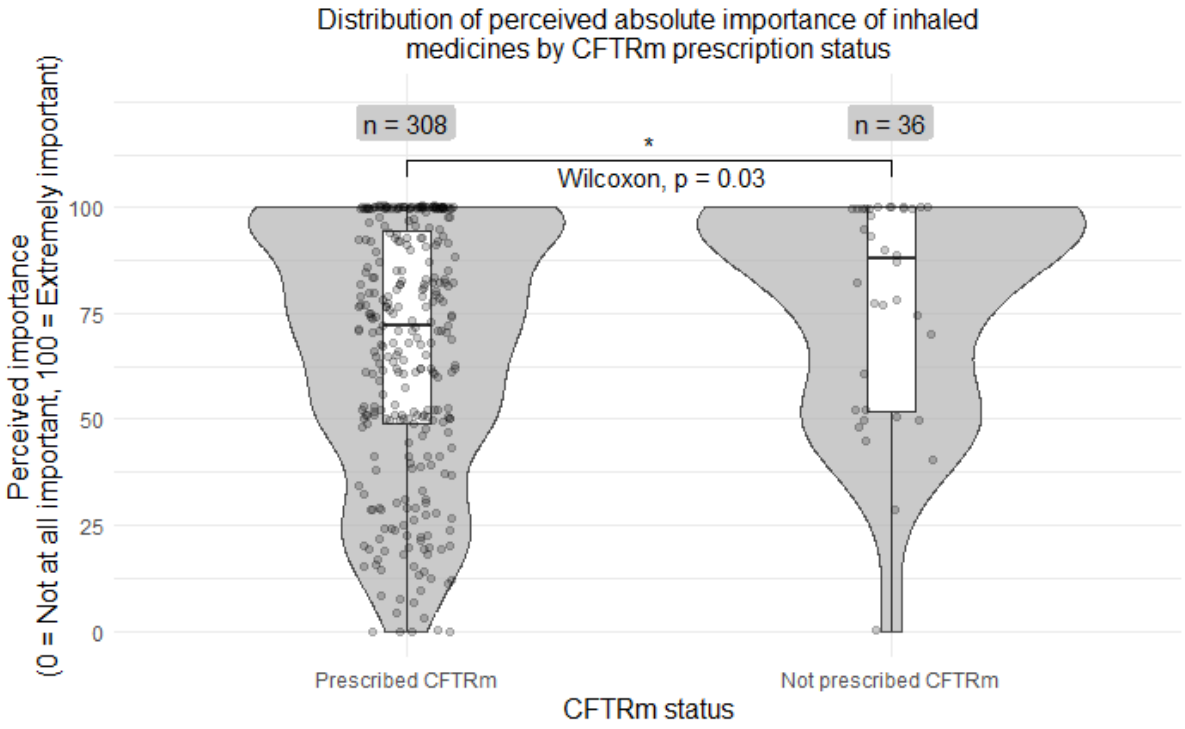

Figure 11: Distribution of perceived importance of inhaled medicines by CFTRm prescription status.

7.3.5 Key areas of theory development

The quantitative data confirmed variation among pwCF in their perceptions of the importance of inhaled medicines following the introduction of ETI. Diminished or sustained perceived importance may itself represent an outcome but also a generative mechanism, driving reduced adherence as an outcome.

Reasons why inhaled medicines were considered less important post-CFTRm.

Of the 138 respondents who indicated that they considered inhaled medicines less important after starting a CFTRm, 111 (80.4%) provided free-text comments suitable for categorisation. These comments offered theoretical insights across five main areas.

Insight 1.1: Health improvements drive a reduction in perceived importance.

Multiple respondents reported improvements in their health since commencing a CFTRm, including reduced sputum production, a reduction in cough, improved objective clinical measure (e.g. lung function), increased general wellbeing and reduced frequency of exacerbations. Additionally, some respondents cited reduced detection of bacteria in microbiology samples as a reason for reduced perceived importance of inhaled medicines.

> *"Since taking Kaftrio I don't cough…I feel fitter than ever and able to compete in sports. In the past I used DNase [dornase alfa] to help clear my chest. There is no longer anything to clear" (Male, 26-34y, prescribed CFTRm, not prescribed inhaled medicines, perceived importance of inhaled medicines 8/100).*

Insight 1.2: When inhaled medicines have no noticeable effect, perceived necessity is lower.

Respondents cited a lack of noticeable health benefits from inhaled medicines driving a general belief that inhaled medicines are no longer necessary.

> *"It's difficult to think something is really important when you don't feel any immediate benefits of taking them." (Female, 44-55y, prescribed CFTRm, prescribed inhaled medicines, 65/100).*

Insight 1.3: Perceived health status drives adherence to inhaled medicines.

Multiple respondents reported that they saw inhaled medicines as better reserved for times of ill-health, such as during exacerbations or an increase in symptoms, rather than as daily maintenance.

> *"Differing levels of efficacy depending on how ill I am. If congested or unwell with an infection they are very useful, but not very if I am well." (Male, 16-25y, prescribed CFTRm, prescribed inhaled medicines, 23/100).*

> *"With the introduction of Kaftrio my lungs feel so much drier, and I don't feel the need or benefit from the inhaled drugs. However, I do turn to them if I start to feel*

productive on my lungs." (Female, 44-55y, prescribed CFTRm, prescribed inhaled medicines, 51/100).

This was rationalised further by considering inhaled medicines as "in reserve" for a time when the CFTRm may no longer be as effective. Also, one responder highlighted their concern of the body becoming resistant to the effect of inhaled medicines with prolonged use.

"Since taking Kaftrio and Kalydeco I have stopped using my nebulisers as I feel I don't need them and I would rather save them for a time in the future in case the tablets [CFTRm] stop working" (Female, 26-34y, prescribed CFTRm, not prescribed inhaled medicines, 77/100).

"...I think Kaftrio is helping my lung function be at its maximum...only when I'm ill should I need to use inhaled medications (this would also reduce my body getting used to inhaled medications leading them to no longer be effective)" (Female, 26-34y, prescribed CFTRm, prescribed inhaled medicines, 51/100).

Insight 1.4: CFTRm are considered as an alternate, highly effective/superior, and less burdensome treatment for CF than inhaled medicines.

Finally, some respondents cited how they considered CFTRm as superior treatment option compared to inhaled medicines. Additionally, several saw CFTRm as a less burdensome, alternative treatment option, which was considered more suitable in the current era.

"I feel there are maybe better ways to treat patients in modern ways that are cheaper and more practical for the patient to carry out around normal life" (Female, 26-34y, prescribed CFTRm, prescribed inhaled medicines, 29/100).

"Before Kaftrio they [inhaled medicines] were essential. Now Kaftrio alone keeps me well and I do not feel a need to use a nebuliser." (Male, >65y, prescribed CFTRm, not prescribed inhaled medicines, 10/100).

"Without my modulator I can't breathe. I have not been unwell since having modulators, I was unwell before [whilst] taking inhaled meds - they are not in the same league" (Female, 44-55y, prescribed CFTRm, prescribed inhaled medicines, 77/100).

Reasons why inhaled medicines were considered equally or more important post-CFTRm.

Of the 344 respondents, 166 (48.3%) indicated that they felt inhaled medicines were equally as important post-CFTRm, with eight (2.3%) indicating they considered them more important. Of these 166 respondents, 128 (77.1%) left free-text comments which were appropriate for categorisation.

Insight 2.1: Inhaled medicines considered important for continuing to address specific health concerns.

Respondents highlighted ongoing health risks from CF, particularly bacterial persistence and existing lung damage, as key reasons for the sustained importance of inhaled medicines. They also recognised that nebulisers deliver medicine directly to the lungs, reinforcing its continued relevance.

> *"Although the Orkambi and Kaftrio have totally changed my life I still think nebuliser antibiotics are very important. Probably less so for younger CFs [pwCF] but CF has already caused lots of damage before I started Orkambi and then Kaftrio" (Female, 35-44y, prescribed CFTRm, not prescribed inhaled medicines, 92/100).*

Furthermore, in keeping with insight 1.3 from the previous section, many considered the value of inhaled medicines to be during times of exacerbation, rather than as a daily preventative measure.

> *"I have come off all nebulised medication since starting Kaftrio, however I was recently hospitalised where nebulised medication was necessary for my recovery. Since the hospital stay, I have again come off the nebulisers" (Male, 35-44y, prescribed CFTRm, not prescribed inhaled medicines, 29/100).*

Respondents also reported how they felt differently about inhaled mucolytics compared to inhaled antibiotics.

> *"Since starting Kaftrio however, I think it is more important to take aztreonam than Pulmozyme [DNase], as I am no longer productive so don't feel that it is essential to take mucolytics, whereas antibiotics are still important in case there is infection that I am unaware of." (Female, 16-25y, prescribed CFTRm, prescribed inhaled medicines 83/100).*

Insight 2.2: PwCF follow treatment recommendations from care providers.

Some respondents identified the advice of healthcare providers and their understanding of the evidence-base for inhaled medicines as important factors. However, respondents did not always agree with their healthcare providers' recommendations. Nonetheless, this disagreement did not necessarily result in low adherence. Unfortunately, since these responses are not linked to objective adherence data for inhaled medicines, I could not explore that relationship further.

> *"I feel like I take some of the inhalers now "just because." My CF team says there isn't enough evidence out there to change their decision yet." (Male, 44-55y, prescribed CFTRm, prescribed inhaled medicines 41/100).*

> *"For some antibiotics inhaling them seems to be more effective than taking them orally. This is what I've been led to believe by doctors and I haven't seen anything in my own experience to disprove this." (Male, 26-34y, prescribed CFTRm, not prescribed inhaled medicines, 100/100).*

Insight 2.3: When inhaled medicines have a clear, noticeable effect, perceived necessity is higher.

This counterfactual position is consistent with insight 1.2 above. A clear, noticeable benefit shaped respondents' views on the sustained importance of inhaled medicines. For some, these benefits were short-term, such as improved chest clearance and a better sense of overall health.

> *"When I stop taking them for over 5 days, I can feel my chest getting tight and I can breathe so well" (Female, 16-25y, prescribed CFTRm, prescribed inhaled medicines, 95/100).*

For others, the long-term benefits were important.

> *"[inhaled medicine] Helps to prevent infections protecting long term lung function." (Male, 26-34y, prescribed CFTRm, prescribed inhaled medicines, 80/100).*

There appeared to be a more relaxed attitude toward occasionally missing doses of inhaled medicines. This may be influenced by the objective health benefits of CFTRm, which may reduce the perceived impact of missed doses.

> *"… since Kaftrio I don't notice any adverse symptoms if I miss a few doses like I used to (e.g. I don't always take Pulmozyme (DNase) on holiday if I don't have access to*

a fridge)" (Female, 44-55y, prescribed CFTRm, prescribed inhaled medicines, 77/100).

"I know missing the odd nebuliser will be ok tho (sic) with Kaftrio." (Male, 44-55y, prescribed CFTRm, prescribed inhaled medicines, 92/100).

Furthermore, having an established habit or routine for taking inhaled medicines before being prescribed CFTRm appeared to sustain adherence.

"... It has been a routine in my life for years, so I have just carried on regardless of taking Kaftrio..." (Male, 44-55y, prescribed CFTRm, prescribed inhaled medicines, 92/100).

Insight 2.4: Perceiving ETI and inhaled medicines to have complementary roles in management of CF increased perceived necessity.

Considering the additive benefits of CFTRm and inhaled medicines was highlighted as a reason why for sustained perceived importance.

"Adding medication to me doesn't mean to remove one because you've added another unless it's a direct replacement." (Female, 35-44y, prescribed CFTRm, prescribed inhaled medicines, 51/100).

"Kaftrio is not a complete cure for CF, it only helps with the symptoms. Whilst I feel much better, ignoring all other treatment will result in my lungs and body becoming worse." (Male, 35-44y, prescribed CFTRm, prescribed inhaled medicines, 71/100).

Another important contributor may be the differential response to CFTRm at an individual level. Those who had a relatively lower improvement in their health following CFTRm initiation may feel that inhaled medicines retain or increase in importance.

"Modulators didn't change my lung function, but they did give me more energy. I still need inhaled medication to keep my lungs are clear as possible." (Female, >55y, prescribed CFTRm, prescribed inhaled medicines, 100/100).

Insight 2.5: An aspiration of longevity drives necessity for inhaled medicines.

With the potential for an extended life expectancy with CFTRm, pwCF are now considering how decisions around treatment taking may interact with aging.

"Kaftrio has made a very significant difference to my experience of symptoms with significant improvement for my overall wellbeing. As a consequence, I am determined to maintain my high level of adherence to both oral and nebulised

medications to ensure I am as well as possible as an older person with CF." (Male, >55y, prescribed CFTRm, prescribed inhaled medicines, 71/100).

Insights from those not prescribed CFTRm.

Of the 344 respondents, 33 (9.6%) indicated they were not prescribed CFTRm and as such the item about whether CFTRm had changed their perception of the importance of inhaled medicines was not applicable. However, 27 respondents left free-text comments which were appropriate for categorisation. Generally, these responses were consistent with themes already identified. The only additional insight was that the inhaled medicines seemed especially important for those not prescribed CFTRm.

"... If I don't do this regularly, I get a build-up of secretions causing long-term damage and increased infections especially since I am not on a CFTR modulator." (Female, 26-34y, not prescribed CFTRm, prescribed inhaled medicines, 71/100).

The survey results quantitatively supported key aspects of the Programme Theory related to the drivers of the perceived importance of inhaled medicines in the post-ETI era. Many PwCF prescribed ETI reported health improvements, such as reduced cough and sputum production, which contributed to a decreased perceived importance of inhaled medicines. Conversely, ongoing symptoms were cited as a key reason for perceptions of maintain importance to inhaled medicines. Several respondents reported taking an "as required" approach, where adherence to inhaled medicines was closely tied to acute symptom burden, supporting the mechanism of subjective primacy, which appears to drive adherence behaviour for some pwCF in the post-ETI era and is captured in CMOCs ETI_02d and PBM_12 in the final Programme Theory CMOC index presented later in this thesis. Additionally, the perceived additive benefits of ETI and considerations regarding healthy aging with CF helped sustain the perceived importance of inhaled medicines.

Free-text data from survey respondents informed the development of several new CMOCs in the topic areas of changes in the way pwCF now engage with non-ETI treatments and one new CMOC in the topic area of the changing nature of pulmonary exacerbations. Ten existing CMOCs were supported or developed using free-text survey data.

Finally, respondents rated seven factors from 1 (not important) to 5 (very important) in terms of their influence on adherence decisions. The mean ratings for these factors ranged from 3.18 to 3.85/5. Routines for treatment-taking and perceived effectiveness of the medicine received the highest ratings, whereas perceived burden and the relationship with healthcare providers were rated the lowest. A summary of the ratings presented in Table 11.

Table 11: Importance rating of each pre-defined factor for determining adherence to inhaled medicines.

Factor	Mean (SD) of perceived importance. 1 (not important) to 5 (extremely important)
If they have a routine for taking the medicine	3.85 (1.14)
How important they think the medicine is	3.80 (1.15)
How well they are feeling at the time	3.54 (1.33)
Other life pressures (e.g. at work or home)	3.45 (1.28)
How taking the medicine makes them feel	3.42 (1.28)
The effort required to take the medicine	3.39 (1.31)
The relationship with their clinical team	3.18 (1.45)

SD = standard deviation.

In addition to the seven pre-determined factors, one new factor was generated inductively from the free-text responses: emotional factors. There were three categories of responses that offered some mechanistic insight into how emotional factors may influence adherence: medicines as a reminder of illness; self-worth and hopelessness.

> *"Doing my nebs brings back bad memories for me. Reminds me I'm poorly. So, I stay away from anything that makes me feel like that. Or reminds me of that" (Female, 26-34y, prescribed CFTRm, prescribed inhaled medicines, 11/100).*

> *"Self-Worth" (Male, >55y, prescribed CFTRm, prescribed inhaled medicines, 77/100).*

> *"I given up" (Male, 35-44y, not prescribed CFTRm, not prescribed inhaled medicines, did not rate importance of inhaled medicine).*

Of the 414 respondents, 80 (19.3%) left free text comments in this section that were appropriate for categorisation. 13 respondents left free text comments which were unsuitable for categorisation, e.g. "*no*", "*not really*" or "*Experience*". The categories generated offered more insight in to how the seven pre-defined factors may influence adherence, as shown in Table 12.

Table 12: Categorisation of free-text responses and corresponding pre-determined factors

Free-text category	Factor	Illustrative quotation
Forgetting	If they have a routine for taking the medicine	*"Remembering to take the medication."*
Perceived health benefits	How important they think the medicine is	*"I don't feel like it makes much difference. But I take it every day because I wanted to see if I would feel any different. Plus, it could also have an impact in my future life, so I just take it."*
Fluctuant daily fatigue	How well they are feeling at the time	*"As I mentioned, for me sensory issues due to my autism do affect how I take all of my treatments as well as my energy levels..."*
Mental Health	How well they are feeling at the time	*"A lot of CF patients are 'neurodivergent'... and this makes taking medicine much harder"*
Other time commitments	Other life pressures (e.g. at work or home)	*"Having the time to fit in all your medications can be tough if you've had a busy day"*
Physical location	Other life pressures (e.g. at work or home)	*"Sometimes if I'm on a short break ...I may consider leaving my nebulisers at home if it's just an overnight stay - I would rather not do this."*
Financial constraints	Other life pressures (e.g. at work or home)	*"...additional charges to hot water and electricity to do these things come at a cost..."*
Relationships/support at home	Other life pressures (e.g. at work or home)	*"...as a busy mother, at times my health, especially nebulised medicine can sit at the bottom of the list of priorities, as it isn't as crucial as it used to be since starting Kaftrio..."*
Side-effects	How taking the medicine makes them feel	*"I feel so much better for not taking them constantly. When I start taking them again at home, I start to feel sluggish again."*
Burden of cleaning, preparation or storage	The effort required to take the medicine	*"The whole cleaning of the nebuliser was always a total pain in the arse. I would resent doing that more than actually taking it"*
Time	The effort required to take the medicine	*"...They are a waste of the time I could spend living. They trap you at home and destroy any chance of a social life or having fun."*
Frequency of doses	The effort required to take the medicine	*"Taking three doses a day (Azli®) can be a challenge..."*
Accountability	The relationship with their clinical team	*"I think I am slightly more likely to take my Dornase Alpha because it is monitored via a connected nebuliser. This slightly unpleasant feeling of being watched gives me a psychological nudge to do it when I may otherwise choose not to."*

CF = cystic fibrosis

7.4 Discussion

7.4.1 Main findings

The perceived importance of inhaled medicines was lower and more variable in those prescribed CFTRm compared to those who were not. Whilst this is both interesting and plausible, caution must be applied to drawing firm conclusions as this survey was not specifically designed nor powered to detect statistically significant differences in this measure. Among those prescribed a CFTRm, 41.8% viewed inhaled medicines as less important since starting the treatment. This perspective was attributed to a reduction in symptoms, a lack of perceived benefit from inhaled medicines and considering inhaled medicines more appropriate for acute illness rather than routine maintenance treatment. Conversely, just over half of those prescribed CFTRm considered inhaled medicines equally or more important than before. Their rationale included an awareness of cumulative lung damage, clinician recommendations, a discernible benefit from inhaled medicines, and the belief that it helps sustain the benefits of CFTRm into later life.

The free text responses provided insights into the reasons for this informed development of Programme Theory, generating causal insights. One key aspect appears to be that cough and sputum production, two of the commonest symptoms of CF, are reduced, and in many cases appear to have ceased, following initiation of CFTRm. This clearly influences thoughts and behaviours regarding inhaled medicines for many pwCF.

7.4.2 Strengths

An approximate 25–30% response rate, including 414 pwCF, was considered highly satisfactory given the limited timeframe for survey completion and data analysis prior to the realist focus groups. This was comparable to 424 responses to the CF Foundation's 2020 Patient and Family Standard of Care Survey (283). Considering the smaller size of the UK CF population (~11,000) compared with the USA (~33,000), and that the US survey was open for three months (August–October 2020), the response rate achieved here is noteworthy (284).

Survey development was strengthened by consultation with multiple stakeholders to ensure relevance and accessibility. This likely contributed to the commendable response rate and representation across the geo-demographic spectrum. Collaboration with the CF Trust Involvement Group provided key readability and accessibility feedback and enabled wider survey distribution via the CF Trust research email list. While it seemed the CFHealthHub mailing list yielded higher reach and response rates, working with the CF Trust enhanced the quality of the survey and founded a collaboration with their Research and Involvement teams.

The CF Foundation recently published survey design recommendations for pwCF, many of which my survey followed (285). These included a completion time under five minutes, accessible distribution via email or SMS, respondent anonymity, and culturally aware demographic questions. As reported in section 7.3.3, the characteristics of respondents are similar to those of the UK CF population, increasing the generalisability of the findings.

7.4.3 Limitations

The majority of respondents, 346 (83.6%) were cared for at specialist UK adult CF Centres where CFHealthHub was currently active. This is likely due to by the fact that the majority of recruitment came via the CFHealthHub consent to future research mailing list. Respondents from CFHealthHub Centres may have more favourable opinions towards inhaled medicines, as their clinicians likely buy in to the CFHealthHub philosophy that inhaled medicines remain important and supporting adherence is part of the clinician role. These pwCF may also have been more likely to have received the CFHealthHub intervention, which is intended to explicate the necessity of inhaled medicines and increase adherence, whereas those in non-CFHealthHub Centres would be less likely to have been exposed to the intervention. This may have biased the sample to over-report the importance of inhaled medicines. Therefore, these findings may be less generalisable to the pwCF cared for at non-CFHealthHub Centres. Reassuringly, whilst respondents from CFHealthHub Centres reported higher absolute importance of inhaled medicines (median 75/100, IQR 50 to 97) compared to those from non-CFHealthHub Centres (median 61.5/100, IQR 46.3 to 77.8) this was not statistically

significant (p = 0.24), though this survey was not powered to detect significant differences in quantitative outcomes.

The sampling was opportunistic, rather than theoretical, due to time constraints and the impending closure of CFHealthHub. These findings could be validated in future study with purposive sampling of pwCF with lower and higher adherence. Due to the lack of purposive sampling, it was challenging to directly test theory statements, particularly related to adherence outcomes. However, many free text comments contained sufficient detail to allow insight into the contexts and theorising of mechanisms which were driving outcomes related to perceived importance and use of inhaled medicines. This survey was designed to get a broad overview of the dominant collective opinions of pwCF at a more superficial level and the opportunistic sampling approach led to the receipt over 400 responses.

7.5 Conclusions

The results of this national survey indicated that there is widespread variation in the perceived importance of inhaled medicines for pwCF in the post-ETI era. Consistent with key findings in Chapters 4-6, perceptions of health status and the presence or absence of noticeable effects from inhaled medicines appear are key to driving perceptions and adherence behaviours, which helped develop my answer to the second and third research questions (*"How have ETI and the COVID-19 pandemic shaped the experiences and care needs/preferences of pwCF?" and "What factors are associated with adherence to inhaled medicines for pwCF in the post-ETI era?")*. Elements of Programme Theory were then tested and refined further through realist focus groups with pwCF, as described in Chapter 8.

8. Realist focus groups with pwCF

8.1 Introduction

The findings from the national survey provided confirmation that there were a variety of outcomes related to perceived importance of inhaled medicines and its relationship to adherence in the post-ETI era. A surprising amount of depth came from the free-text survey responses, allowing direct generation, refinement, and development of Programme Theory statements, which helped develop my answer to the second and third research questions (*"How have ETI and the COVID-19 pandemic shaped the experiences and care needs/preferences of pwCF?" and "What factors are associated with adherence to inhaled medicines for pwCF in the post-ETI era?")*. This chapter describes the final stage of qualitative data collection in this Realist Evaluation, where I conducted three realist focus groups with pwCF, resulting in the final iteration of the Programme Theory, which answered the second research question and provided qualitative data to inform the answer to the third research question.

8.2 Methods

8.2.1 Participant recruitment

On completion of the survey described in chapter 7, respondents were automatically directed to a separate survey where they were invited to leave a preferred contact email address if they were interested in attending the focus groups. Those who did so were approached via email and asked to provide their availability across 12 potential focus group sessions over a two-week period from 12th August 2024 to 22nd August 2024 using an online Google Form (Google LLC, Mountain View, CA, USA).

8.2.2 Focus group design

Three focus group sessions were selected in order to maximise participation among available participants. Each participant was invited to just one of the three sessions. Theory categories which were prioritised for development included:

- ETI has a transformative impact on CF.

- Changes in the ways pwCF now engage with clinicians.
- Changes in the ways pwCF now engage with non-ETI treatments.
- The changing roles and requirements of the CF MDT
- The role of and challenges associated with virtual care and remote monitoring.
- The delivery of adherence support for inhaled medicines to pwCF.

A standard topic guide was used to provide structure to each focus group session and ensure all topics were covered. Whilst this phase of the Realist Evaluation was predominately focussed with the testing and development of theories, I remained open to gleaning new elements of theory. The topic guide for the focus groups is shown in Appendix 6.

8.2.3 Data collection

Three focus group sessions took place virtually via Google Meet (Google LLC, Mountain View, CA, USA) between 12th August 2024 and 22nd August 2024. At the start of each focus group, participants completed an online Google Form to record baseline characteristics, in line with those asked in the survey, to increase transparency of the group and identify certain contextual factors which may provide causal insights. Audio-visual recordings were made and used to produce verbatim, naturalised transcripts of each focus group session, with only identifiable data being redacted. I kept a reflexive journal, which was completed after each focus group.

8.2.4 Data analysis

Focus group session transcripts were reviewed line-by-line in Microsoft Word. Important data were constantly compared to the existing Programme Theory and used either to generate, support or develop CMOCs. The transcripts were then reviewed by the research supervisor to compare insights and perspectives.

Additionally, findings were organised in relation to the eight existing factors which appeared to influence adherence in the national survey, as described in Table 7. This allowed identification of broader patterns in the data which represent key elements of context and/or underlying mechanisms which influence thoughts and behaviours.

8.3 Results

8.3.1 Participant characteristics

A total of 73 respondents to the national survey indicated they would be interested in participating in a focus group session. Of these, 22 declared their availability for the proposed sessions. The selected focus group sessions enabled inclusion of 18 participants, from which 16 ultimately attended. Focus groups were scheduled to last two hours, with the longest lasing two hours and 15 minutes.

There was a roughly equal split of gender representation, including one participant identifying as non-binary. Most participants (12/16, 75%) were cared for at a CFHealthHub Centres. All participants were prescribed ETI. The majority of participants were prescribed inhaled medicines (13/16, 81.3%). The most frequently represented age groups were 44-55 years (five participants), 26-34 years (five participants) and 35-44 (three participants). The 16-25 and >55 age groups were represented by single participants respectively. These characteristics are summarised in Table 13.

Table 13: Characteristics of focus group participants

ID	Focus Group Session	Gender	Age group (years)	UK CF Centre	Prescribed ETI	Prescribed inhaled medicines	Perceived importance of inhaled medicines (1 low to 10 high)	Change in perceived importance of inhaled medicines post-ETI
PwCF_01	1	NB	16-25	CFHH-A	Y	N	8	Reduced
PwCF_02	1	M	26-34	Non-CFHH	Y	Y	3	Reduced
PwCF_03	1	M	44-55	CFHH-B	Y	N	5	Reduced
PwCF_04	1	F	44-55	CFHH-C	Y	Y	10	Unchanged
PwCF_05	1	M	>55	CFHH-D	Y	Y	10	Increased
PwCF_06	1	F	26-34	CFHH-E	Y	Y	1	Reduced
PwCF_07	1	M	35-44	CFHH-B	Y	N	6	Reduced
PwCF_08	1	F	26-34	CFHH-F	Y	Y	5	Reduced
PwCF_09	2	M	44-55	CFHH-G	Y	Y	6	Reduced
PwCF_10	2	M	44-55	Non-CFHH	Y	Y	5	Reduced
PwCF_11	2	F	44-55	CFHH-H	Y	Y	6	Reduced
PwCF_12	2	F	44-55	Non-CFHH	Y	Y	10	Unchanged
PwCF_13	2	M	35-44	CFHH-I	Y	Y	5	Reduced
PwCF_14	3	F	26-34	Non-CFHH	Y	Y	9	Unchanged
PwCF_15	3	F	35-44	CFHH-F	Y	Y	10	Unchanged
PwCF_16	3	M	26-34	CFHH-J	Y	Y	9	Unchanged

Key: ETI (elexacaftor/tezacaftor/ivacaftor), NB (non-binary), M (male), F (female), CFHH (CFHealthHub, referring to a Centre that has been part of the CFHealthHub programme), Y (yes), N (no

8.3.2 Key areas of theory development

In this section, I broadly discuss different aspects of theory development, with reference to illustrative quotations. The final CMOC index, representing the refined Programme Theory, is show in Table 14.

Habit/Routine

Consistent with the extant literature, habit/routine continues to appear to be an important factor that is associated with adherence to inhaled medicines. This can either act as a feature of context (the presence or absence of habit) or a mechanism (the formation and maintenance of habit), both of which may be associated with the outcome of higher adherence. For some participants, the absence of a firmly established routine created a vulnerable context in which attempts to increase adherence faltered. In the quotation below, the context of weakly embedded habits interacted with a mechanism of binary thinking, leading to a collapse of adherence after minor disruptions.

> *"I think they suggest doing it as soon as you brush your teeth, so it's linked to a routine you already do…but it just never sticks for me…I'm also quite an "All or Nothing" person. So, if I miss one day I'm like, 'that's it now like there's no way of doing it at all'." (PwCF_08).*

As revealed in the semi-structured interviews earlier in this thesis, some clinicians view inpatient admissions as an opportunity to facilitate adherence to inhaled medicines. Several participants described how the structured nature of inpatient admissions created favourable conditions for habit formation. In this context, habit formation is externally scaffolded by routines during an inpatient admission. The mechanisms of illness salience and external support with treatment taking leads to temporarily improved adherence.

> *"…a hospital admission. So that would kind of almost scare me into doing it… I think it's the fear of "I'm actually really unwell now so I'm gonna do it"…at that point the CF kind of takes over, my whole life and I don't have other things to be thinking about, like I probably would be off work, or wouldn't be unwell enough to go out with friends or do any exercise so I feel like I have time for it [taking inhaled medicines]" (PwCF_08).*

Routines formed during inpatient admissions can be effective in the short term, however, post-discharge, they are hard to maintain when the supportive structures from the inpatient context are withdrawn. Competing demands trigger a change in prioritisation, leading to erosion of the habit and a decline in adherence.

> ***"PwCF_16:*** *After my recent hospital admission, I sort of got really good at so doing things. I think it helps start off in hospital because it's a very sort of sterile environment for being able to use your medicines and things because … you do get sort of that extra support, as there's always somebody called checking on you …"*
>
> ***Researcher****: So given that you had that support when you're in hospital and getting things started, how did you find it when you have built that habit in the hospital and then you move back home.*
>
> ***PwCF_16****: It continues for a little while, but then something could knock it off. So… you then have to get up early and be out all day and you'll get home and you're like "I just [want to] sit down and just sort of watch TV or whatever". And so, get to the end of the day and get in bed and think "ahh, I've not done anything [inhaled medicines]." So, I'll feel bad for not doing it. But I'm like "it's fine, I'll pick it up tomorrow" then it either slips more and more or I'll pick it back up again."*

Temporary interruptions to routine, such as holiday travel, is also a disruptive contextual factor, however behaviours and outcomes around travel can vary. For some, there is conscious decision to pause treatments, driven by the perception of low health risks. For others, the same outcome is driven by emotional or motivational disruption. When the temporary disruption passes, some pwCF can easily reinstate firmly embedded habits of treatment-taking but for those with more vulnerable habits, this can lead to prolonged periods of low adherence. These contrasting accounts illustrate how similar contexts can activate different mechanisms, shaped by risk perception or self-identity, leading to divergent outcomes.

> *"There are periods, like if I go on holiday…I might have a two week break from nebulising anything. Because for two weeks, I'm not going to come to too much harm, but the moment I'm home again I'll just religiously take them because I can." (PwCF_04).*
>
> *"…that mentality of "I'm on holiday" really affects my routine and then even getting back home…it can have a bounce back effect of getting back into the routine can be difficult as well". (PwCF_01).*

A strong identity as someone who takes treatment, shaped over time or in response to critical health events, appears to be a key mechanism for resilience, allowing maintenance of adherence despite disruptions. In these cases, habit is reinforced by deeply ingrained self-identity and perceived criticality of treatment, enabling maintenance high adherence even across dynamic contexts.

> *"it's habitual, so I do it. I'm going away in a few weeks' time, and I have to plan a lot because I'm gonna be taking those drugs with me and I have to make sure there's a fridge and, you know, I've been doing it for so long you just go 'that's just me that's what I do'." (PwCF_12).*

> *"No, everything revolves around it [treatment]... it's how Mum brought us up as well, but I think post-transplant it is so crucial that you have insulin, steroids, anti-rejections at 10am and 10pm, it's just part of every day of my life really to be honest. It's like having a shower really for me." (PwCF_15).*

Interestingly, for some pwCF with strong and resilient habits around inhaled medicines prior to ETI, adherence to inhaled medicines still declined post-ETI. In this context of significant health improvement and reduced symptoms, the mechanism of reduced perceived necessity for inhaled medicines can be triggered. This change in perception, despite the presence of an established routine, ultimately leads to treatment withdrawal or reduced adherence likely due to intention overriding habit (286). This highlights how contextual changes, such as the introduction of ETI, can override even long-standing habits when core mechanisms related to motivation and perceived benefit are disrupted.

> ***"Researcher**: ... could you think of any times or things that would happen that might make you think they [inhaled medicines] were more necessary than you feel now.*

> ***PwCF_07**: If I had a chest infection or I felt like there was a chest infection coming...I live by routine, so I always did nebulisers, I never struggled to find the time to do them but I would be more conscious of making sure I did the full amount every day rigorously if I felt sort of chesty or if I felt there was a potential chest infection. But I, yeah, I can honestly say I have not seen the need for them".*

<u>*Perceived necessity of inhaled medicines*</u>

Past experiences of severe health deterioration or near-death events served as a key contextual factor in triggering the mechanism of high necessity beliefs. In these cases,

the mechanism of fear of recurrence and belief in the life-preserving role of treatments was activated, resulting in strong and consistent adherence behaviours.

> *"I nearly died twice. I think given the opportunity to have a nebuliser that I could actually tolerate. And to take the antibiotics that kept me out of hospital. For me, it's always been a case of life and death I take them because they keep me alive." (PwCF_04).*

However, in a similar clinical context, others draw different conclusions when the mechanism of perceived connection between inhaled medicines and health protection is not triggered. Instead, pwCF can experience a cognitive disconnection leading to uncertainty about the value of inhaled medicines and lower adherence.

> *"We were getting ready for a lung transplant basically because I was so unwell and...that's probably the closest I've come [to death] but I feel like I still not made the connection in my head, like "these nebulisers will actually help." (PwCF_06).*

Improvements in health following the introduction of ETI has created a new context in which the necessity of inhaled medicines is actively questioned. For some, the mechanism of diminished perceived necessity, in combination with re-engagement in valued life activities, led to the intentional de-prioritisation of inhaled medicines in favour of alternative wellbeing strategies.

> *"I guess I take the view that really a good night's sleep was possibly more important than the drug that possibly isn't working. So, I will choose to sleep or... choose socialising because that has positive effects on your health ... above these medications where I don't really know if they work." (*PwCF_13).

In some cases, health improvements, specifically changes in sputum culture results, occurred despite withdrawing inhaled medicines. This context creates ambiguity around the role of inhaled medicines, triggering a mechanism of doubt or scepticism about necessity, which further reinforces low adherence.

> *"My pseudomonas for the first time ever went from a heavy growth to a scanty growth, yet I wasn't taking the [inhaled] medication... it doesn't inspire me to continue taking that medication every day." (PwCF_12).*

These findings highlight how the perceived necessity of inhaled medicines, an important mechanism underpinning adherence, is not static, but highly context dependent. Severe

illness and prior health crises can heighten this perception and drive high adherence. However, perceived improvements in health, whether through ETI or observed microbiological results, can undermine this belief, even among those with previously high adherence. This suggests that sustaining adherence to inhaled medicines in the context of improving health post-ETI requires new strategies to reinforce the ongoing value and role of inhaled treatments.

Current physical health

Physical health status and symptom burden are dynamic contextual cues which shape the mechanisms through which pwCF engage (or disengage) with inhaled medicines post-ETI. For many pwCF, the reduction or absence of sputum following initiation of ETI, altered their perception of inhaled medicines, especially mucolytics. Where sputum production previously served as a visible and validating symptom representing the necessity and efficacy of mucolytics, its absence has reduced their perceived necessity, leading to low adherence.

> *"I am a CF person...who doesn't use nebs...I don't feel like I get a benefit out of them... especially with DNase [mucolytic] and now obviously Kaftrio's come along... I don't cough much up. So, for me doing my nebs was just pointless... mucolytics weren't going to do anything for me." (PwCF_06).*

When symptoms remain unchanged despite missed doses of inhaled medicines, low adherence is reinforced as pwCF reassure themselves that the risks of persistent low adherence are low, until symptom burden increases, at which point necessity for inhaled medicines is restored.

> *"If I haven't got a cough or if I'm feeling generally okay that day...I won't take it [inhaled medicines]. Then, I'll get to the next day and be like "I was fine yesterday. So, I'm gonna be fine today." It's not until things start to drop that I think I should have taken it [inhaled medicines] and then that's the motivator that it's there for a reason." (PwCF_14).*

This revealed a temporal dimension to adherence-related mechanisms, in that delayed or absent feedback undermines the perceived necessity of inhaled medicines, until symptoms return.

> *"I do really well with sort of stuff for a month or so and then I'll sort of get out the habit and it takes sort of 21 days to build the habit and then only a couple of days to sort of lose that habit so it can be really frustrating. And it isn't until you get sort of really under the weather that you can like "Oh, hang on a minute. Probably ought to sort of try and get back on the horse here." (PwCF_16).*

Additionally, wellness can lead to a form of cognitive distancing from CF itself.

> *"I kind of forget I have CF said that makes me less likely to do them." (PwCF_07).*

Several participants confirmed hypotheses relating to the changing nature of pulmonary exacerbations post-ETI. They reported that exacerbations no longer manifest with typical symptoms. This creates a new context in which mechanisms relying on physical, symptom-specific cues to trigger increased adherence or contacting clinicians to discuss treatment escalation (e.g. a course of antibiotics) are not triggered, leading to delayed intervention and clinical deterioration.

> *"Although it [ETI] helps, it's not a fabulous cure... it's been harder to identify them [infections] because it does kind of mask when I'm getting the symptoms...and when I get them, they're quite bad ones again." (PwCF_04).*

> *"Since I've been on Kaftrio I've had a couple of bad chest infections, and they did come out of nowhere. Going from feeling fine to having pneumonia and spending four nights in hospital so I can imagine that might be because Kaftrio meant it wasn't as obvious as it would've been before." (PwCF_06).*

These findings highlight a critical post-ETI challenge: symptom- and health status-driven mechanisms of adherence, which may operate outside of conscious decision-making, can be disrupted in the absence of familiar bodily cues or immediate feedback loops.

Noticeable effects of the medicine

Another area of theory development relates to the subjective, tangible experience of taking inhaled medicines. For several participants, the lack of noticeable symptom-related benefit reduced the perceived necessity of inhaled medicines, and in turn, made adherence more difficult to sustain. This was occasionally compounded by the presence of immediate unpleasant post-treatment effects, such as pain and coughing which discouraged use despite awareness of potential long-term benefit.

> *"I despised doing nebulisers… it just made me cough for the next hour or so…even though it was better for the long-term quality of health, the short term, erm, life quality was, you know…just broadly miserable." (PwCF_02).*

> *But [after taking nebulisers] when you're coughing and coughing and coughing it starts to hurt your throat and …your chest and your shoulders and it just affects your whole mood for the day." (PwCF_01).*

Interestingly, one participant offered an opposite perspective, highlighting how they perceived post-treatment coughing and expectoration as restorative.

> *"So yes, I got the hypertonic saline…that was fantastic, because I could feel it made a difference. And I would take that and then I would go running and I would cough everywhere and then I would feel great for the rest of the day. And the DNase is on the other hand I couldn't really feel any difference with it and so I found it really difficult to do that. I do it, but it just felt pointless the whole time." (PwCF_03).*

This perspective further strengthens the proposed relationship between the context of noticeable treatment effects, the mechanism of necessity and the outcome of adherence. When pwCF do experience a noticeable benefit from inhaled medicines (context), this appears to increase their perceived necessity of the treatment (mechanism), ultimately supporting higher adherence (outcome). This stands in contrast to the more common pattern observed in this study, where the absence of a noticeable benefit reduced perceived necessity and led to low adherence. Taken together, these accounts suggest that subjective symptom burden plays a critical role in sustaining adherence behaviour, even in the presence of burdensome treatment regimens.

Balancing demands and responsibilities

The time-consuming nature of taking inhaled medicines continues to pose a significant burden to pwCF, particularly as their health improves post-ETI. PwCF have always had to balance the demands of treatment with other life commitments and priorities, but improvements in health have changed the perceived benefits of prioritising treatment. As health improves and life opportunities, such as the ability to work and socialise, increase, the opportunity cost of maintaining high adherence also rises, making routine use of inhaled treatments more likely to be deprioritised.

> *"I have way more energy now…I have a full-time job now." (PwCF_03).*

> *"I think it [combined time required to complete all prescribed treatments] came out to 17 and a half hours a week… but then you also have to fit in time to sleep, time to eat, time to go see people, do fun things that you like to do…" (PwCF_01).*

> *"I'm really good at either controlling my diabetes or taking my medicine or doing the nebulisers or the physio. I just can't at the moment do it all." (PwCF_14).*

Inhaled medicines are not only time-consuming in terms of administration, but the setup, cleaning, and maintenance of equipment adds to the overall burden. These aspects have become more prominent post-ETI, as pwCF compared this labour-intensive process with the relative ease of taking ETI orally:

> *"it's [taking inhaled medicines] sort of like an hour and a half in the morning, an hour in the evening." (PwCF_16).*

> *"I'll do my pills because they're in a medibox…it's all done for me… Because I've got to be the one to do my nebulisers that's adding an extra five minutes of me having to do the nebulisers, having to put the nebuliser together having to sit down and breathe the treatment in. So, if it was all done for me, if it was all pre-mixed…I think maybe that would help me personally do them. [regarding tablets] it's just pop them out in the morning. Take them. Done. Don't think about it for the rest of the day" (PwCF_06).*

> *"That's why it's just been such a change. I don't have to sit down, medication up, distribute it within my…take the [inhaled] medication. it's just completely changed. It's the most minimal impact on your life to take Kaftrio with the most maximum effect". (PwCF_07).*

Where previously CF may have dominated day-to-day life, participants described a change in focus, and a willingness to trade-off optimal health status for lower treatment burden.

> *"I just see all life's a balance, isn't it, of all these different things and I think I've come to realise that it isn't just the medication that makes us feel well. It's all the other stuff, it's socialising, it's eating, you know, just all the other choices you take. Prior to Kaftrio it was kind of all about the treatment, the medication. That's what drove me life. And I don't feel like it does anymore… I might not [care] if my lung function was 70 or 65% if I got rid of DNase." (PwCF_13).*

Some participants described trying to "reclaim" time by reducing or stopping treatments that felt particularly long, frustrating, or inefficient:

"I've just stopped using it [inhaled medicines] because really it was just 20 minutes a day…that I could get back." (PwCF_07).

"Tobramycin… seems to take forever to go through my nebs… for some reason that is when my mind starts to just go 'you know what, just don't do it.'" (PwCF_06).

Participants also pointed to the spatial and logistical burden of inhaled medicines, particularly when travelling. The effort required to transport, store, and explain medications in such contexts led to decisions to omit inhaled medicines, particularly in the context of improved health alongside the perception that brief interruptions to treatment pose low health risks.

"The nebuliser…and the pills all take up space in my case, but they take up space in my holiday time…And then getting through customs…can be pretty difficult…because you've got to get all your medical notes…and they still want to go through your cases and check everything." (PwCF_01).

I wouldn't dream of taking all that on a plane with me and then to hotels and other things… I'd have a suitcase just full of all the powders to mix up and the machine itself." (PwCF_09).

Taken together, these findings suggest that the perceived burden of inhaled medicines, amplified by time, effort, and disruption, plays a central role in treatment de-prioritisation post-ETI. As health improves, and life expands to include more valued activities, the effort-to-benefit ratio of inhaled treatments becomes harder for pwCF to justify, particularly in the absence of symptoms or noticeable effects.

Relationship with health care providers

The relationship between some pwCF and their care providers has changed, both due to the impact of ETI and the COVID-19 pandemic. There is conflict between what pwCF consider optimal health, which may involve a trade-off of health benefits with burden reduction, and what clinicians consider optimal, namely maintaining high adherence to all prescribed medicines.

"I do think sometimes, the clinics struggle to have an adult conversation about your real life and medication. So, their goal is to have you take 100% of your medication…which was unrealistic before Kaftrio and I think is even less realistic now…they haven't moved to a position where it reflects the day-to-day decisions people with CF make about how much risk versus tiredness versus "I want to see

> *me friends" that you take on a daily basis. They don't really look at it like that…I wouldn't care if it [my lung function] was 70 or 65% if I got rid of DNase…But the hospital…wouldn't think like that. They would like to want you to maintain like 70 odd per cent [adherence], no matter what, even if you ended having to do four hours treatment a day." (PwCF_13).*

This discordance is a contextual feature which leads to pwCF concealing decisions related to adherence, to avoid the potential emotional discomfort associated with being "*hassled*" by clinicians for reducing or withdrawing treatments autonomously.

> *"I've even stopped doing my Flutter which the hospital don't know I bet." (PwCF_07).*

> *"…you don't necessarily want to be hassled, like I didn't about to stopping me acapella. You just don't necessarily tell them what you're doing." (PwCF_13).*

As discussed above, and consistent across the findings of this study, subjective symptom burden is considered an important determinant of adherence in the post-ETI era. This conflicts with clinician perspectives, where objective measures of health such as lung function, established evidence and an aversion to perceived risks of reducing treatments are given greater priority in informing their recommendations. As a result of this, pwCF feel obliged to use objective data to "prove" that their suspicions that certain treatments are not required.

> *"Tobramycin just did not suit my lungs at all…and I kept telling my team and over and over again. It's like "no you've got to keep up with a treatment… I decided to try and prove the point…so, I took my lung functions for 10 days to show the evidence of what was happening [lung function declined after tobramycin was initiated] and eventually the listen so I came off of Tobramycin". (PwCF_11).*

> *"I used to use the acapella PEP [positive expiratory pressure] device…Took myself off at about a year and a half ago, didn't mention it a clinic and me lung function didn't change it all. And yet when I told them I didn't want to take it anymore, they were quite paranoid about it even though I would suggest there was evidence from my record to show that wasn't making any difference at all". (PwCF_13).*

Additionally, the clinicians uncertainty regarding inhaled medicines discovered in the interviews in Chapter 4 is recognised by pwCF, leading them to feel frustrated and not being given clear recommendations.

> *"I have challenged why I still take them [inhaled medicines] even after being on Kaftrio for nearly four years. And I just don't get any answers. They say "well, we haven't got any sort of information to back up people coming off these things." (PwCF_09).*

Furthermore, when clinicians convey a general sense of optimism about the transformative impact of ETI, some pwCF perceived this as downplaying their ongoing health concerns, undermining trust in the therapeutic relationship.

> *"In terms of relationship though with my team, I would say that's changed probably more negatively ...it's almost like they feel everybody's cured... I know my Lung function is relatively good compared to others, but even when my lungs are still bleeding, I was being told "there's nothing you can't do now you need to go out and do the 5K run and build up from there". And I'm like, it's just never gonna happen, my lungs... if my lungs bleed or ... there was a little understanding of the individual. I felt and I began to lose trust in my team...I felt less supported in all honesty because I think the general feeling is that Kaftrio has cured everybody, and it's been brilliant." (PwCF_11).*

Care delivery preferences.

The acceleration in adoption of virtual care and remote monitoring across the NHS, necessitated by the COVID-19 pandemic, has led to sustained changes in the way that CF care is delivered, though there is variation in both the ways that virtual care implemented and the way that this has affected pwCF. For pwCF who feel well and have fewer concerns to discuss, shorter virtual appointments offer a more convenient alternative to in-person consultations, due to the reduced time commitment.

> *"...I wasn't having to go into hospital. I haven't been other than annual reviews...so that's been a big change and a big improvement to me because ... It's a lot easier to fit that in with them work and lifestyle...and with Kaftrio...the more well you are, the less there is to talk about so... it's like, 15 minutes 20 minutes ... a quick appointment. So yeah, those two things covid and Kaftrio have really improved the time required...". (PwCF_07).*

> *"[Pre-Covid in-person appointments] ... took a half a day or a day... trying to take that off work constantly would have been difficult and now it's like a 15–30-minute Zoom session. I don't have to tell anyone I'm doing it...So yeah, it's a game changer." (PwCF_03).*

Virtual consultations are particularly effective for pwCF who can clearly articulate their care needs, a capacity developed through longer experience of living with CF and established, trusting relationships with care providers.

> *"It was more time consuming going in and that [virtual appointments] saves my energy…I've been doing this for donkeys' years. I'm kind of quite used to communicating with doctors and explaining how I am and knowing which bits to mention." (PwCF_12).*

> *"I know pretty much everyone on my team, and I think it's just from doing face to face moments…that has built the rapport with them for me to be able to go "Yep, I can talk to this Consultant about this, I can't really talk to this Consultant about this". I spoke to one of my male Consultants about my periods and for me, I would have never dreamed about doing that as a kid…" (PwCF_06).*

> *"I think with the XXX team, it's because I had a lot of time with them face to face. So, we're established a good relationship before we went online. So that probably helped a lot." (PwCF_03)*

> *"Yeah, same [as PwCF_03 above] for me. I think I probably would have had the similar experience but because I knew them for a number of years it [transition to remote appointments] didn't… hurt the relationships". (PwCF_07).*

However, certain issues are less suited to virtual consultations, and the absence of non-verbal communication in that setting means pwCF do not benefit as much from feedback and reassurance from care providers. It also creates the potential for certain, more subtle, indicators of health, in particular mental health, to go unnoticed and unaddressed.

> *"I've got some gastrointestinal issues…. If I'm on a Zoom meeting…my Consultant can't feel my stomach…I think it works better for me going to a face-to-face appointment" (PwCF_06).*

> *"I don't think you can pick up on someone's…erm, like how they're really doing on a video call…they didn't pick up on the signs that I was getting a bit upset… although I was doing well physically, it was mentally that they didn't pick up on." (PwCF_14).*

> *"I've had one or two [telephone appointments] and a really dislike them. It didn't feel as personal, it was more difficult to keep the relationship up with the clinics staff…It proved more hassle than just going in clinic…so I go in person every three months." (PwCF_13).*

> *"If it's a phone call…it's so brief and is purely just me being like "yeah, I'm fine". And then that's it. There's no kind of that personal, erm, like checking in and seeing what's like going on in my life and stuff, which I know they don't have to be doing but it just gives it a more personal element I guess." (PwCF_08).*

Consequently, pwCF value the flexibility to choose between virtual and in-person appointments according to their needs and priorities. Some clinicians interviewed in the semi-structured interviews (Chapter 4) reported conducting a face-to-face Annual Review to balance the convenience of virtual care with the need to utilise in-person consultation to detect subtle health changes and maintain the therapeutic relationship. This approach was also endorsed by pwCF, who appreciated having at least some scheduled in-person appointments to allow for more detailed assessments, the collection of clinical and microbiological samples, and the monitoring of a broader range of health indicators.

> *"Taking out a whole day to go to an appointment where it's kind of just me being like "yeah, I'm fine…." . It's easier … doing that by phone then like having the Annual Review that is in person and to kind of just touch base on kind of…in more depth". (PwCF_07).*

> ***"****I actually asked if I could go in now and again because I felt it was a bit strange. I found it difficult that I didn't see them at all because I think the body language and how you are physically is missed sometimes when you can only see someone from the sort of neck upwards." (PwCF_12).*

> *"But I do want to be able to come in every now and again to do the cough swabs, and … blood tests and chest scans…I can also do a full Spiro [spirometry] test, double check my weight on the specialty scales…I can pop to the outpatient pharmacy…I don't have to go in so often, but I want to be able to come in sometimes just to top up and make sure I've got everything in order." (PwCF_01).*

> *"I want to change one of those [appointments] to Virtual, I can just say, "can this one be virtual and I'll come in the next time and that's absolutely fine… my husband takes time off work [to attend clinic with me] …so it's been a really big benefit to cut one of those out as a virtual clinic." (PwCF_11).*

While some pwCF described a sense of liberation with the adoption of virtual appointments, others experienced a sense of loss regarding previously strong relationships with care providers, and feelings of abandonment, particularly when the transition from a long-standing, in-person model to virtual care was abrupt.

"When I started Kaftrio…the healthcare that I had just stopped…They were obviously still there, but from going into hospital, say, every two months…I refer to them as my health family. They were always there I would see them regularly…to then not having any admissions in a whole year, I kind of felt neglected." (PwCF_14).

"I feel like I've maybe lost that [strength of relationship] a bit because I end up seeing a Consultant that I've never actually really met before… it's not as productive, erm, conversations because I think I'm kind of like "well they don't know my whole history and every CF patient is obviously so different that they're not going to know what's right for me kind of thing". And so, I feel though I'd have kind of lost that by not going as frequently." (PwCF_08).

"I think as a woman of my age [44-55 years]…it's a little bit scary…I hope they don't go completely so virtual, you know, I don't want to feel forgotten…I think I am able to reach out to them occasionally when I do feel like I'm just never seen, I sometimes go "actually I need to have a bit of contact here because I'm still managing a lot"…I just try to communicate with them and try and get my needs met when I'm not very well and the rest of the time it's handy not having to go in so much". (PwCF_12).

In one instance, a participant described engaging in harmful behaviours as a means of eliciting attention from their care providers.

"with CF being such a big part of life…I really struggled and I did overdose on insulin twice, because…I just found it really hard that I felt on my own…with covid happening, appointments went to video…so, they didn't pick up on the signs that I was getting a bit upset…I remember, not taking medicine so I could go into hospital, because I needed that fix of being loved and cared for by the CF Team who'd kind of forgotten about and it made me feel like a number rather than a patient." (PwCF_14).

CF can be an isolating condition.

A key contextual feature which may explain some of the unique features of the strong therapeutic relationship which exists between pwCF, and CF clinicians was the feeling of isolation several pwCF felt as members of the CF community. This stemmed from the clinical need for pwCF to be kept apart from each other, meaning, for some, their only source of support with CF is their specialist CF MDT.

"Since COVID we've done Zoom meetings and even through discovering Zoom we started doing CF group therapy sessions, which has been really helpful for me because obviously CF people can't be within 6 feet of each other and so it's always been a very isolating disease. Anyone who knows exactly what you're going through, you can't be anywhere, you can't be in the same room with them and so transferring

to Zoom we have discovered Zoom therapy. And so, we've started doing that and we've started discussing our problems and that's really helped". (PwCF_01).

"I suppose I'd become accustomed to having less to do with my team, but I think having CF, especially when you're poorly or you're used to that constant contact with your team, you feel very alone." (PwCF_15).

"I did once meet somebody with CF when I was, again before the whole research about mixing came in, I was about 11 on the ward and played together ... and then sort of all the research came on and everyone was barred from seeing each other and so ever since I've never spoken to anybody else with CF or anything like that. It's all through the CF Team stuff, you read on Reddit and online and stuff that those experiences. You don't really get it anywhere else." (PwCF_16).

Interestingly, the act of bringing pwCF together in focus groups was itself well-received and, for some, constituted a positive experience. Participants described feeling validated in their own experiences, gaining insight from others, and being reassured that their difficulties were not unique.

"I'm really pleased that I've come on this [focus group] because I don't get to see anybody else, I don't speak to anybody else with CF and it's just been really interesting listening to other people, you know, their experiences and situations." (PwCF_11).

"I thought it was just me who struggled.... it's reassuring that other people do struggle". (PwCF_16).

Evolving health needs for pwCF

Some participants suggested that, as more pwCF present with fewer acute care needs, care providers may have greater capacity to support those with more complex requirements, as well as to address concerns not directly related to CF, such as musculoskeletal pain and mental health.

"Because there are so many people who are benefiting from it [ETI], it's certainly freed up time or at least energy for there to be a bit more of a relationship between patients and care Centres for those ... who've got ongoing issues... I've found that there's more time, to, you know talk through other issues for me, which has been massively positive." (PwCF_03).

"I think there are more people with fewer demands. So, they're [care providers] not constantly firefighting everybody all the time. People who need to be prioritised,

they get more time because there are fewer people who have got just so many more issues going on." (PwCF_06).

"I had trouble with my back and so I wasn't able to exercise for a bit. They [CF Team] referred me to a Physio…they've been incredibly helpful." (PwCF_03).

"I had an issue that wasn't CF-related, but I had trouble with the doctors [GP]. I emailed him [CF Consultant] and managed to get me to see someone." (PwCF_10).

In Focus Group 2, which coincidentally comprised a relatively older demographic, participants expressed confusion regarding responsibility for managing age-related concerns, such as cardiovascular risk monitoring, highlighting a potential disconnect between primary and secondary care, leaving aspects of care unaddressed.

"all the CF clinics are having to get involved with stuff that's "half-CF… like high blood pressure, cholesterol…I got an invite to go the GP to get all the tests done for that when I got over 40 and the results all came back a bit iffy and because I've got CF the advice didn't really match what happens with a CF diet, so I've ended up going back CF Clinic with that and they've said "just ignore it, it's fine for somebody with CF". There's a bit of a mismatch between knowledge at the GP level and knowledge at CF clinic." (PwCF_09).

"I've found something lacking in the relationship [with CF care providers] when it comes to aging…. I've talked to them about blood pressure, they know it's an issue, but don't have any protocol or way to deal with it…the GP didn't either so they will test you and say there's an issue, but then refer it to the CF clinic…but their response was "but we don't know anything about blood pressure… we'll refer you to the GP"… it isn't quite working at the moment…that is the small strain on a relationship that I have at the moment because I am starting to get some small issues around aging and I don't really know who to talk to about it…somebody needs to decide who's responsibility it is and educate themselves." (PwCF_13).

"We sort of feel a bit like …medical guinea pigs to CF teams because we're the first ones sort of reaching 40s and 50s still going strong with CF. It does feel a bit of the time they're just chucking stuff at the wind and seeing what sticks." (PwCF_09).

The impact of childhood experiences on adult behaviours

Participants spoke openly about their childhood experiences, particularly those involving the burden of CF, often describing a paternalistic and inflexible approach to care within paediatric Centres. These experiences represented important contextual

factors, as participants' responses to them shaped attitudes and behaviours related to engagement with medicines adherence and healthcare more broadly into adulthood.

> *"The neb thing for me mainly stemmed from when I was a kid…If I was going to sleep over a friend, having to take all my nebuliser treatments and then having my friends look at me doing my nebulisers…made me feel [like]… a "freak". Especially going through the immense amount of bullying I went through as a child because I was having to nebulisers, having to do tablets, always having to be singled out…Going out and doing social matters [was]… a red flag…. I couldn't do it. So that was a massive effect on my nebs… [which] just followed me through life… if I go abroad or go away…for the day, I'm still very apprehensive of "if I leave my nebuliser in my room. What are people gonna think?" So… that's…a burden for me." (PwCF_06).*

> *"All I ever really got from children's [paediatric CF team] was… "you have to do this. You must do this. It's good for you because" and every time I went to clinic, my mum would speak for me…I'd always just look at my mom as if to like, right you're gonna answer for me because I don't want to." (PwCF_06).*

> *"I was diagnosed at five months old. Mom was having to tip Creon into my mouth and having to make me sit and do the vest for hours on end…Mom went to the clinic and said" I want to take her off of the dornase because it's not helping her" and they said "no" …they were threatening to call CPS [Child Protection Services] if I wasn't taking my medications properly. And so, Mom, for eight years, said that "she's doing great with them" and I wasn't and then they called her up on not refilling the prescription for it." (PwCF_01).*

Several participants highlighted the role of parental involvement as a key structural support for adherence during childhood. However, this became a source of tension during transition, when pwCF were expected to assume responsibility for their own care without feeling ready or able for this.

> *"I was a teenager and kind of took my care on myself. Whereas before my parents were always kind of making sure I did it. I think I've always struggled with actually doing it." (PwCF_08).*

> *"When I started having sort of take a reign on my own care when she [mum] stepped back when I became a teenager…moving up to the adults [CF Centre], me and my Consultant we were butting heads… I would just lie through my back teeth… I knew he'd be able to tell whether I were doing my medication from blood tests, but I'd be adamant… "yep I do all my medications each day every day" stand there with a smile on my face.". (PwCF_06).*

Stigma emerged as a dynamic contextual factor. Feelings of shame associated with CF in early life may diminish over time, likely as a result of increased maturity, strengthened necessity beliefs regarding treatment, and growing self-confidence. This contributes to increased adherence with age.

> *"I think it's because I have to do them…so people just have to fit in with me. I was really ashamed of my CF when I was young…I tried to hide it whenever possible which…I sounded like I smoked hundred fags a day from the age of… a child. I think maturity and being an adult has made me go "Right, these things I need to do are really important for me. So, if someone sees me doing that in the car…whatever, so be it…, I do it most of the time, I try not to miss it." (PwCF_12).*

For others, increased engagement with care was driven by a desire to live well and make the most of life, especially realising how their capacity for engaging in social activities has increased post-ETI.

> *"My mum was really strict about my medicines growing up… I really resisted them as a teenager …it's only really sort of in the last sort of few years I've really taken interest in everything around my health… I've got two little nephews now that I sort of want to have like more time to spend with them and be as healthy as possible… I played football with my nephew last Tuesday for example and again something I couldn't have done before Kaftrio." (PwCF_16).*

A key area which shaped personal narratives around the lived experience of CF was the transition from paediatric to adult care. When this involved an abrupt transfer of responsibility from trusted paediatric CF care providers to unfamiliar adult CF care providers alongside the expectation of reduced parental involvement in consultations, pwCF felt unprepared and unsupported. This disruption led to negative experiences of care and reduced engagement, particularly where pwCF did not feel ready to assume full responsibility.

> *"I remember it being horrendous…there was no smooth transition…it was like a cut off…You were done with Paediatrics…everybody was then changed. There were no introductions…your parents obviously used to go with you to your appointments. Once you went to Adults [CF Centre] it was "what's your parents doing here? You're old enough now to know what you're doing", but I still relied on my parents…it's like they expect you to just know all the knowledge, know all your history overnight and they kind of just shun everybody away because you're now an adult." (PwCF_14).*

"When I was younger, I didn't really want to understand CF and it wasn't until I hit adult that they were like "you need to understand because this is your life". It was literally going from light to dark. It was a huge change." (PwCF_14).

PwCF want to experiment with their treatment.

CF clinicians are understandably cautious about recommending withdrawal of established inhaled medicines for those on ETI. However, pwCF have a much more optimistic and open view towards this. Where clinicians cite a lack of evidence to support withdrawal, pwCF recognise that the only way to generate evidence is structured trials of treatment withdrawal. This is leading pwCF to take the decision to arrange their own withdrawal "trials," with or without the support or knowledge of care providers.

"When you're talking to them [CF care providers], "just to be on the safe side, just keep taking them, there's no evidence" ...but there's never going to be evidence unless people start coming off them and seeing what happens in a safe controlled way." (PwCF_09).

"[CF care providers say] there's no evidence one way or the other at the moment so they always err on the side of caution...[but] there's probably quite a big difference between the amount of risk the average person with CF is willing to take. against what risk the clinic this willing to take...People are basically testing themselves by taking themselves off medication without telling clinic and just seeing what happens...I used to use the acapella PEP device...took myself off at about a year and a half ago, didn't mention it a clinic and me lung function didn't change it all. And yet when I told them I didn't want to take it anymore, they were quite paranoid about it even though I would suggest there was evidence from my record to show that wasn't making any difference at all. And what level of evidence clinics would want to be able to say "yes, we're happy with you reducing it." (PwCF_13).

And so, when I went on Kalydeco [Ivacaftor]...I of course experimented and tried to take away some of them nebulisers that I did...and it didn't really work...I got ill and that was disappointing obviously and so I had to sort of get into the real world. Although the Kalydeco was really helping I couldn't come off these drugs and I had to sort of carry on really a bit as normal. So, yeah, that was sort of a bit disappointing". (PwCF_12).

Underlying scepticism of the value of large, population-based withdrawal trials also drives a desire for personal experimentation.

"Every single one of us is completely different... there's limited use to the massive trial of people coming on and off because they might get a general idea...but...we're just so individual... it'll be up to us to maybe push the issue to give ourselves a the

trial…of not taking it…if there's problems, yep fair enough, we'll keep taking them… leave it up to us to be sensible and be honest with them." (PwCF_09).

"…a massive trial would not be as beneficial as each individual person with their clinics." (PwCF_12)

"…what they want to do is a trial…do my lung function before, take it [DNase] consistently for 2 weeks and then do it [lung function] after. If it doesn't make a difference, then I'll stop it all together." (PwCF_13).

8.3.3 Refined Programme Theory

Data from the focus group transcripts was analysed as per Figure 8. The final CMOC index consisted of 78 CMOCs across nine theory areas, as shown in Table 14.

Table 14: CMOC index underpinning the refined Programme Theory.

Theory ID	Title	CMOC
ETI has had a transformative impact on CF		
ETI_01	The transformative effects of ETI have led to reduced emphasis on non-ETI treatments	The introduction of ETI during the emotionally intense period of the COVID-19 pandemic, coupled with its widespread availability and significant clinical benefits (C) meant that both clinicians and pwCF perceived ETI as a transformative solution and are optimistic that it may "fix" the problems associated with CF (M: reasoning) resulting in pwCF leading lives more akin to that of the general population (O1) with a reduced emphasis on adherence to non-ETI treatments such as inhaled medicines (O2) and increased opportunity for relationships and work (O3).
ETI_02a	Clinicians value subjective reports of improvement over traditional objective measures and therefore reduce monitoring and treatment	When clinicians observe significant health improvements in pwCF post-ETI (C1) they come to view pwCF as more clinically stable and less vulnerable (M1: reasoning). As a result, they may place greater weight on subjective reports of wellness even when objective measures show decline (M2: reasoning) which leads them doubt the accuracy of objective measures which conflict with the subjective report (O1) and to adjust their clinical thresholds and deliver less intensive monitoring and treatments (O2).
ETI_02b	Clinicians value objective measures of improvement over subjective reports and therefore recommend continuing existing treatments	When clinicians observe discordance between objective indicators (e.g. FEV_1) and self-reports of wellness (C1), some clinicians value objective health indicators as a more reliable indicator of health status (M1: response, objective primacy). Although the relevance of a decline in objective measures may be contested by pwCF, who do not perceive themselves as unwell (M2: reasoning, subjective primacy), clinicians maintain their trust in the validity of objective measures (M3: reasoning, objective primacy, epistemological dissonance). As a result, they recommend continuation or reintroduction of treatment based on the objective clinical data (O1), while also scheduling reviews to monitor changes over time and reassess treatment needs (O2).
ETI_02c	When subjective and objective measures both indicate a satisfactory health status, clinicians place less emphasis on adherence support	When pwCF feel subjectively well and this aligns with stable objective health measures (e.g. FEV_1) (C), clinicians reason that current adherence must be effective in maintaining stability (M1: reasoning), reducing perceived need to discuss adherence or encourage change (M2: response) resulting in de-prioritisation of discussions around adherence (O).
ETI_02d	When subjective and objective measures both indicate a poorer health status, clinicians and pwCF	When there is concordance between subjective symptoms (e.g. increased sputum) and objective health measures (e.g. decreased FEV_1) (C), epistemological dissonance is mitigated (M: reasoning) leading to greater agreement on the need for treatment escalation (O)

	agree that treatment escalation is needed	
ETI_02e	PwCF value short-term subjective health indicators over long-term probabilistic benefits when making adherence decisions	PwCF who have fewer or no symptoms post-ETI (C) interpret this as health improvement (M1: reasoning), reducing the perceived necessity of inhaled medicines (M2: reasoning) leading to a reduction in their use of inhaled medicines (O1). Even when pwCF understand there are long-term benefits of inhaled medicines (C2), this abstract knowledge of probabilistic long-term benefits is superseded by subjective health improvement (M3: reasoning, retroduction, temporal discounting and subjective primacy) leading to sustained low adherence (O2). Additionally, if pwCF do not understand or accept the long-term benefits of inhaled medicines (C3) they will still discount future benefits (M3: reasoning, retroduction, temporal discounting) leading to low adherence (O2)
ETI_03	PwCF may wish to trade-off optimal health outcomes by reducing treatment burden leading to shared decision-making	Some clinicians and pwCF believe pwCF benefit most from ETI when it's added to, rather than replaces, existing treatments (C1). Some pwCF may consider ETI a more efficacious alternative, especially if they never perceived much benefit from inhaled medicines (C2), which causes them to question the need for inhaled medicines now they are taking ETI (M1: reasoning), leading to reduced use of inhaled medicines (O1). When pwCF feel significantly better post-ETI or have reached a satisfactory health state (C3) they may question the need to continue older regimens (M2: reasoning), preferring to trade-off optimal clinical outcomes with burden reduction (M3: response) leading to reduced use of inhaled medicines (O2). When treatment reduction is followed by a sustained health benefit and absence of deterioration (C4), this reinforces the rationale that the inhaled medicines are not necessary (M4: reasoning) and sustains low adherence (O3). This can make it harder for clinicians to support pwCF to maintain high adherence which may require different strategies to communicate long-term benefit (O4). Conversely, an acceptance of this rationale may encourage adoption of shared decision-making regarding treatment (O5).
ETI_04	The positive effects of ETI can attenuate symptom-related prompts for treatment-taking	When PwCF experience significant benefits from ETI (C), they may have lower adherence to inhaled medicines (O) as CF becomes less salient in their daily lives and they no longer experience symptomatic prompts which may have previously initiated treatment-taking (M: reasoning, retroduction).
Mental Health implications for pwCF related to ETI		
MH_01	PwCF prescribed ETI are anxious about secondary inefficacy	For pwCF who's health improves significantly after years of illness (C), fears about the permanence of these improvements can create anticipatory grief and fragile hope (M: reasoning) leading to emotional distress and worsening mental health (O).

MH_02	PwCF who are not prescribed ETI, either through ineligibility or intolerance, may feel excluded	PwCF who are ineligible for ETI (C1) and pwCF who have experienced significant health improvements from ETI and then have to discontinue ETI due to side-effects (C2) may experience feelings of exclusion (C1-M1: response) or loss (C2-M2: response) contributing to emotional distress and worsening mental health (O)
MH_03	PwCF may be distressed after experiencing an exacerbation whilst prescribed ETI, requiring clinicians to reassure and set expectations	PwCF who consider themselves "cured" by ETI (C1) may interpret an unexpected exacerbation as evidence that ETI has stopped working, which shatters their perception of ETI as a cure/effective treatment (M1: reasoning) resulting in emotional distress and sharing this with clinicians (O2). Clinicians who have these conversations with pwCF (C2) reflect on communication strategies when initiating ETI (M2: response) then actively and explicitly set expectations that ETI may reduce but does not eliminate exacerbations (M3: response) meaning pwCF adjust their expectations and are less distressed at times of future exacerbation (O2).
MH_04	PwCF now have to contend with an unanticipated, increased life expectancy for which they may not be prepared.	PwCF who made significant life decisions based on the expectation of a shortened lifespan yet are now facing a longer, healthier future (C), may experience anxiety and regret about not having pursued long-term goals like careers or financial planning (M: reasoning). This mismatch between past decisions and current possibilities/expectations contributes to increased emotional distress (O).
MH_05	There is uncertainty as to whether deteriorations in mental health post-ETI are side-effects or responses to changing circumstances	When pwCF experience a deterioration in mental health since starting ETI (C1) and perceive this as a side-effect of ETI (C2/M1: reasoning) adherence to ETI may reduce (O1) because the negative effects of the psychological distress outweigh the perceived benefit of ETI (M2: reasoning). The uncertainty around the aetiology of deteriorations in mental health for those taking ETI (C3) makes it difficult for clinicians to know if they are providing the most appropriate care (M3: reasoning) so they consider research in this area important (O2).
The changing nature of pulmonary exacerbations		
PEX_01	Pulmonary exacerbations present differently post-ETI, leading to delayed recognition and treatments	PwCF who are prescribed ETI may experience fewer or no symptoms, even when there is an acute decline in lung function (C1). They are therefore less likely to recognise when they are having an exacerbation (M1: response) meaning clinicians cannot rely on pwCF reporting exacerbations (M2: reasoning) increasing the reliance on objective measures such as lung function (M3: response). This increases the risk of delayed intervention (O1) and deterioration to more severe, acute clinical conditions, such as pneumonia (O2).
PEX_02	Post-ETI, pulmonary exacerbations can be managed with oral antibiotics rather than hospital admission for IV antibiotics.	PwCF who are prescribed ETI experience milder exacerbations and/or an improved resilience to infection (C), meaning oral antibiotics are increasingly seen as effective at resolving symptoms without the need to escalate to IV treatment (M1: resource/reasoning), meaning fewer pwCF therefore require admissions for IV antibiotics (O).

PEX_03	Discordance between symptoms and lung function result in uncertainty about when to recommend treatment for suspected exacerbations	PwCF prescribed ETI experience a discordance between subjective symptoms and changes in objective lung function (C). This creates uncertainty for clinicians (M1: response), who were accustomed to interpreting changes in FEV_1 as a reliable marker for infection or deterioration (M2: resource). Clinicians therefore adapt their clinical reasoning and decision-making processes (M3: response), which can lead uncertainty into optimal care delivery, for example when to recommend treatment with antibiotics (O).
PEX_04	Fewer exacerbations post-ETI reduces the perceived health threat of CF	A reduction in pulmonary exacerbations and chest infections post-ETI (C) reduces the perceived health threat of having CF (M1: reasoning) making inhaled medicines seem less important (M2: reasoning) leading to reduced adherence (O).
Changes in the ways pwCF now engage with clinicians		
PBE_01	When pwCF are well, their preferences for care delivery change, requiring adoption of personalised approaches.	When PwCF perceive themselves as well and/or this view is shared by clinicians (C1), pwCF and/or clinicians may view continuation of routine appointments or monitoring (M1: resource) as unnecessary or, for pwCF specifically, forgettable and inconvenient (M2: response), especially when faced with competing responsibilities (M3: reasoning). This may lead to reduced attendance or disengagement with some aspects of care (O1). Clinicians, observing reduced attendance (C2/O1), may be prompted to embrace shared decision-making approaches to agree personalised follow-up intervals (M4: response), which allows pwCF to have input into the frequency and nature of their appointments (O2).
PBE_02	Virtual appointments may improve engagement for pwCF who face barriers to attending in-person appointments	For pwCF with milder disease who may have difficulty attending face-to-face appointments (C), the option to attend appointments virtually (M1: resource) increases their ability and willingness to engage with care (M2: response), ensuring continued access to specialist CF care (O).
Changes in the ways pwCF now engage with non-ETI treatments		
PBM_01	Autonomous treatment reduction by pwCF post-ETI may conflict with clinicians' perspectives that treatment should be continued, straining the therapeutic relationship.	PwCF who feel well or better after starting ETI (C) may view ETI as a cure (M1: reasoning), reducing the perceived need for other treatments (M2: reasoning). This fosters greater autonomy (M3: response) and, in some cases, leads them to independently stop inhaled medicines (O1). Some openly discuss this with clinicians, while others do not (O2). In reclaiming autonomy (M2: response) pwCF may place more value on informal or selective sources of evidence, while overlooking their limitations (M4: reasoning, confirmation bias) which reinforces their decisions to reduce treatment (O3). Meanwhile, clinicians who are aware of the limitations of trial evidence and cautious about its interpretation (C2) may experience concern or frustration when pwCF cite incomplete or oversimplified interpretations of data (M5: reasoning). They anticipate challenges in communicating nuance and correcting misinterpretations (O4), especially when pwCF are confident in their own information sources

		(C3). This tension requires clinicians to balance the duty to support informed choice with the desire to maintain rapport and trust (M6: reasoning), which may strain the therapeutic relationship (O5).
PBM_02	PwCF may conceal low adherence prompting clinicians to explore this sensitively or objectively. In certain cases, such as pseudomonas infection, clinicians feel more strongly about pwCF maintaining adherence to inhaled medicines	PwCF who feel pressure to demonstrate adherence (C1) may conceal low adherence (O1) due to fear of judgment or to avoid the displeasure of being hassled (M1: reasoning). Clinicians aware of this risk (C2) may use CFHealthHub to facilitate an open discussion around adherence (M2: resource). However, if pwCF remain stable despite low adherence but have evidence of persistent *Pseudomonas* infection (C2), clinicians may hesitate to reduce treatment intensity (O2) due to perceived risk of sub-optimally treated infection (M3: reasoning).
PBM_03	When lung function declines without worsening symptoms, it is difficult for clinicians to advocate for increasing adherence.	When pwCF discontinue other treatments post-ETI and experience a decline in lung function (C), clinicians may struggle to persuade them to restart treatment (O1). This is because pwCF who still feel well despite this decline (C2) and view their current health as "good enough" compared to their pre-ETI baseline, consider restarting treatment as unjustified (M1: reasoning). Clinicians may try to encourage re-engagement by highlighting previous peak lung function readings and framing continued treatment as key to long-term wellbeing (M2: response), but younger adults may not connect with these future-oriented arguments due to temporal discounting bias (M3: reasoning, retroduction). Therefore, some pwCF choose not to restart treatment (O2), and clinicians may then negotiate a new, lower but stable health target (O3) to maintain engagement (M4: reasoning).
PBM_04	Negative childhood experiences can affect attitudes towards adherence and engagement with clinicians in adulthood	PwCF who have experienced medical trauma or social stigma related to their condition in childhood, such as being bullied or feeling ashamed when adhering to treatment in public (C1), or who have previously encountered prescriptive or judgmental clinical approaches to adherence (C2), may develop psychological barriers to engaging in adherence discussions (M2: reasoning/response). These may include fearing judgement, or reliving earlier feelings of shame (M3: reasoning/response, retroduction), particularly when their current adherence is low (C3). To protect their emotional well-being and avoid damage to the therapeutic relationship (M4: reasoning), they may disengage from conversations about adherence (O1), and experience heightened emotional discomfort when such conversations are initiated (O2).
PBM_05a	Personal beliefs and symptom perception influence adherence	When pwCF are uncertain about the value of inhaled medicines for them (C1), some pwCF trust personal experience, such as the fact they feel well and asymptomatic despite not taking inhaled medicines over clinical trial evidence (M1: reasoning, subjective primacy), leading to lower adherence (O1). Conversely, those who perceive symptoms as CF-related (C2) may see greater value in inhaled medicines (M2: reasoning) and be more receptive to clinician advice (M3: response), increasing adherence at times of increase subjective symptom burden/ acute illness (O2). Additionally, pwCF who perceive that their body can develop resistance to inhaled

		medicines through prolonged use (C3) may reserve inhaled medicines for time of acute illness (O3) in order to reduce the perceived risk of resistance (M4: reasoning).
PBM_05b	Some pwCF rely on clinicians' recommendations and published evidence when resolving uncertainty around treatment decisions	When pwCF are uncertain about the value of inhaled medicines for them (C), some trust clinical trial evidence and clinician recommendations (M1: reasoning), over their own subjective health state, leading to sustained adherence (O).
PBM_06	PwCF who have fewer symptoms post-ETI consider inhaled medicines ineffective or unnecessary	When pwCF no longer experience clear symptoms or exacerbations due to ETI (C1) and/or have microbiological sample results which are negative for infection (C2), and where the benefits of inhaled medicines are not immediately noticeable (C3) or new side-effects emerge (C4), pwCF may consider inhaled medicines ineffective (M1: reasoning), unnecessary (M2: reasoning) or harmful (M3: reasoning), leading to reduced adherence (O1). Clinicians who historically justified these treatments by citing symptom relief or exacerbation prevention (C4) now find these arguments less persuasive for pwCF (M5: reasoning), leading to challenges in sustaining engagement with prescribed treatment (O2).
PBM_07	When treatments are burdensome and have no noticeable effect, adherence will be lower.	When pwCF are prescribed treatment every day (C), treatments which are perceived as more burdensome (M1: reasoning) are less likely to be taken as prescribed (O1). This is exacerbated when the more burdensome treatments have no noticeable effect (M2: reasoning). When pwCF feel better post-ETI (C2) motivation for using burdensome treatments, such as inhaled medicines, falls (M3: reasoning, retroduction), leading lower adherence (O2).
PBM_08	PwCF who experience restored wellness post-ETI reduce other treatments to enjoy a period of normality with low treatment burden	PwCF who perceived historically high treatment burden (C1) and notice a health significant improvement in health post-ETI (C2) may choose to reduce or stop other treatments (O) reasoning that, although they may require them again in the future, they have the opportunity to experience a rare period of subjective wellness and reduced treatment burden (M: reasoning).
PBM_09a	PwCF who had low adherence to inhaled medicines pre-ETI continue to have low adherence	PwCF who had low adherence to inhaled medicines pre-ETI and experience significant improvements in their symptoms post-ETI (C), become sceptical about the ongoing need for inhaled medicines (M1: response), perpetuating low adherence (O). They may justify their low adherence by citing improved health rather than other reasons, to avoid conflict or strain in the therapeutic relationship (M2: reasoning).
PBM_09b	Despite high pre-ETI adherence, significant lifestyle changes can lead to lower adherence	PwCF who had high adherence to inhaled medicines pre-ETI (C1) continue to have high adherence (O1) when they consider this a routine/habit (M1: resource). However, if there has been a significant change to their life post-ETI, such as parenthood (C2), the requirement to balance this responsibility with the burden of treatment

		(M2: response) leads them to reduce adherence (O2). Additionally, even pwCF with high pre-ETI adherence (C1) can have lower adherence post-ETI (O2) if they no longer recognise that inhaled medicines impact on their health (M2: reasoning).
PBM_10a	Hospital admissions are a key resource for offering adherence support due to increase disease salience and supportive external scaffolds	When pwCF are admitted to hospital for treatment (C) clinicians can use this opportunity to discuss the role of inhaled medicines (M1: resource) as link between pre-admission adherence and the need for hospitalisation becomes salient (M2: reasoning). Additionally, during admission, pwCF experience a structured environment with regular prompts and external support with treatment taking (M3: resource). These structures facilitate automation of treatment taking by reducing the amount of reflective motivation required to initiate treatment taking (M4: reasoning, retroduction). Furthermore, during admission, pwCF are exposed to fewer competing life demands (e.g. capacity for socialising and work) which removes barriers to adherence (M5: resource). This increases engagement with adherence support (M6: response) and higher adherence (O1).
PBM_10b	Habits for treatment-taking formed in hospital may not be sustained post-discharge	Once pwCF who have formed habits of treatment taking during admission are discharged back to their own environment (C1), they no longer benefit from the structures to support adherence (M1: resource) and must consciously balance the burden maintaining adherence with other life pressures (M2: reasoning) leading to a decline in adherence (O2). PwCF can then feel disappointed or guilty (M3: reasoning) which may either motivate re-engagement (O3, retroduction) or further demotivate attempts to increase adherence (O4, retroduction).
PBM_10c	Interruptions to stable routines can result in short periods of lower adherence before re-establishing prior habits post-interruption	When habits for treatment taking are formed in the pwCF's home environment, where routines are stable and self-directed, rather than during a hospital admission (C1) then brief interruptions in routine, such as holidays, may lead to a brief period of reduced adherence (O1), if the pwCF perceives a low health risk from this period of reduced adherence (M1: reasoning). However, once they return to their home environment and normal routine (C2) the habitual behaviour reactivates (M2: response) and adherence returns to its pre-interruption level (O2).
PBM_10d	Interruptions to stable routines can result in sustained periods of low adherence if the habit was not strongly embedded	For some pwCF who believe they have a habit for treatment taking but have a history of inconsistent adherence (C1) may adopt a permissive mindset that frames holidays as "time-off" from treatment (M1: reasoning). If the habit was not strongly embedded (C2, retroduction) then returning from holiday does not automatically result in resumed habitual treatment-taking (O1).
PBM_10e	Where adherence is identity-based, pwCF may make adaptations to maintain adherence during an interruption	For some pwCF with well-established routines and a long history of high adherence (C1) holidays are not perceived as a time for permissive low adherence (M1: reasoning) meaning they make plans to ensure structures are in place to maintain adherence (M2: response) as high adherence forms part of their identity (M3: reasoning) resulting in sustained high adherence (O).

PBM_10f	Where adherence is symptom-based, improvements post-ETI result in lower adherence	For some pwCF with a long history of high adherence and routines built in response to symptom burden (C1) the clinical improvements following ETI reduce the perceived necessity of inhaled medicines (M1: reasoning) leading to a complete cessation of treatment (O1). However, should symptoms return (C2) they are likely to draw on previous habitual behaviour (M2: response) and increase adherence (O2).
PBM_11	Remote monitoring of adherence by clinicians increases accountability and subsequently adherence	When pwCF are aware that their adherence data is being monitored by clinicians (C), the knowledge that their adherence is visible to the healthcare team (M1: resource) increases their sense of accountability (M2: response, retroduction) leading to higher adherence (O), as they recognise that their behaviour can impact their ongoing care and relationship with the clinicians (M3: reasoning, retroduction)."
PBM_12	Symptom perception, understanding of medicines functions and awareness of infection influence adherence	When pwCF no longer produce sputum after starting ETI (C1) they reason that mucolytics are no longer necessary (M1: reasoning), as they interpret the absence of sputum-related symptoms as evidence that the medication's function, sputum clearance, is no longer relevant (M2: reasoning), leading to decreased use of mucolytics (O1). When perceptions of a medicines function are tightly linked to a specific symptom or clinical outcome measure (e.g. FEV_1) (C2), pwCF may not identify a deterioration through other symptoms (e.g. wheeze and chest tightness) as a valid reason to resume that medicine (M3: reasoning) meaning inhaled medicines adherence remains low despite deterioration (O2) unless the symptoms of deterioration aligned with their perceived indication (retroduction). In contrast, they may recognise lung infections as asymptomatic (C3), reasoning that inhaled antibiotics still have a role, based on an understanding of infection risk (M4: reasoning), leading to continued or prioritised use of inhaled antibiotics, unaffected by a change in symptoms (O3). When sputum tests continue to detect pathogenic organisms and/or pwCF are aware of chronic infection (C4) they reason that inhaled medicines, especially antibiotics, reduce the risk of worsening infection or acquiring new infections (M5: reasoning), leading to continued use of inhaled medicines (O3).
PBM_13a	Personalised approaches to treatment withdrawal supports shared decision-making between pwCF and clinicians	PwCF who feel significantly better following ETI (C1), and/or who have previously stopped inhaled medicines without noticeable health decline (C2), may reason that their continued necessity is uncertain (M1: reasoning, therapeutic rationalisation). This prompts a desire for a structured treatment withdrawal period (O1), involving monitoring of both subjective and objective health measures to guide future treatment decisions (M2: resource). This “n-of-1 trial,” reflects pwCF’s preference to collaborate in decision-making (M3: reasoning) and depends on mutual honesty and trust between pwCF and clinicians about adherence and symptom experiences (M4: resource). PwCF may see this personalised evidence as more relevant than large population-based withdrawal trials (M5: reasoning)

PBM_13b	A decline in health indicators during a structured treatment withdrawal period may increase motivation for reinstating treatment and maintaining adherence	When pwCF are supported to undertake a structured inhaled medicines withdrawal period (C1), and they observe a decline in health indicators (C2), they may reason that the inhaled medicines are still clinically beneficial for them (M1: reasoning) grounded in both objective health indicators and their own lived experience (M2: reasoning). This restores confidence in the value of inhaled medicines and strengthen their internal motivation for adherence (M3: response), leading to higher adherence (O2).
PBM_14	Appreciation of the non-curative nature of ETI leads to sustained adherence to inhaled medicines	PwCF who believe that ETI is not curative, and CF remains life-threatening (C) maximise use of available treatment as they consider this necessary to maintain health and prevent deterioration (M: reasoning) leading to sustained adherence to inhaled medicines (O).
PBM_15	Increased adherence at times of exacerbation may not be sustained post-exacerbation	PwCF experiencing an exacerbation, particularly one requiring hospital admission (C) increase their adherence to inhaled medicines (O1) as they consider inhaled medicines to be important to manage the acute exacerbation (M1: reasoning). Once the exacerbation resolves and they are discharged (C2) those who did not hold a strong belief in the necessity of inhaled medicines for long-term health maintenance (M2: reasoning, retroduction) may then reduce adherence to inhaled medicines (O2).
PBM_16	When there is a noticeable benefit from taking inhaled medicines, adherence will be higher	When pwCF identify some symptomatic improvement from taking inhaled medicines (C) they may perceive that they remain important (M: reasoning) and maintain higher adherence levels (O)
PBM_17	Trust in clinician recommendations can override subjective health indicators when determining adherence decisions	When clinicians continue to advise pwCF to take inhaled medicines post-ETI (C1), even when pwCF do not feel an impact from inhaled medicines (C2) they may continue to use the medicines as prescribed (O) due to trust in their health team (M: reasoning, retroduction).
PBM_18	Beliefs regarding ongoing benefits of adherence to inhaled medicines results in sustained adherence	When PwCF believe that inhaled medicines will provide ongoing health benefits, such as reduction in infections, hospital admissions, chest clearance or protection of lung function (C), the perceived necessity of inhaled medicines is higher (M: reasoning) leading to sustained/higher adherence (O).
PBM_19	PwCF are less concerned about maintaining as strict an approach to adherence to inhaled medicines in the post-ETI era	PwCF who are prescribed ETI (C1) may no longer worry if they miss a dose of inhaled medicines (M1: reasoning) because the risks they associate with the condition are lower (M2: reasoning, retroduction), meaning adherence to inhaled medicines is over (O1) due to a more relaxed approach to adherence (O2). However, if sustained low adherence leads to an increase in symptoms or perceived health risk (C2) then this may prompt pwCF (M4: response) to increase adherence again (O3)

PBM_20	When ETI has led to increased energy and a more noticeable impact of inhaled medicines, adherence is higher	PwCF who have had an increase in energy post-ETI (C1) or now find inhaled medicines more effective by way of improved mucus clearance post-ETI (C2) may have higher adherence to inhaled medicines (O1) as ETI has removed some of the barriers to adherence (M: reasoning)
PBM_21	When ETI has had little noticeable impact on health, adherence to inhaled medicines may be considered more important	PwCF who have had little or no improvement from ETI (C) continue to view inhaled medicines as important (O1), as their health state has not changed and inhaled medicines remains a valid and necessary part of managing their CF lung disease (M1: reasoning, retroduction). Similarly, PwCF who were already well prior to starting ETI (C2) also continue to see inhaled medicines as important (O1), reasoning that it contributed to their stability and should be maintained (M2: reasoning, retroduction). In both cases, this leads to sustained adherence to inhaled medicines (O2).
PBM_22	For pwCF not prescribed ETI, inhaled medicines may represent the best option for managing lung disease and adherence is sustained	PwCF who are not prescribed ETI (C) may experience an increase in symptoms at times of low adherence to inhaled medicines which increases the perceived necessity for inhaled medicines as there are no alternatives for managing their lung health (M1: reasoning, retroduction) leading to sustained adherence (O).
PBM_23	Prior experience of health benefits from inhaled medicines sustains adherence in the post-ETI era	PwCF who perceived inhaled medicines as transformative for their health (C) may continue to maintain high adherence (O) due to the strongly held belief and gratitude for inhaled medicines (M: reasoning), unaffected by the addition of ETI (C2).
PBM_24	A desire to optimise health status during pregnancy drives higher adherence	When pwCF become pregnant (C) they have higher adherence (O1) as the perceived importance of inhaled medicines to promote their health is higher during pregnancy (M1: reasoning), due to their felt responsibilities to their unborn child (M2: reasoning, retroduction)
PBM_25	PwCF have to balance treatment-taking with other life demands/preferences	When PwCF are required to balance multiple aspects of treatment with other life demands, such as work, social or personal desires, and physical or emotional fatigue (C), adherence to inhaled medicines may be lower (O) as other treatments or life demands are perceived as more urgent or important, and thus are prioritised higher (M: reasoning)
PBM_26	Abrupt changes experienced during transition from paediatric to adult CF care can lead to long-lasting impacts on engagement and adherence	The transition from paediatric to adult CF care often involves an abrupt loss of established relational and procedural supports (M1: resource), including trusted paediatric staff and the routine involvement of parents in appointments (M2: resource). PwCF who relied on parental support for medication adherence and health advocacy (C1) were not fully prepared to take on this responsibility independently at the point of transition (M3: reasoning). When adult services omit a phased handover or recognition of ongoing parental involvement (C2), pwCF feel overwhelmed, unsupported, and emotionally unprepared (M4: reasoning). This can result in

		disengagement from care, withholding of information in consultations (O2), and a delayed development of self-management and ownership over their health (O3).
Clinician uncertainty about optimal use of inhaled medicines		
INH_01	Uncertainty about the role of inhaled medicines post-ETI leads to reduced clinician confidence and adoption of shared decision-making	Where ETI has led to uncertainty and disagreement between clinicians and pwCF about the necessity of established treatment regimens such as inhaled medicines (C), clinicians experience a loss of confidence in giving firm recommendations (M1: response). Reflection on previous certainty leads to adoption of strategies to manage this uncertainty, including openly sharing it with pwCF (M2: response), and shifting to a learning mindset (M3: response). This leads to inconsistent advice across the team (O1) but a shift towards shared decision-making and collaborative relationships with pwCF (O2).
INH_02	When maintained subjective wellness conflicts with deteriorating objective health measures pwCF may be reluctant to increase treatment taking. Clinicians look to published evidence to help construct persuasive arguments in favour of treatment.	When pwCF experience declining lung function but are reluctant to restart or continue treatments (C1), clinicians use adherence and lung function data (M1: resource) to illustrate trends and build persuasive explanations for continuing treatments (M2: reasoning). However, when pwCF report feeling well despite lung function decline (C2), clinicians may place more weight on subjective reports of wellness (M3: response), leading to reduced confidence in advising treatment escalated (M4: reasoning). Clinicians value trial-based evidence to support their recommendations and reduce reliance on personal judgment (M4: resource/reasoning). Access to such evidence increases clinicians' confidence in communicating their advice (M5: reasoning), making pwCF more likely to accept treatment recommendations (O1). As this evidence is lacking (C3), pwCF who would previously have been advised to escalate treatment based on declining lung function may continue with existing regimens or lower adherence levels (O2).
INH_03	When pwCF autonomously stop inhaled medicines, clinicians recommend close monitoring of health indicators	In the event that pwCF stop inhaled medicines of their own accord (C) then clinicians may change their approach from recommending re-initiation of the previous treatment regimen to negotiate a monitoring strategy to detect any deterioration or harm resulting from treatment reduction (M1: response). For this strategy to be successful (O1) it is important for the pwCF to adhere to the monitoring regimen (M2: response), so the clinician has the information they need to make clinical recommendations (M3: resource). Clinicians may respond to detection of a clinical deterioration (C2) with increased confidence in recommending initiation of treatment (M4: reasoning).
INH_04	Reduced sputum production post-ETI leads to the uncertainty regarding the necessity of inhaled mucolytics to be questioned. In some cases, clinicians engage in shared decision-making but in	When pwCF have a significant reduction or cessation of sputum production post-ETI (C1) clinicians and pwCF re-evaluate the necessity of existing treatments, such as inhaled mucolytics and chest physiotherapy (M1: reasoning). The longstanding normative use of these treatments in CF (C2) makes clinicians feel uncomfortable about reducing or withdrawing them (M2: response). This uncertainty leads to inconsistent recommendations (O1) but encourages clinicians to adopt shared decision-making, considering the preferences of pwCF and the holistic clinical picture (O2). However, in certain cases, such as pwCF with severe, established CF lung disease

	others, where the indication for treatment is stronger, they do not advocate for treatment reduction	(C3) clinicians and pwCF experience less uncertainty regarding the role of established CF treatments, as the severity of the disease reinforces the clinical rationale for high levels of treatment (M3: reasoning) Therefore, clinicians are less inclined to agree to reductions in treatment regimen (O3).
INH_05	Reduced microbiological sample testing in the post-ETI era leads to uncertainty about *Pseudomonas* status. Most clinicians therefore recommend continuing inhaled antibiotics and investigation more intensively.	When pwCF have a significant reduction or cessation of sputum production post-ETI less microbiological result data are available (C1), so clinicians rely on less sensitive cough swabs to detect *Pseudomonas* (M1: resource). This means clinicians are uncertain about the true microbiological status of the lungs (O1) which also increases uncertainty regarding inhaled antibiotics (O2). Some clinicians may respond to this uncertainty by continuing to advocate for the use of inhaled antibiotics (O3) due to the requirement for firm evidence to go against established treatment guidelines in a professional capacity (M2: reasoning). Alternatively, they may also respond by testing for *Pseudomonas* more intensively (M3: response), such as through induced sputum or bronchoscopy, and if all those results are negative over a number of years (C3) then they may consider reducing or withdrawing inhaled antibiotics (O4).
INH_06	When pwCF disagree with clinicians who are certain of the need for inhaled medicines post-ETI, it is considered maladaptive, but they accept the pwCF's autonomy to maintain the therapeutic relationship	When clinicians are confident that pwCF starting ETI should continue all inhaled medicines (C1) they consider it their duty to emphasise this to pwCF (M1: reasoning) doing so through education (M2: response), supported by published evidence (M3: resource). When pwCF decide to reduce or discontinue medicine despite this guidance (C2) clinicians accept their autonomy (M3: response) but interpret this as maladaptive or misinformed (M4: reasoning) which can lead to subtle strains in the professional relationship (O1, retroduction). However, clinicians also recognise that respecting pwCF autonomy (M3: response) even when their decision seems unwise (C3) improves rapport and strengthens the professional relationship (M5: reasoning), which helps maintain long-term engagement in care (O2).
INH_07	Clinicians are more comfortable with reduction of inhaled mucolytics than antibiotics	Where pwCF are determined to reduce the use of inhaled medicines post-ETI (C) clinicians, while respecting autonomy (M1: response), may respond pragmatically and advise changes to the regimen which still involve the sustained use of antibiotics in particular (O1) as there is less uncertainty as to their role compared to other inhaled medicines (M2: reasoning).
Clinician-led prioritisation of focus in outpatient appointments		
CLP_01	Clinicians prioritise issues for discussion at consultations based on resource constraints and individual needs	When clinicians prioritise aims for consultations based on the immediate needs of the pwCF and the time constraints of the clinic (C), these decisions are influenced by both the limited time available and the cognitive burden on pwCF (M: reasoning/resource). Consequently, less pressing aspects of care may be deprioritised, potentially leaving important issues unaddressed (O).
CLP_02	Engaging with CFHealthHub changes the way clinicians	Engagement with the principles and actions of CFHealthHub (C) increases clinicians understanding of the challenges of adherence (M1: resource) leading to the adoption of more empathetic discussions (M2: response).

	discuss adherence, adopting a more open, non-judgemental discussion to foster the therapeutic relationship.	This increases pwCF's comfort in discussing their adherence, though some pwCF may still withhold full honesty (O). Additionally, being part of CFHealthHub (C) may influence clinicians towards wanting pwCF to continue all existing treatments (M3: response, retroduction) as they are invested in the concept that adherence to inhaled medicines is important and worth supporting (M4: reasoning, retroduction) resulting in a reluctance to advise pwCF who are taking ETI to reduce other treatments or lend their support to this strategy when pwCF suggest it or enact it autonomously (O)
		The changing roles and requirements of the CF MDT
ROL_01	The prominence of non-respiratory issues leads to clinician discomfort due limited experience and confidence in these areas	As respiratory health in pwCF has improved due to ETI (C1), non-respiratory issues, such as mental health, and lifestyle challenges have become more prominent (O1/C2). Clinicians, who are more comfortable advising on respiratory issues (C3), are facing the uncertainties of role expansion (M1: reasoning), as they are required to address a broader range of health needs for the pwCF under there care, meaning their work has become more complex and unpredictable (O2).
ROL_02	Reduced acute care needs of pwCF have shifted some CF clinicians' roles towards administrative rather than clinical tasks	A reduction in the volume and intensity of acute CF care delivery, driven by health improvements from ETI (C) means clinicians can reallocate time and resource (M1: response) enabling access to more equitable care for those with greater needs (O).
ROL_03	Engaging with pwCF about issues beyond their illness builds stronger therapeutic relationships and increases satisfaction	In CF clinics where clinicians have long-term, ongoing relationships with pwCF and take time to engage with them about life beyond their illness (C), the continuity of care and personal interest shown by clinicians fosters trust and allows pwCF to feel seen and valued beyond their medical condition (M1: reasoning) leading to stronger therapeutic relationships, improved communication, and may enhance engagement with treatment (O1, retroduction). This also increases clinician satisfaction (O2) as they witness the positive impact of their care on the lives of pwCF (M2: reasoning).
ROL_04	Reduced frequency of appointments weakens the therapeutic relationship, meaning some pertinent health issues may not be discussed	In the post-ETI era, pwCF are generally more well, attend clinic less often, and also have reduced requirement for ad hoc between-clinic appointments (C1). This is also the case during the transition from paediatric to adult CF care (C2). With fewer appointments, clinicians have less opportunity to build or maintain strong relationships (M1: resource) and may feel less familiar with pwCF and their families (M2: response) and are concerned about pwCF will not feel able to raise appropriate issues with them (M3: response). As a result, clinicians place greater emphasis on keeping communication channels open to maintain trust and ensure timely contact through clinical consultations (O).

ROL_05	CF teams must adapt to meet evolving care needs of pwCF post-ETI	Increased longevity in the CF population due to ETI will expose pwCF to previously unfamiliar co-morbidities, such as cancer and cardiovascular disease (C). General practitioners, while responsible for managing these conditions in the general population, may lack confidence in interpreting clinical findings in the context of CF-specific physiology and dietary recommendations (M1: reasoning) leading them to defer care decisions to CF specialists (O2). However, CF clinicians may also feel ill-equipped to manage these aging-related conditions, viewing them as outside their traditional scope of expertise (M2: reasoning), and may redirect pwCF back to general practice (O3). This reciprocal deferral reflects a broader uncertainty over which provider 'owns' responsibility for managing the evolving needs of an aging CF population (C2). The mutual uncertainty and deferral between care providers results in fragmented or absent management of co-morbidities, leaving pwCF with unmet health needs as they age (O4).
The role of and challenges associated with virtual care and remote monitoring		
VRT_01	There is variation in preferences for virtual care vs in-person care, meaning personalised approaches are needed	When clinicians and pwCF both find virtual care effective (C1), clinicians may feel that reverting to in-person-only care is unnecessary, leading to the continued use and normalisation of virtual appointments (M1: resource). However, there remains variation in preferences for fully virtual care versus hybrid models (C2), depending on individual needs and the context of their care (M2: reasoning). Some pwCF may prefer virtual care (O1) as they find it more convenient (M3: reasoning), while others prefer in-person consultations (O1) as they offers relational benefits and specific opportunities, such as microbiological specimen collection (M4: reasoning).
VRT_02	Adopting virtual care can lead to inadequacy of health data collection, making it difficult for clinicians to make treatment recommendations	For pwCF who are reluctant to engage with monitoring or testing requirements (C1), as they find this burdensome or unnecessary (M1: reasoning), virtual care offers greater flexibility to delay or avoid these requirements (M2: resource), reducing adherence to monitoring requirements (O1). This can leave clinicians with limited data (O2), making it harder to make informed recommendations during virtual consultations (M3: response), leading them to revert to recommending in-person care (O3). Additionally, virtual consultations may allow intentional or non-intentional concealment of symptoms (e.g. sputum production) (M4: response) which would be detected on physical examination during in-person consultations. This scepticism of how reality is portrayed or identified during a virtual consultation (M5: response) leads to clinician discomfort in adoption of virtual care (O4). Furthermore, some clinicians miss the personal, one-on-one communication possible during in-person appointments (M6: reasoning), which can reduce the quality of care (O5).
VRT_03	Hybrid virtual and in-person care models can streamline care and reduce travel burden but may	In Centres where a hybrid model for virtual and in-person appointments is adopted (C1), consultations with multiple MDT members at the same time (M1: resource) for clinically "straightforward" pwCF (C2) can streamline care by reducing repetition (M2: reasoning). However, this structure requires pwCF to request individual consultations if needed and clinicians are concerned that they may not voice this need (O1) either by not realising it is an option (M3: reasoning) or not feeling they have the agency to make this request (M4:

	prohibit pwCF from discussing specific health issues	reasoning). Flexibility within hybrid models, such as allowing pwCF to choose between virtual or in-person appointments (M5: resource), can improve satisfaction (O2), particularly for pwCF who face barriers, such as long travel distances or having to take time off work (C3).
VRT_04	Concerns about home spirometry accuracy leads clinicians to rely on alternative health indicators, especially when perceived risk is low, or revert to in-person spirometry	Where there is variation between home and hospital spirometry readings for pwCF (C1), clinicians apply judgement to assess the reliability of home measurements on a case-by-case basis (M1: response). In cases when home spirometry readings are considered inaccurate (C2) and the clinician has clinical concern (C3), they recommend hospital spirometry (M2: resource), as there is perceived need for accurate measurement is higher (M3: reasoning). However, if pwCF appear clinically well (C3), clinicians may discount the home readings suggesting FEV_1 decline (M4: response) but choose not to advise hospital spirometry (O2), accepting a degree of diagnostic uncertainty due to the lower perceived clinical risk of having inaccurate lung function data (M5: reasoning). The discordance between home and hospital spirometry readings (C1) can lead to pwCF to discontinue home monitoring (O3) due to feelings of frustration (M6: reasoning).
VRT_05	Clinicians tailor the balance between virtual and in-person appointments based on individual risk assessments	When implementing a tailored model of hybrid care (C1) clinicians assess each individual's risk (M1: response) and those who are deemed high risk (C2) are preferentially offered in-person appointments to reduce the risk of "missing" important things during virtual appointments (M2: reasoning).
VRT_06	Recognising the risk of missing key pieces of information during virtual appointments, clinicians may recommend a certain number of in-person appointments per year	In Centres where both virtual and in-person appointments are utilised (C1) and clinicians recognise things can be missed during virtual appointments that would less likely be missed during in-person appointments (C2) clinicians may adapt to recommending at least one or two appointments per year, including the Annual Review, are in-person (O1), to both align with the preferences of the pwCF for access to virtual care (M1: reasoning) and mitigate the clinical risk associated with aspects of care being missed or overlooked in virtual appointments (M2: reasoning). When pwCF need to access to care which is not suitable for virtual discussion (C3), offering flexibility between virtual and in-person appointment requesting (M3: resource) can ensure pwCF are able to access appropriate care when required (O2)
VRT_07	Virtual care can increase capacity for CF Centres, which is important as adult CF caseloads increase	As caseloads for adult CF Centres increases (C), adoption of virtual care (M1: resource) enables clinicians to meet this increasing demand efficiently (M2: reasoning). This supports equitable distribution of care across a large caseload (M3: resource) ensuring that all adults with CF have access to specialist CF care (O).
VRT_08	A long-standing therapeutic relationship, built through years of in-person appointments can help	When pwCF and clinicians have a long-standing therapeutic relationship (C), developed through years of in-person interactions (M1: resource) and pwCF have self-efficacy around articulating their care needs (M2:

	improve the experience of virtual appointments	reasoning), both clinicians and pwCF find virtual consultations more acceptable and effective (M3: reasoning), resulting in improved engagement and care delivery (O, retroduction).
VRT_09	Telephone appointments can feel impersonal and diminish the therapeutic relationship	When telephone consultations are the only modality for virtual appointments (C), pwCF may feel that the interaction is impersonal, lacking the non-verbal cues and continuity that sustain therapeutic relationships (M1: reasoning). This can lead to a diminished sense of trust or connection with clinical staff (M2: reasoning), particularly when appointments are brief, disrupted by technical issues, or with unfamiliar professionals (C2), resulting in pwCF opting to attend in-person appointments instead (O1) or feeling consultations are of limited value (O2). This is especially likely when individuals value long-term relationships with familiar clinicians and feel that virtual alternatives compromise their ability to be open (M3: reasoning).
VRT_10	Abrupt changes from in-person to hybrid/virtual care models can lead to feelings of abandonment	When PwCF, who have developed strong, in-person therapeutic relationships with their healthcare team and are used to frequent, hands-on care, transition to virtual care due to the onset of ETI (C), they may experience feelings of neglect and abandonment (O). This is because virtual care disrupts the personal, emotional connection they had with clinicians (M: response).

8.4 Discussion

8.4.1 Main findings

The Realist focus groups allowed testing and refinement of the Programme Theory with pwCF. The Programme Theory was structured into topic areas, containing several CMOCs as shown in Table 14. This section contains a brief discussion of key findings from the focus groups in these topic areas, which is followed by a fully synthesised discussion with explicit CMOC linkage in Chapter 10.

Consistent with the findings of the previous aspects of this study, habit/routine, subjective health indicators and noticeable effects of medicines appear to be driving changes in the way pwCF now engage with non-ETI treatment, in particular inhaled medicines. Several pwCF described a wish to be supported to experiment with treatment rationalisation, in the hope of finding a personalised balance between treatment burden and optimal health status, given the transformative impact of ETI. This ambition creates some tension with clinicians, who are uncertain about the optimal use of inhaled medicines post-ETI.

PwCF also discussed changing models of care, utilising virtual appointments and remote monitoring, predominately driven by convenience, at times of good health and where appropriate self-efficacy to advocate for health needs exists. Conversely, when significant changes to established models of care are implemented without individual tailoring, pwCF who are accustomed to frequent, in-person appointments, can experience feelings of abandonment, which, in the extreme, may lead them to undertake harmful behaviour as a means of prompting attention from care providers. As the care needs of pwCF evolve due to increased life expectancy and the inevitable development of co-morbidities, there is a growing need for greater collaboration between primary and secondary care providers, requiring the CF MDT to adapt its roles and responsibilities.

8.4.2 Strengths

Recruitment for the focus groups was embedded at the end of the national survey, providing a low-burden route for potential participants to express interest, which likely enhanced recruitment from survey respondents. The total number of survey respondents

who expressed an interest in focus group participation was 73/414 (17.6%). Offering participants the opportunity to indicate availability across 12 different sessions helped to optimise attendance, particularly among a population with complex health needs.

A theory-driven topic guide helped ensure that key areas of theory were tested, however the design remained open to the emergence of new theories during the focus groups. In particular, the important aspect of felt abandonment had not emerged earlier in this study, yet represented a key theoretical finding which informed recommendations for care providers in Chapter 11. This flexible approach strengthened the credibility of the work and optimised the explanatory potential of this realist study.

As with the national survey, participants represented all age groups and were well distributed across adult several adult CF Centres. The focus group structure and realist questioning enabled surfacing of variation to elicit relationships between context, mechanism, and outcomes, whilst encouraging participants to engage with and respond to perspectives that aligned with or challenged their own. For example, there were participants who enjoyed the shared context of improved health post-ETI, but had divergent outcomes with regards to the decision to (dis)continue inhaled medicines.

8.4.3 Limitations

Recruitment was opportunistic rather than purposive, meaning focus groups were not structured around theory-driven categories developed from earlier phases of the evaluation. Future work with purposive sampling would support further testing and refinement of the Programme Theory.

The focus groups involved 16 pwCF, therefore the findings may not generalise to the wider CF population. Additionally, with the majority of participants being over 26 years of age, the findings may not reflect thoughts and behaviours in younger pwCF. Furthermore, whilst all pwCF who attended the focus groups being prescribed ETI helped understand this as a contextual factor, additional theoretical insights may have been gleaned from pwCF who were not prescribed ETI.

Conducting the focus groups over a narrow 2-week window and in defined sessions between 9am and 5pm may have proven a barrier to involvement for those with

fluctuating health or work/caring responsibilities. Several participants withdrew before their allocated focus group citing these reasons.

Conducting focus groups virtually may have introduced accessibility barriers for some individuals and potentially constrained the spontaneity or richness of discussion compared to in-person sessions. However, as discussed in Chapter 2, there are strict guidelines in place advising segregation to reduce risk of infection transmission between pwCF, therefore an in-person focus group would have been unethical.

Additionally, as with the survey in Chapter 7, the majority of participants are assumed to have been recruited CFHealthHub consent to future research mailing list, and had already responded to a research survey, demonstrating a commitment to participating in research and openness to share their perspective. Therefore, pwCF across the lower spectrums of engagement were unlikely to be recruited to this study.

8.5 Conclusions

These focus groups allowed testing of hypotheses relating to the perspectives of pwCF regarding inhaled medicines and care needs/delivery preferences, informed by the findings in the previous chapters and captured within the refined Programme Theory CMOC index. This directly supported my answer to the second research question (*"How have ETI and the COVID-19 pandemic shaped the experiences and care needs/preferences of pwCF")* and helped qualitatively develop my answer to the third research question *("What factors are associated with adherence to inhaled medicines for pwCF in the post-ETI era?")*. Habit remains important, though some of the challenges involved in sustaining habits in dynamic and complex environments were highlighted. The noticeable impacts of ETI have fundamentally challenged perceptions and recognitions of the role of inhaled medicines, leading pwCF to express a desire to experiment with treatment in the ambition of reducing burden. The health and social impacts of both ETI and the COVID-19 pandemic have driven efforts to redesign the CF model of care. While reducing appointment frequency and increasing virtual consultations offer clear advantages in some contexts, they also present some challenges.

Elements of the study described so far were limited by the lack of objective adherence data (as quantified measure of outcomes) and the potential for selection bias. Therefore, the final stage of the Realist Evaluation was to test the hypothesis that some of the factors identified in this study, including habit, perceived necessity and treatment burden are associated with objective adherence to inhaled medicines in the post-ETI era, across the population of pwCF in a single UK CF Centre.

9. Quantitative exploration of factors associated with adherence to inhaled medicines

9.1 Introduction

The findings of the Realist Evaluation described in chapters 4-8 revealed significant variation in perspectives and behaviours related to inhaled medicines for pwCF prescribed ETI. PwCF report that habit and routine remain important determinants of adherence, alongside other factors such as perceived necessity and treatment burden. Whilst significant theoretical insights had been gained from the aforementioned data, testing elements of theory using quantitative methods helps validate and increase confidence in the Programme Theory. In particular, this provided quantitative data to directly answer the third research question (*What factors are associated with adherence to inhaled medicines for pwCF in the post-ETI era?"*).

The adoption of the CFHealthHub digital platform and preferred use of nebulisers with electronic data capture capability at a single adult CF Centre led to objective adherence data being available for approximately 80% of pwCF on the caseload. By integrating objective adherence data with routinely collected clinical information, it was possible to examine associations between a range of factors and adherence, across an entire adult CF Centre population. This approach mitigated the selection bias outlined in recruitment to earlier aspects of the Realist Evaluation and facilitated quantitative testing of some elements of the Programme Theory.

As well as testing elements of Programme Theory, an improved understanding the factors which may be associated with adherence to inhaled medicines in the post-ETI era was important for three additional reasons. Firstly, to compare if factors previously associated with adherence remain important, or if the nature of relationships have changed. All previous studies using electronically captured inhaled medicines adherence data in CF pre-date the introduction of ETI (34, 187, 287). Secondly, this understanding may inform development of effective interventions to support adherence in the post-ETI era. Thirdly, this analysis may identify subgroups of pwCF who are most

likely to benefit from interventions, enabling efficient resource allocation. The objectives of this analysis were:

1) To describe variations in adherence in relation to a selection of socio-demographic, health, and treatment-specific psychological factors.
2) To examine the independent associations between these factors and adherence, with a particular focus on the contribution of treatment-specific psychological factors.

9.2 Methods

9.2.1 Design and setting

This was a single-centre, cross-sectional, retrospective analysis of information captured prospectively as part of routine care. Data were extracted from the Electronic Medical Record (EMR), compliant with regulatory approval obtained from NHS Health Research Authority (IRAS reference 210313).

Participants were identified from a complete list of pwCF registered the adult CF Centre in April 2023. All pwCF who newly registered at the Centre over the course of data collection (July 2023 to March 2024) were also considered for inclusion. Those who had not yet fully transitioned from paediatric to adult CF services and those no longer actively registered, e.g. in the event of death or transfer to another CF Centre, were excluded. All pwCF were considered eligible for inclusion if they had an active prescription for inhaled medicines, or they should have been prescribed inhaled medicines as determined following case note review by two Consultant physicians. There was no formal sample size calculation for the analysis as the entire population of interest were eligible and all available data were included.

9.2.2 Data collection and processing

The following data were extracted using a highly structured data collection form created and managed in Microsoft Excel. A summary of the variables is included in Table 15.

Each participant was assigned a unique identification (ID) number (e.g. p_001, p_002) to ensure pseudo-anonymisation. A pseudo-anonymisation key linked each participant's ID to their hospital ID number and, where available, the CFHealthHub ID number and was stored on the secure NHS Trust server. The key was used only to check accuracy of data collection and link data extracted from CFHealthHub and the EMR to the participant. The psychology annual review date marks the point of data extraction from the EMR for each individual participant.

The selection of factors to explore in this analysis was initially informed by the extant CF literature and the NIHR Innovations in Clinical Trial Design and Delivery for the Under-served (INCLUDE) study. The INCLUDE study was designed to identify groups who may be medically under-served and suggest ways of promoting their inclusion in research (288). This approach enhanced the potential of the analysis to contribute to understanding adherence, and how it may relate to under-served groups across other long-term conditions.

Demographic factors

Age in complete years (y) was converted to a categorical variable with four levels: 16-18y; 19-25y; 26-34y and ≥35y). This categorisation method is preferred in CF studies due to the U-shaped relationship between age and adherence (150, 151). In Chapters 7 and 8, maturity, increased self-confidence, and desire to continue to age well emerged as contextual and mechanistic features that may influence adherence outcomes.

Biological sex at birth was limited to male or female. Previous studies demonstrated lower adherence in adolescent females compared to males (289). Ethnicity data were dichotomised to "White British" or "not White British", as 94.5% of the UK CF population identify as White British (38). Previous work has identified Asian pwCF have worse outcomes than Caucasian pwCF in the UK (290). The findings of the evaluation so far had not directly examined sex or ethnicity as contextual factors.

Socio-economic factors

Socioeconomic status was classified using the Index of Multiple Deprivation (IMD) decile, corresponding to the participants' postcode using the English indices of

deprivation 2019 online tool (291). Deciles were converted to quintiles, in keeping with previous work in CF, where quintile 1 reflected the highest level of deprivation (deciles 1-2) and quintile 5 the lowest deprivation (deciles 9-10) (292, 293). Socio-economic deprivation is associated with worse outcomes in CF and lower use of inhaled medicines (292, 294-296). Additionally, those who are socio-economically disadvantaged are considered an under-served group as per the INCLUDE study and is an important social determinant of health more broadly (288, 297). A 2016 review called for studies to better understand the contribution of socio-economic status to outcomes in CF (298). Socioeconomic status had not yet been explored in the Realist Evaluation.

Free text highest educational attainment data were categorised as per the UK Biobank study method, providing five ordinal levels of educational attainment (299). Educational attainment is associated with health inequalities and reduced patient activation (10). Whilst the role of parental educational attainment in paediatric CF outcomes and adherence has been studied, less is known about the influence of educational attainment on behaviours and outcomes for adults with CF (300-302). Educational attainment had not yet been explored in the Realist Evaluation.

Distance from the participants home to the CF Centre was calculated using the Google Maps Application Programming Interface, as per a response to my post on Stack Overflow (303). Distance was categorised as low (<10 miles), medium (10-25 miles) and high (>25 miles). No previous UK CF studies exist to inform categorisation, therefore this method was adapted from that used in a previous CF study in the USA (304). Given that adult CF care is the UK is delivered in specialist CF Centres, rather than being accessible in most local NHS trusts, travel time may present barrier to engagement with specialist CF services. Whilst pwCF living rurally emerged as a contextual factor that may lead to preference for virtual consultations, it had not been reported as a determinant of adherence in the Realist Evaluation so far.

Caring responsibilities for children under 5 years (the typical age of entry to school in the UK) was a binary variable. As identified in the Programme Theory (CMOC PBM_09b), parenthood impacts on the daily lives of PwCF, who may adjust their treatment-taking behaviours to accommodate the pressures of parenthood (305).

Digital exclusion was a binary variable based on a "no" response to the question "*Do you have access to the internet?*" There is no singular definition of digital exclusion, but is considered to involve both access to and capability to use the internet (306, 307). By not seeking to understand capability, this definition sets a high threshold for defining digital exclusion and is a limitation of this data set. Digital exclusion had not yet been explored in the Realist Evaluation.

Language barrier pertained to the requirement for a translator in clinical consultations. The absence of translator requirement does not guarantee English language comprehension, though in common practice a translator would be sought if clinicians were concerned about this. Language barriers had not yet been explored in the Realist Evaluation and were likely a barrier to participation in the survey and focus groups reported in Chapters 7 and 8. Alternate residential circumstances data was defined as a someone who was currently living in an institution or had no fixed abode. "Looked after child" was defined as a participant having been under the care of their local authority at a point in their childhood (308). Neither alternate residential circumstances nor being a "looked-after child" had been explored in the Realist Evaluation. As data pertaining to these three factors are not routinely collected in the EMR, a panel of clinicians in the CF MDT with extensive knowledge of the entire cohort were asked to identify those who fit these criteria. Whilst not directly studied in CF before, all three characteristics represent potentially under-served groups as per the INCLUDE study (288).

Health-related factors

An active CFTRm prescription was a binary variable derived from the EMR active medication list. Both prescription of inhaled medicines and adherence are recognised to be lower in those prescribed CFTRm (111-113, 309, 310). Health improvements post-ETI had emerged as a key factor leading to reduced use of inhaled medicines for many pwCF and is part of several CMOCs in the refined Programme Theory CMOC index (e.g. ETI_01, PBM_01,03,05a,06).

CF-related Diabetes (CFRD) was a binary variable derived from the EMR diagnosis list. Multi-morbidity may result in people being under-served as per the INCLUDE study (288). Additionally, the recommended treatment for CFRD is insulin, requiring pwCF to include

this into their overall medicine routines and, as identified in Realist Evaluation already (e.g. CMOC PBM_25), may be prioritised over inhaled medicines at times (CMOC CLP_01) (79).

The highest BMI and FEV_1 in litres in the 12 months prior to the date of data extraction were extracted. BMI was converted into a binary variable as to whether it would be considered optimal or not, defined by a BMI ≥22kg/m^2 for females and ≥23kg/m^2 for males, as these are associated with the best outcomes for pwCF and are still the recommended weight targets as per the CF Foundation (78, 223). Weight management had emerged as a key complexity related to CF care in the post-ETI era, though its relationship with adherence to inhaled medicines had not been explored in the Realist Evaluation so far.

FEV_1 was converted to $\%FEV_1$ using the Global Lung Initiative (GLI) 2012 equation then categorised into three levels: <40% (severe); 40 to 69.9% (moderate) and ≥70% (mild), consistent with previous work in CF (45, 311-313). Previous work has suggested that disease severity, of which $\%FEV_1$ is a key component, may influence adherence (182). In the Realist Evaluation, both clinicians and pwCF identified lower baseline lung function, indicative of more severe disease, as a key reason in favour of maintaining inhaled medicine use post-ETI. (CMOC INH_04).

Neurodivergence was a binary variable defined as having an assigned diagnosis code of “autism spectrum disorder”, “autistic disorder”, “autism”, “attention deficit hyperactivity disorder”, “attention deficit disorder”, “learning difficulties”, “learning disability” or “on learning disability register” (314). Neurodivergence can interfere with the typical mechanisms of habit formation, which emerged as an importance factor that may influence with adherence in the Realist Evaluation so far (315). Neurodivergence emerged in both the survey and focus group as being suspected to affect adherence potentially due to differential cognitive processing and risk-benefit decision-making but had not been incorporated into the Programme Theory.

Chronic *Pseudomonas* infection, a binary variable, was defined as per the CFHealthHub criteria (316). *Pseudomonas* is the most common chronic lung pathogen in adults with

CF (38). When it is first isolated, eradication therapy is recommended using nebulised +/- oral or intravenous antibiotics (79). *Pseudomonas* is characterised by an ability to persist despite treatment and as such those with chronic *Pseudomonas* infection require long term inhaled antibiotic treatment (79). Whilst other infections may be treated with inhaled antibiotics, chronic treatment of *Pseudomonas* is the only one with systematic review evidence of benefit (152). Concern about *Pseudomonas* infection was identified by both clinicians and pwCF as key reason against reduction/withdrawal of inhaled medicines post-ETI in the Realist Evaluation so far (CMOCs PBM_02, INH_05).

Mental health was assessed using the Patient Health Questionniare-9 (PHQ-9) and Generalised Anxiety Disorder-7 (GAD-7), which are recommended to be used for annual screening in all adults with CF (317). PHQ-9 and GAD-7 scores were extracted as continuous variables and then categorised into standard severity levels for symptoms of depression or generalised anxiety disorder respectively (318, 319). Depression is a recognised risk factor for lower adherence in CF and other long-term conditions (320-323). Anxiety may have a curvilinear relationship with adherence where some degree of anxiety can result in higher adherence (324). The relationship between anxiety and adherence in CF is less clear, but as a mental health condition which is prevalent and routinely screened for, it is appropriate for inclusion (325). PwCF reported mental health in general as having a predominantly inhibitory impact on adherence to inhaled medicines in the Realist Evaluation so far.

The mean number of prescribed doses of inhaled medicines per day over the 12 months prior to data collection were extracted from CFHealthHub, where available, or the EMR. This value was converted to a count, with decimal mean values rounded up. Whilst a higher number of prescribed doses has been reported as a barrier to adherence in qualitative studies (280, 326), quantitative studies have shown that adherence is higher in those prescribed more treatment (151). Treatment burden, of which number of treatments prescribed is one facet, was an important contextual factor that appeared to influence adherence, captured in the Programme Theory (CMOCs ETI_03, PBM_07-08).

Treatment-specific psychological factors

Whilst the aforementioned factors have evidence of association with adherence in CF and engagement or inequalities in long-term conditions more broadly, behaviour theory, and the findings of this study so far, suggests other factors are more proximal to the actual behaviour, in this case adherence to a prescribed inhaled medicine regimen. Previous work in CF and in particular work developing the CFHealthHub intervention has focussed on the role of treatment-specific, psychological factors, which were also identified in the earlier phases of the Realist Evaluation (147, 327).

Most of the demographic, socio-economic or health-related factors generally describe barriers to adherence, and in particular the INCLUDE study focussed exclusively on barriers and under-served groups, however when it comes to treatment-specific factors these are likely to both facilitate and inhibit adherence across a spectrum. These psychological factors are challenging to capture in routine care, and in this work, each was captured using a 5-point Likert scale response (strongly disagree, disagree, uncertain, agree, strongly agree), asking for the individual's level of agreement with a specific statement representing that factor.

The COM-B model suggests that for a behaviour, such as adhering to a prescribed medicine regimen, to occur, there are three broad requirements: capability; opportunity and motivation (161). Motivation can either be automatic (i.e. resulting from emotion, impulse or habit), or reflective (i.e. involving evaluation and planning). Reflective motivation, is thought to be comprised of the understanding and evaluation of both necessities and concerns related to treatment, as described in the Necessities-Concerns Framework (328). Perceived necessity and concern related to inhaled treatment was assessed using two questions derived from the Beliefs about Medicines Questionnaire (BMQ):

- "Nebulised treatment protects me from becoming worse" (necessity).
- "Having to use nebuliser treatments worries me" (concern).

These two questions, from the 18 items which comprise the total BMQ, were used as previous studies have shown they did not generate problems with regard to item content

or misunderstanding (329). Previous work in CF has shown that both necessity and concern, assessed using the BMQ, are associated with adherence in adolescents and children with CF (330, 331). Furthermore, necessity may be closely related to perceived importance, which was is variable amongst adults with CF who participated in the qualitative work of the Realist Evaluation so far. Pre-ETI studies report variable perceived importance of inhaled medicines, so whilst this is not a new phenomenon, the introduction of ETI may lead to this view being more prevalent (332).

Intending to take a medicine is also considered a key feature of reflective motivation. Intention describes the decision to act in a certain way, which could either relate to taking or intentionally not taking a dose of inhaled medicine (327). Previous work demonstrated that pwCF with low adherence reported stable intention not to adhere to treatment and that changes in intention directly relate to the decision to increase adherence (327). Intention to perform treatment was assessed using a single statement, adapted from the COM-B self-evaluation questionnaire used in the CFHealthHub intervention (333):

- "I want to do nebulised treatments."

Self-efficacy describes an individual's belief in their capacity to act in a certain way (334). Self-efficacy mediates the relationship between depression and low adherence in other long-term conditions and was positively associated with adherence in previous CF studies (335-338). Conversely, another study found no relationship between self-efficacy and adherence (339). Self-efficacy was assessed using a single question, previously used as part of the CFHealthHub RCT.

- "I am confident that I can do nebulised treatments."

Habit can be defined as "*a cognitive process whereby a contextual cue automatically triggers an impulse to act, based on a cue-behaviour association learnt through consistent repetition in the presence of the cue*" (192). Habit was strongly associated with adherence to inhaled medicines in adults with CF pre-ETI era (279). As a result of this, the CFHealthHub behaviour change intervention was designed to facilitate habit formation, which subsequently increased adherence in the RCT (34, 147). The

conceptual framework underpinning the CFHealthHub intervention is to first address issues relating to reflective motivation for using inhaled medicines as prescribed, then focus on capability and opportunity and eventually form habits for treatment taking. Once habit is formed, the instigation of the activity moves from reflective to automatic motivation, which intends to sustain the behaviour. Habit was assess using a single question derived from the Self-Report Behavioural Automaticity Index (SRBAI) which has been previously used in CFHealthHub studies (34, 340).

- "Using nebulised treatment is something I do without thinking."

The final treatment-specific, psychological factor explored was perceived treatment burden. Given the multi-system manifestations of CF, most pwCF are required to adhere to many treatments, such as inhaled medicines, digestive enzymes, physical therapy, insulin and, now, ETI (341). Compared to other long-term conditions, the burden of treatment in CF has been described as "*extraordinary*" (342). The findings of the Realist Evaluation to date identified how pwCF are required to balance many things alongside their treatment, and high perceived burden is a key barrier to adherence.

Simplifying treatment burden was considered the top priority for the CF community in the 2018 James Lind Alliance Priority Setting Partnership (115). The relationship between perceived burden and adherence in CF is a central feature in much of the existing literature (282). The construct of perceived treatment burden is often considered to comprise of the duration, frequency, and complexity of a prescribed treatment regimen. Taking this definition, it is somewhat surprising that adherence is higher in those prescribed a greater frequency of daily doses of inhaled medicines (151). Furthermore, in a study where the prescribed regimen of colomycin (an inhaled antibiotic used for chronic *Pseudomonas* treatment) was changed from twice to once daily did not alter adherence (343). Finally, in the CFHealthHub RCT, adherence increased whilst perceived burden decreased in the intervention arm, i.e. despite taking more doses of medicine, the perceived burden was lower (34).

Therefore, I did not rely simply on the daily prescribed dose count to characterise burden in this analysis. Instead, two items from the Cystic Fibrosis Questionnaire-Revised were used, which are internally consistent in reporting perceived treatment burden (278, 344).

- “Using nebulised treatment each day is difficult.”
- “Using nebulised treatment makes my daily life more difficult.”

A commonality between the vast majority of studies exploring these psychological factors is the reliance on self-reported or MPR adherence data, which is less accurate than electronically captured adherence data (146). Therefore, a novel aspect of this analysis was the opportunity to explore the associations between these factors using electronically captured adherence data.

Whilst these six treatment-specific factors are distinct, they are likely inter-related. For example, very low perceived necessity would likely result in low adherence. In someone with very low adherence, the perceived burden may also be low, as taking no treatment may be an effective way to reduce burden.

Table 15: List of independent variables included in the regression analysis.

Variable	Explanation
Demographic factors	
Age	Age in complete years
Sex	Biological sex assigned at birth
Ethnicity	Dichotomised into White British or Other
Socioeconomic factors	
IMD Quintile	IMD quintile, ranging from quintile 1 (most deprived area) to quintile 5 (least deprived).
Education attainment	Highest educational attainment level
Distance from Home to CF Centre	Distance in miles, categorised as low (<10 miles), medium (10-25 miles) or high (>25 miles).
Caring responsibilities for children under 5	Whether the person with CF has caring responsibilities for children below school age
Digital Exclusion	Response to the question – Do you have access to the internet?
Language barrier	Requirement for English Language translator
Alternative residential circumstances	If people are living in institutions or having no fixed abode
Looked-after child	Has been under the care of their local authority at a point in their childhood
Health-related factors	
On CFTRm	Indicates if the pwCF is prescribed a CFTRm
CF-related diabetes	Coded diagnosis of CFRD
BMI	Highest BMI in the 12 months prior to data collection
$\%FEV_1$	Highest $\%FEV_1$ in the 12 months prior to data collection
Chronic *Pseudomonas* infection	Classified as having chronic *Pseudomonas* infection as per CFHealthHub criteria (316)
Neurodivergence	Formal diagnosis of autism spectrum disorder, learning disability or attention-deficit hyperactivity disorder
Severity of depressive symptoms	PHQ-9 score
Severity of anxiety symptoms	GAD-7 score
Mean prescribed nebuliser doses per day	Mean number of doses of inhaled medicine prescribed daily over the 12 months prior to data collection
Adherence-specific factors for inhaled medicines (Likert Scales 1-5, with 1 indicating "strongly disagree" with the statement and 5 indicating "strongly agree)	
Necessity	"Nebulised treatment protects me from becoming worse"
Concerns	"Having to use nebulised treatments worries me."
Intention	"I want to do all my prescribed nebulised treatments"
Self-efficacy	"I am confident that I can do nebulised treatments"
Habit	"Using nebulised treatment is something I do without thinking"
Perceived treatment burden	"Using nebulised treatment each day is difficult" and "Using nebulised treatment makes my daily life more difficult"

IMD = Index of Multiple Deprivation. CF = cystic fibrosis. CFTR = CF transmembrane conductance regulator protein. CFRD = CF-related diabetes. BMI = body mass index. $\%FEV_1$ = percentage of predicted forced expiratory volume in 1 second. PHQ-9 = Patient Health Questionnaire-9, GAD-7 = General Anxiety Disorder-7.

Adherence to inhaled medicines (outcome variable)

Adherence to inhaled medicines data covering the 12 months prior to the date of data collection was extracted, where possible, from CFHealthHub. For those without a CFHealthHub account, adherence was calculated manually from device download data in the EMR. For each day, per cent adherence was calculated as the number of doses taken divided by the number of doses prescribed. The aggregated mean daily per cent adherence over the 12-month period was used as the outcome measure in this analysis. Medicines overuse may inflate adherence measurements without necessarily offering additional health benefit, and in fact may increase the risk of side effects or toxicity. Therefore, to most accurately reflect the effective use of inhaled medicine in adherence calculation, the daily adherence percentage was capped at 100% (345).

Each participant was classified based on the completeness of their adherence data. Complete adherence data were defined as adherence data covering the entire 12-month study period. Incomplete adherence data referred to adherence records spanning at least 3 months within the 12-month period. For participants with incomplete adherence data, the mean adherence was assumed to represent the full 12 months. If adherence data covered less than 3 months within the study period, data from the preceding 12 months were sought. For those with at least 3 months of data in this preceding 12 months, the mean adherence was assumed to represent the entire 12-month study period. A single, mean imputation strategy was used for participants with no adherence data in either of these categories, which is described in section 9.2.3.

To mitigate the risk of transcription error, data were extracted by two researchers, and in the event of discrepancy, the source data were reviewed and a consensus reached on the correct data to be extracted (346). The data were checked for accuracy and completeness before analysis.

Potential for bias

Previous research studies using electronically captured adherence data may have been affected by selection bias, limiting generalisability of the findings. Previous work has shown that pwCF who participate in research have more advanced disease and higher

socio-economic status than the general CF population (347). Additionally, current health state, personal contextual factors and the demands of the study can affect the decision for pwCF to participate in research (348, 349). In the CFHealthHub RCT, the baseline adherence to inhaled medicines was approximately 50%, which is higher than the real-world estimates of 30-40% (34, 146, 287).

This analysis specifically assessed factors affecting adherence and engagement which also relate to health inequalities. Hence it was important to minimise selection bias (specifically recruitment bias) when the population of greatest interest were those with the lowest adherence. Therefore, this analysis was designed to use routinely collected, real-world data from the EMR, ensuring that data from the entire cohort could be included. This is similar to the approach taken in the UK CF Registry analyses, which include over 99% of the UK CF population (128). This gave the relatively unique ability to explore these factors across an entire Centre cohort of pwCF.

However, whilst selection bias was mitigated, the depth with which treatment-specific factors could be defined and explored was narrowed. Validated questionnaires, e.g. the BMQ, are commonly used in research studies. However, in real-world practice, administering the full versions is often impractical due to resource limitations. As a result, only specific items from these validated questionnaires were used in routine care to assess adherence-related factors. This approach may affect the accuracy of the measurements compared to using the full questionnaires.

As data pertaining to the six treatment-specific factors are collected from a questionnaire that is administered by care providers, there is the potential for social desirability bias to influence the responses given, potentially leading to under-reporting of what are perceived as less-desirable responses/characteristics (e.g. low necessity beliefs). This may reduce the ability to detect relationships between less desirable levels of treatment-specific factors and adherence.

In this CF Centre, there was a functioning programme of adherence support available to all pwCF as part of routine care. Adherence support was primarily delivered by certain MDT members (physiotherapists or CFHealthHub Interventionist), and there was a

culture of paying attention to adherence and supporting it through habit formation, as described in Chapter 6. Whether individual pwCF had been directly involved in receiving the CFHealthHub intervention at the point of data collection was not captured. As the CFHealthHub intervention targeted the treatment-specific factors and adherence, the findings may not be generalisable to Centres who take different approaches to care.

9.2.3 Data analysis

Descriptive and bivariate analysis

Data were analysed using R (v4.3.2) within RStudio (350, 351). Appropriate descriptive statistics were generated for all variables. Following a review of the descriptive statistics, a decision was made on how to use each variable in the subsequent linear regression analyses. Categorisation of continuous variables was informed by rational grouping and extant CF literature. Where there were less than 10 cases in a specific level of an ordinal variable, groups were combined rationally. All independent variables underwent bivariate analysis with mean per cent adherence to inhaled medicines as the dependent variable. Binary variables with <5 occurrences were excluded from the multivariable analysis to mitigate the issue of sparse data bias (352).

Multivariable analysis

Linear regression was chosen because most continuous variables were expected to have a monotonic relationship with adherence, and linear regression is well-suited to model such relationships. The final multivariable model was built using backward selection. In this process, the initial model included all independent variables. Each variable was then tested for removal one at a time, and the variable whose removal lead to the greatest reduction in the overall Akaike Information Criterion (AIC) is eliminated. This process continued, removing one variable at each step, until further removal did not reduce the AIC. The final model contained the variables that resulted in the lowest overall AIC, representing the best-fitting model for the data.

Multicollinearity was assessed using Generalised Variance Inflation Factor adjusted for degrees of freedom ($GVIF^{1/(2*DF)}$). This is particularly important as the six treatment-specific factors are likely inter-related, as previously described. Model residuals were

inspected in line with the assumptions of linear regression and sensitivity analyses were performed when assumptions were in question.

To further help understand and apply the findings of the linear regression analysis, in particular the intersection of key factors, a classification and regression tree analysis was performed, which is recognised as a simple but powerful approach to better understand the findings of a linear regression (353). This method is consistent with previous studies using CFHealthHub adherence data, allowing differences between clinically meaningful subgroups to be compared (311). In this analysis, data were partitioned across the three variables with highest amount of variance explained in the final multivariable regression model, as defined by adjusted partial R^2. At each partition, appropriate hypothesis tests were performed to compare the distribution of mean adherence between groups. As adherence data was positively skewed, non-parametric Wilcoxon signed-rank and Kruskal-Wallis tests were performed. The Type I error rate for all hypothesis tests was set at 0.05, and the null hypothesis in each case stated that there was no difference in adherence between the groups.

Sensitivity Analyses

A complete-case sensitivity analysis was conducted, including only cases with complete adherence data, to assess associations using the primary multivariable model without the influence of adherence data imputation. Where assumptions of primary multivariable regression were in question, the outcome variable was transformed and alternate regression analyses performed, to explore if the results of the primary analysis were consistent under a different set of assumptions. Additionally, continuous variables that had been categorised were analysed in their original forms to explore the impact of categorisation on the final model output.

Imputation for missing data

Adherence data

Previous studies using CFHealthHub adherence data have shown that individuals with missing passively collected data, which is subsequently obtained through active chasing, tend to have lower adherence than the group average (354). Therefore, adherence data are not assumed to be missing at random, and an individual's lack of

complete adherence data likely reflects below-average adherence. Thus, imputing missing data with the group average would likely overestimate the true adherence value.

Previous studies categorised CFHealthHub adherence data according to four clusters, representing very low (approximately 0 to 25%), low (25.1 to 50%), moderate (50.1 to 75%) and high (>75%) adherence (355). Those with missing adherence data are most likely in the "very low adherence" cluster according to this method, in keeping with the results of a previous study (354). Therefore, all participants with adherence data were categorised using this method and the mean adherence of all participants in the very low adherence cluster (2.78%) was imputed for those with missing adherence data.

IMD Quintile

For those whose postcodes did not return IMD data from the UK Government IMD tool, all postcodes within a 0.1km radius of that participant's postcode were identified using *https://www.freemaptools.com/find-uk-postcodes-inside-radius.htm*. In all five cases, all neighbouring postcodes, shared the same IMD quintile and this was imputed.

9.3 Results

A total of 240 pwCF were identified as being cared for at the adult CF Centre between April 2023 and March 2024. Of these, 214 (89.2%) were identified as either being prescribed inhaled medicines or should be prescribed inhaled medicines (as per a two-Consultant consensus) and formed the cohort for this analysis.

9.3.1 Data completeness

Most variables had complete data at the participant level. All demographic factors had 100% data completeness. Within socio-economic factors, there were five cases (2.3%) with missing IMD quintile and one case (0.5%) with missing educational attainment. Within health-related factors, two cases (0.9%) had missing %FEV_1. Within treatment-specific factors, one case (0.5%) had missing data for all six variables. Forty cases (18.7%) had missing electronically captured adherence data. Missingness across these variables is summarised in Table 16.

Table 16: Description of missingness across analysis variables

Variable	Missing values from total (N=214), n (%)
IMD quintile	5 (2.3)
Highest educational attainment level	1 (0.5)
$\%FEV_1$	2 (0.9)
Necessity	1 (0.5)
Concern	1 (0.5)
Intention	1 (0.5)
Self-efficacy	1 (0.5)
Habit	1 (0.5)
Burden	1 (0.5)
Adherence (outcome variable)	40 (18.7)

IMD = Index of Multiple Deprivation. $\%FEV_1$ = percentage of predicted forced expiratory volume in 1 second. Only variables with at least one missing data point are included. All other variables had 100% completeness.

Imputation was performed for adherence data and IMD quintile as described in the methods. Imputation for $\%FEV_1$ in the two cases of missingness was not performed, as it is a highly individualised measurement with no reasonable method for accurate imputation. A single participant had no data for treatment-specific factors or highest educational level. These data were also not imputed, for the same reasons as $\%FEV_1$, and this participant's data, whilst retained for the descriptive and bivariate analysis was removed from the multivariable analysis.

9.3.2 Participant characteristics

The analysis included 214 participants representing all those who were either prescribed inhaled medicines or should have been prescribed inhaled medicines. Characteristics of the study cohort are described in Table 17.

Table 17: Characteristics of the study cohort

Variable	n (%)
Demographic Factors	
Age (years), median (IQR)	30 (23 to 38)
16 - 18	29 (13.6)
19 - 25	42 (19.6)
26 - 34	66 (30.8)
≥ 35	77 (36.0)
Sex: Male	111 (51.9)
Ethnicity: White British	202 (94.4)
Socio-economic Factors	
IMD quintile, median (IQR)	3 (1 to 4)
1 (most deprivation)	70 (32.7)
2	34 (15.9)
3	40 (18.7)
4	39 (18.2)
5 (least deprivation)	31 (14.5)
Educational Attainment	
1 (lowest)	9 (4.2)
2	77 (36)
3	39 (18.2)
4	1 (0.5)
5 (highest)	87 (40.7)
Distance to CF Centre, median (IQR)	12.7 (7.1 to 29.4)
≥10 miles	91 (42.5)
10-25 miles	58 (27.1)
>25 miles	65 (30.4)
Looked after child: Yes	6 (2.8)
Carer for children <5 years old: Yes	33 (15.4)
Digitally Excluded: Yes	1 (0.5)
Alternate Residential Circumstances: Yes	5 (2.3)
Language Barrier: Yes	1 (0.5)
Health-related Factors	
Prescribed CFTRm: Yes	190 (88.8)
CF-related diabetes: Yes	119 (55.6)
BMI (kg/m^2), median (IQR)	24.6 (21.8 to 27.8)
BMI in target (Male ≥23, Female ≥22): Yes	147 (68.7)
%FEV_1, median (IQR)	84.8 (63.8 to 97.5)
<40% (severe lung disease)	13 (6.1)
40 - 69.9 % (moderate lung disease)	53 (24.8)
≥70% (mild lung disease)	146 (68.2)
Chronic *Pseudomonas*: Yes	106 (49.5)
Neurodivergence: Yes	9 (4.2)
Symptoms of depression (PHQ-9), median (IQR)	5 (2 to 9)
None (0 - 4)	106 (49.5)
Mild (5 - 9)	61 (28.5)
Moderate (10 - 14)	27 (12.6)
Moderately Severe (15 - 19)	12 (5.6)
Severe (20 - 27)	8 (3.7)
Symptoms of anxiety (GAD-7), median (IQR)	3 (1.0 to 6.5)
None (0 - 4)	128 (59.8)
Mild (5 - 9)	50 (23.4)
Moderate (10 - 14)	20 (9.3)
Severe (15 - 21)	16 (7.5)
Mean prescribed nebuliser doses per day	
1	63 (29.4)
>1 ≤2	20 (9.3)
>2 ≤3	69 (32.2)
>3 ≤4	34 (15.9)
>4	28 (13.1)

Variable	n (%)
Treatment-specific Factors	
Necessity	
1 (lowest)	4 (1.9%)
2	15 (7%)
3	33 (15.4%)
4	86 (40.2%)
5 (highest)	75 (35%)
Concern	
1 (lowest)	110 (51.4%)
2	77 (36%)
3	13 (6.1%)
4	7 (3.3%)
5 (highest)	6 (2.8%)
Intention	
1 (lowest)	29 (13.6)
2	24 (11.2)
3	33 (15.4)
4	75 (35.0)
5 (highest)	52 (24.3)
Self-efficacy	
1 (lowest)	9 (4.2)
2	16 (7.5)
3	16 (7.5)
4	74 (34.6)
5 (highest)	98 (45.8)
Habit	
1 (lowest)	46 (21.5)
2	60 (28.0)
3	23 (10.7)
4	42 (19.6)
5 (highest)	42 (19.6)
Burden	
1 (lowest)	21 (9.8)
2	52 (24.3)
3	59 (27.6)
4	49 (22.9)
5 (highest)	32 (15)
Other Factors	
Adherence data completeness	
Complete	142 (66.4)
Incomplete	32 (15.0)
No data	40 (18.7)

IQR = interquartile range. IMD = Index of Multiple Deprivation. CFTRm = cystic fibrosis transmembrane conductance regulator (CFTR) protein modulator. BMI = body mass index. %FEV_1 = percentage of predicted forced expiratory volume in 1 second. PHQ-9 = Patient Health Questionnaire-9, GAD-7 = General Anxiety Disorder-7.

9.3.3 Descriptive statistics for adherence

Adherence across the study cohort was positively skewed, as shown in Figure 12. Mean adherence was 26.4% (95% confidence interval [CI] 22.2 to 30.7) and median adherence was 6.9% IQR (2.6 to 49.2).

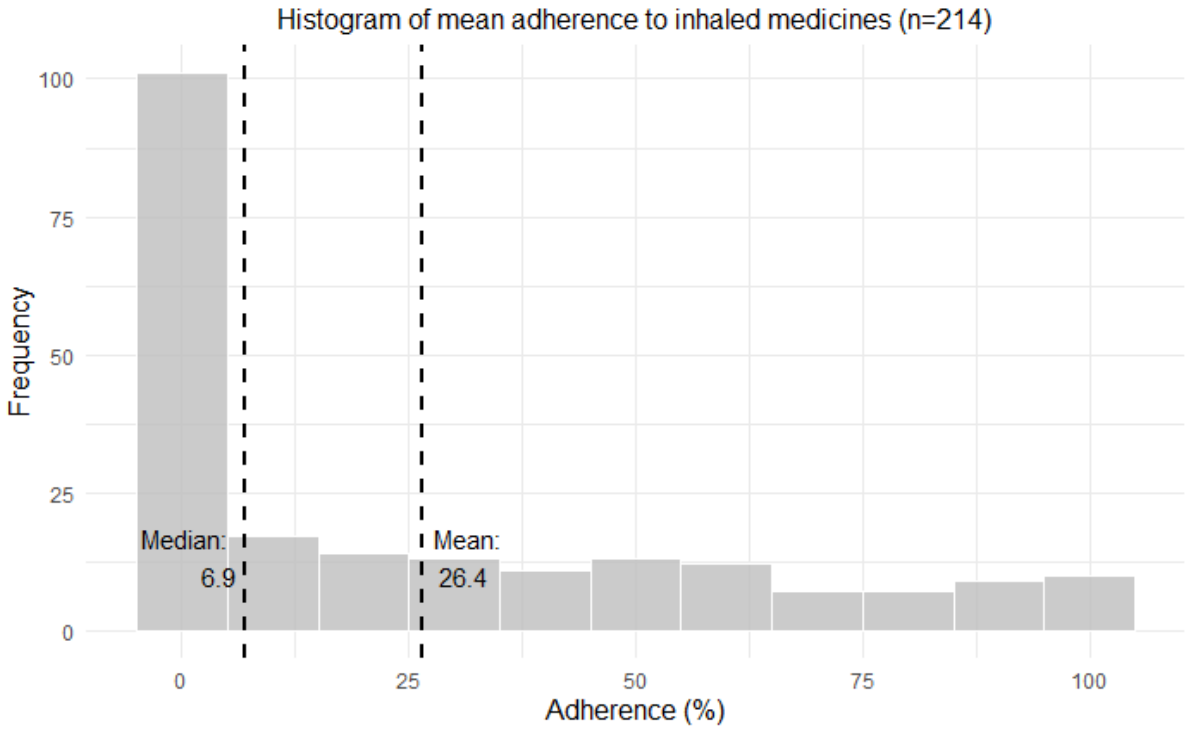

Figure 12: Distribution of adherence to inhaled medicines in the study cohort.

Mean and median adherence by each independent variable subgroup is show in Table 18. The lower range for the 95% CI was capped at zero (denoted in the table with an asterisk[*]) as negative percent adherence is implausible. As the binary variables language barrier and digitally excluded both had only a single occurrence, they were excluded from bivariate and multivariable analyses.

Table 18: Mean and median adherence for each independent variable

Variable	n (%)	Percentage adherence (median, IQR)	Percentage adherence (mean, 95% CI)
Demographic Factors			
Age (years)			
16 - 18	29 (13.6)	2.8 (2.2 to 22.7)	13.8 (6.1 to 21.5)
19 - 25	42 (19.6)	11.1 (1.8 to 60.2)	30.4 (19.8 to 41)
26 - 34	66 (30.8)	2.8 (1.5 to 27.3)	18 (11.8 to 24.2)
≥ 35	77 (36)	23.1 (2.8 to 63.1)	36.2 (28.2 to 44.2)
Sex			
Male	111 (51.9)	12.2 (2.5 to 52.3)	30.1 (23.8 to 36.4)
Female	103 (48.1)	3.1 (2.6 to 39.4)	22.5 (16.8 to 28.1)
Ethnicity			
White British	202 (94.4)	6.9 (2.6 to 48.7)	26.4 (22 to 30.7)
Other	12 (5.6)	5 (2.2 to 50.9)	27.2 (5.5 to 48.9)
Socio-economic Factors			
IMD quintile			
1 (lowest)	70 (32.7)	2.8 (2.2 to 32.7)	21.2 (14 to 28.3)
2	34 (15.9)	2.8 (0.4 to 47.5)	23.7 (13.6 to 33.8)
3	40 (18.7)	7.7 (2.6 to 55.6)	29 (17.3 to 40.8)
4	39 (18.2)	16.6 (2.8 to 43.3)	25.4 (16.7 to 34.1)
5 (highest)	31 (14.5)	41.1 (2.8 to 59.4)	39.1 (26.4 to 51.8)
Educational Attainment			
1 (lowest)	9 (4.2)	2.8 (2.8 to 30.1)	28.3 (0 to 58.3)
2	77 (36)	2.8 (1.8 to 33.7)	21.8 (14.9 to 28.7)
3	39 (18.2)	17.9 (2.8 to 54.7)	30.3 (19.7 to 41)
4	1 (0.5)	49.2 (NA)	49.2 (NA)
5 (highest)	87 (40.7)	11 (2.8 to 53.5)	28.6 (21.8 to 35.3)
Distance to CF Centre (miles)			
≥10	91 (42.5)	18.1 (2.8 to 52.3)	30 (23.3 to 36.7)
10 to 25	58 (27.1)	2.8 (1.7 to 22.5)	18.9 (11.4 to 26.5)
>25	65 (30.4)	11.3 (1.8 to 52)	28.1 (19.9 to 36.2)
Looked after child			
Yes	6 (2.8)	2.8 (2.8 to 3.4)	4.6 (0 to 9.2)
No	208 (97.2)	7.8 (2.4 to 50.8)	27 (22.7 to 31.4)
Children <5y			
Yes	33 (15.4)	2.8 (0.3 to 20.8)	16.6 (6.6 to 26.6)
No	181 (84.6)	11 (2.8 to 52)	28.2 (23.5 to 32.9)
Digitally Excluded			
Yes	1 (0.5)	0 (NA)	0 (NA)
No	213 (99.5)	7.1 (2.8 to 49.2)	26.5 (22.3 to 30.8)
Alternate Residential Circumstances			
Yes	5 (2.3)	2.8 (2.8 to 3.7)	4.8 (0 to 10) *
No	209 (97.7)	7.3 (2.2 to 50.7)	26.9 (22.6 to 31.3)
Language Barrier			
Yes	1 (0.5)	49.2 (NA)	49.2 (NA)
No	213 (99.5)	6.6 (2.5 to 49.1)	26.3 (22 to 30.6)
Health-related Factors			
Prescribed CFTRm			
Yes	190 (88.8)	8.9 (2.2 to 50.6)	27 (22.4 to 31.6)
No	24 (11.2)	3.3 (2.8 to 41.9)	21.7 (9.2 to 34.2)
CF-related diabetes			
Yes	119 (55.6)	13.6 (2.8 to 52.2)	28.9 (23.1 to 34.8)
No	95 (44.4)	3.3 (0.9 to 37.6)	23.3 (17 to 29.5)
BMI in target (Male≥23, Female≥22)			
Yes	147 (68.7)	9.5 (2.8 to 52.3)	28.3 (23.1 to 33.6)
No	67 (31.3)	2.8 (1.1 to 36.3)	22.2 (14.9 to 29.4)
$\%FEV_1$			
<40%	13 (6.1)	21.5 (2.8 to 61.4)	31.7 (11.1 to 52.2)
40 to 69.9%	53 (24.8)	7.3 (2.5 to 45.7)	26.0 (17.6 to 34.4)
≥70%	146 (68.2)	6 (2.3 to 50.3)	25.8 (20.6 to 30.9)
Chronic *Pseudomonas*			

Yes	106 (49.5)	20.1 (2.1 to 57.2)	31.8 (25.5 to 38.2)
No	108 (50.5)	2.8 (2.8 to 33.7)	21.1 (15.5 to 26.7)
Neurodivergence			
Yes	9 (4.2)	7.3 (2.8 to 97.2)	37.7 (2.3 to 73.1)
No	205 (95.8)	6.6 (2.2 to 49.1)	25.9 (21.7 to 30.2)
Symptoms of depression (PHQ-9)			
None (0 - 4)	106 (49.5)	20.1 (2.8 to 52.3)	29.9 (23.8 to 36)
Mild (5 - 9)	61 (28.5)	8.3 (2.8 to 53.4)	28 (19.7 to 36.3)
Moderate (10 - 14)	27 (12.6)	2.1 (0 to 2.8) *	7.8 (0 to 15.6) *
Moderately Severe (15 - 19)	12 (5.6)	10.5 (1.2 to 20.9)	22.6 (1.1 to 44)
Severe (20 - 27)	8 (3.7)	26 (2.8 to 62.5)	36.9 (5 to 68.9)
Symptoms of anxiety (GAD-7)			
None (0 - 4)	128 (59.8)	20.1 (2.8 to 52.5)	29.4 (24 to 34.9)
Mild (5 - 9)	50 (23.4)	2.8 (2.2 to 35.8)	22.3 (13.3 to 31.2)
Moderate (10 - 14)	20 (9.3)	2.8 (0 to 19.4) *	18.1 (2.5 to 33.7)
Severe (15 - 21)	16 (7.5)	7.5 (0.7 to 42.2)	25.6 (8 to 43.2)
Mean prescribed doses per day			
1	63 (29.4)	2.8 (2.8 to 18)	16.1 (9.4 to 22.9)
>1 ≤2	20 (9.3)	4.6 (2.8 to 52.3)	27.7 (11.1 to 44.4)
>2 ≤3	69 (32.2)	5.4 (1.3 to 29.3)	20.1 (13.6 to 26.6)
>3 ≤4	34 (15.9)	50.1 (16.4 to 67.1)	47.0 (35.9 to 58)
>4	28 (13.1)	33.4 (1.1 to 67.6)	39.2 (25.5 to 52.9)
Treatment-specific Factors			
Necessity			
1 (lowest)	4 (1.9)	2.8 (2.6 to 25.2)	25.1 (0 to 96.6) *
2	15 (7)	2.8 (0.2 to 2.9)	9.9 (0 to 23.5) *
3	33 (15.4)	2.8 (0 to 18.1) *	12.8 (4.1 to 21.4)
4	86 (40.2)	6.2 (2.8 to 44.9)	23.9 (18.1 to 29.7)
5 (highest)	75 (35)	26.8 (2.8 to 68.7)	39 (30.9 to 47.2)
Concern			
1	110 (51.4)	17.2 (2.8 to 59.6)	31.5 (25.1 to 37.9)
2	77 (36)	7.1 (2 to 42.6)	24.2 (17.8 to 30.7)
3	13 (6.1)	2.2 (0.9 to 2.8)	4.4 (0 to 9.8) *
4	7 (3.3)	0 (0 to 2) *	7.6 (0 to 24.6) *
5	6 (2.8)	8.2 (2.8 to 74.4)	35.2 (0 to 84.8) *
Intention			
1	29 (13.6)	2.8 (0.9 to 2.8)	13.5 (2 to 25.1)
2	24 (11.2)	2.8 (1.1 to 30.4)	18.3 (6.2 to 30.4)
3	33 (15.4)	2.8 (0.4 to 45.7)	23.7 (11.9 to 35.5)
4	75 (35)	13.6 (2.8 to 39.6)	25.1 (18.5 to 31.7)
5	52 (24.3)	41 (10.9 to 66.8)	41.5 (32.5 to 50.5)
Self-efficacy			
1	9 (4.2)	2.2 (0 to 2.8) *	11.8 (0 to 35.1) *
2	16 (7.5)	2.8 (1.5 to 4.1)	6 (1.5 to 10.5)
3	16 (7.5)	2.4 (0.1 to 2.8)	3.5 (0.4 to 6.5)
4	74 (34.6)	7.7 (2.8 to 45.4)	24 (17.6 to 30.4)
5	98 (45.8)	28.2 (2.8 to 64.5)	36.9 (29.9 to 43.9)
Habit			
1	46 (21.5)	2.5 (0 to 3) *	6.4 (1.9 to 10.9)
2	60 (28)	2.8 (1.6 to 21.1)	15.8 (9.4 to 22.2)
3	23 (10.7)	26.5 (2.8 to 47.5)	29.6 (17.3 to 42)
4	42 (19.6)	43.6 (4.7 to 61.1)	40.4 (30.3 to 50.4)
5	42 (19.6)	52.5 (19.7 to 78.7)	48.4 (37.4 to 59.4)
Burden			
1	21 (9.8)	45 (2.8 to 67.1)	42.9 (25.7 to 60.1)
2	52 (24.3)	24.1 (2.8 to 54.8)	33.4 (24.5 to 42.3)
3	59 (27.6)	5.9 (2.8 to 45.9)	24.8 (17.1 to 32.4)
4	49 (22.9)	2.8 (1.8 to 36.9)	21.7 (13.4 to 30)
5	32 (15)	2.8 (0.2 to 12.6)	15.2 (4.4 to 26.1)
Adherence data completeness			
Complete	142 (66.4)	28.2 (2.2 to 60.4)	35.7 (30.2 to 41.3)
Incomplete	32 (15.0)	2.7 (0.2 to 15.9)	14.5 (6.2 to 22.9)
No data (imputed)	40 (18.7)	2.8 (2.8 to 2.8)	2.8 (2.8 to 2.8)

Post-descriptive transformations of variables prior to bivariate analyses

On review of the data in Table 18, some variables were transformed with the intention of simplifying the output and interpretation of the bivariate and multivariable analyses. Generally, each of these variables was a multi-level categorical variable with a non-monotonic relationship with adherence. Therefore, to reduce the risk of overfitting and produce more reliable estimates, they were recoded to rationalise the number of independent variables in the final multivariable model whilst retaining the ability to detect differences between groups.

IMD quintile, intention, habit, and burden were ordinal variables, ranging from levels 1 to 5, demonstrating monotonic relationships with adherence. Therefore, they were treated as continuous variables in subsequent analyses. Following combination of groups with size <10, necessity, concern, and self-efficacy did not have clear monotonic relationships with adherence so were not treated continuously. Each was therefore transformed into a binary variable, with the levels exhibiting lower mean adherence combined and compared to the level with the highest mean adherence. For the variables of necessity and self-efficacy, levels 1 to 3 were combined and compared to level 4, while for concern, levels 2 to 4 were combined and compared to level 1. This was chosen over an dummy-coding at each level, as this would have added an additional nine variables to the multivariable analysis.

Educational attainment was dichotomised to classify participants as having attained post-secondary education (Levels 3 to 5, at least A-level or equivalent) or not (Levels 1 to 2, at most GSCE or equivalent). Previous work in CF has also involved rational grouping of educational attainment categories, though at what level the categorisation occurs is not standardised across studies (301, 356).

Both PHQ-9 and GAD-7 scores were collected as continuous variables and categorised as per standard practice to classify severity of symptoms. In both cases the group sizes were positively skewed towards the lower categories of symptom severity, but the relationships between increasing severity of symptoms and adherence were not clearly monotonic. PHQ-9 or GAD-7 scores of 10 or higher for pwCF indicate that the symptoms of depression or anxiety should be clinically assessed and may require intervention

(317). Therefore, PHQ-9 and GAD-7 scores were transformed into binary variables with clinically significant symptoms of depression or anxiety being classified as scores ≥10, consistent with previous CF studies (357-360).

%FEV_1 was collected as a continuous variable and transformed into a 3-level ordinal variable. The mean adherence in the 40 to 69.9% and ≥70% groups was similar (25.8% and 26.0%), and these groups were combined to transform this to a binary variable, where %FEV_1 was <40% (indicating severe CF lung disease) or ≥40% (indicating not severe lung disease).

Mean prescribed daily dose count data were originally collected as a continuous variable and converted to a count by rounding up the next integer. Whilst mean adherence differed at the extremes (16.1% for those prescribed one dose per day vs. 39.2% for those prescribed ≥5 doses), the relationship was non-monotonic. Therefore, the variable was dichotomised to complex (>3 doses prescribed per day) or standard (≤3 doses per day) inhaled medicines regimens, aligning with first-line treatment recommendations for pwCF with lung disease (one or two doses of inhaled mucolytic), or chronic *Pseudomonas* infection (one dose of mucolytic and two doses of antibiotic per day (79)). Descriptive statistics for all transformed variables are shown in Table 19.

Table 19: Summary statistics for the variables transformed to binary variables following descriptive analysis.

Variable	n (%)	Percentage adherence (median, IQR)	Percentage adherence (mean, 95% CI)
Post-secondary education			
Yes	127 (59.3%)	12.2 (2.8 - 53.5)	29.3 (23.7 - 34.9)
No	86 (40.2%)	2.8 (2 - 33.4)	22.5 (15.8 - 29.2)
Severe lung disease			
Yes	13 (6.1%)	21.5 (2.8 - 61.4)	31.7 (11.1 - 52.2)
No	199 (93%)	6.3 (2.4 - 48.2)	25.8 (21.5 - 30.2)
Symptoms of depression			
Yes	47 (22%)	2.8 (0.1 - 18.4)	16.5 (8 - 25)
No	167 (78%)	14.3 (2.8 - 52.7)	29.2 (24.3 - 34.1)
Symptoms of anxiety			
Yes	36 (16.8%)	2.8 (0 - 24.9)	21.4 (10.3 - 32.6)
No	178 (83.2%)	8.9 (2.8 - 51.7)	27.4 (22.8 - 32)
Complex regimen			
Yes	62 (29%)	45.1 (7 - 67.1)	43.5 (35 - 51.9)
No	152 (71%)	2.8 (2.2 - 27.2)	19.5 (14.9 - 24)
Necessity (highest)			
Yes	75 (35%)	26.8 (2.8 - 68.7)	39 (30.9 - 47.2)
No	138 (64.5%)	2.8 (1.9 - 34)	19.7 (15.2 - 24.3)
Concern (lowest)			
Yes	103 (48.1%)	2.8 (1.1 - 38.2)	21.2 (15.7 - 26.8)
No	110 (51.4%)	17.2 (2.8 - 59.6)	31.5 (25.1 - 37.9)
Self-efficacy (highest)			
Yes	98 (45.8%)	28.2 (2.8 - 64.5)	36.9 (29.9 - 43.9)
No	115 (53.7%)	2.8 (1.2 - 26)	17.7 (13 - 22.4)

IQR = interquartile range. CI = confidence interval.

9.3.4 Bivariate analysis

The 24 remaining variables underwent bivariate linear regression with mean adherence as the dependent variable. Eleven variables demonstrated significant associations with adherence, including IMD quintile (coefficient 3.49, 95% CI 0.59 to 6.39, p = 0.019), chronic *Pseudomonas* infection (coefficient 10.7, 95% CI 2.28 to 19.11, p = 0.013) and all six treatment-specific factors, e.g. habit (coefficient 10.89, 95% CI 8.34 to 13.44, p<0.001). The full results are shown in Table 20.

Table 20: Bivariate linear regression model results for all variables with the outcome of mean percent adherence

Variable	Estimate (95% CI)	p value	AIC	R^2
Demographic Factors				
Age (years)		<0.001***	2076.33	0.081
16 - 18	-16.63 (-31.16 to -2.10)	0.025*		
19 - 25 (ref)				
26 - 34	-12.44 (-24.31 to -0.56)	0.040*		
≥ 35	5.73 (-5.81 to 17.27)	0.328		
Sex: Male	7.63 (-0.85 to 16.11)	0.078	2087.31	0.015
Ethnicity: White British	-0.86 (-19.42 to 17.7)	0.928	2090.45	<0.001
Socio-economic Factors				
IMD quintile (continuous, scale 1-5)	3.49 (0.59 to 6.39)	0.019*	2084.85	0.026
Post-secondary education: Yes	6.79 (-1.89 to 15.47)	0.125	2078.64	0.011
Distance to CF Centre (miles)		0.100	2087.79	0.022
<10	11.07 (0.66 to 21.47)	0.037		
10 - 25 (ref)				
>25	9.12 (-2.06 to 20.31)	0.109		
Looked after child	-22.44 (-48.13 to 3.25)	0.087	2087.48	0.014
Carer for children <5y	-11.62 (-23.34 to 0.09)	0.052	2086.63	0.018
Alternate residential circumstances	-22.08 (-50.19 to 6.03)	0.123	2088.05	0.011
Health-related Factors				
Prescribed CFTRm	5.32 (-8.19 to 18.84)	0.438	2089.85	0.003
CF-related diabetes	5.67 (-2.89 to 14.23)	0.193	2088.74	0.008
BMI in target (M≥ 23, F≥22)	6.19 (-2.98 to 15.36)	0.185	2088.68	0.008
Severe lung disease	5.83 (-11.89 to 23.55)	0.517	2066.98	0.002
Chronic *Pseudomonas infection*	10.07 (2.28 to 19.11)	0.013*	2084.21	0.029
Neurodivergence	11.81 (-9.4 to 33.03)	0.274	2089.24	0.006
Symptoms of depression	-12.69 (-22.86 to -2.52)	0.015*	2084.43	0.028
Symptoms of anxiety	-5.97 (-17.36 to 5.41)	0.302	2089.38	0.005
Complex regimen	23.99 (15.16 to 32.83)	<0.001***	2063.32	0.119
Treatment-specific Factors				
Necessity (binary, highest)	19.28 (10.70 to 27.85)	<0.001***	2062.09	0.085
Concern (binary, lowest)	-10.24 (-18.7 to -1.78)	0.018*	2075.36	0.026
Intention (continuous 1 - 5)	6.33 (3.24 to 9.43)	<0.001***	2065.20	0.072
Self-efficacy (binary, highest)	19.21 (11.02 to 27.40)	<0.001***	2060.47	0.092
Habit (continuous 1 - 5)	10.89 (8.34 to 13.44)	<0.001***	2019.19	0.252
Burden (continuous 1 - 5)	-6.44 (-9.87 to -3.00)	<0.001***	2067.67	0.061

AIC = Akaike Information Criterion. BMI = Body mass index, CFTRm = Cystic fibrosis (CF) transmembrane conductance regulator protein (CFTR) modulator, IMD = index of multiple deprivation. M = male. F = female. * = p<0.05, ** p<0.01, ***p <0.001.

9.3.5 Multivariable primary analysis

All cases with no missing data for any variable following imputation were included in the multivariable model (n=211/214). Of the 24 factors assessed, the backward selection process led to the retention of seven variables in the final model: age group; IMD quintile; caring responsibility for children <5y; severe lung disease; neurodivergence; complex inhaled medicines regimen and habit. Age group 16-18y was the only variable significantly associated with lower adherence (co-efficient -15.88, 95% CI -28.14 to -

3.62, p = 0.011), whereas increasing IMD quintile and habit, along with the presence of neurodivergence and complex inhaled medicines regimens were significant associated with higher adherence. The model results are shown in Table 21.

Table 21: Multivariable linear regression model results (primary analysis)

Variable	Estimate (95% CI)	p value	Adjusted Partial R^2
Age (years)			0.047
16 - 18	-15.88 (-28.14 to -3.62)	0.011*	
19 - 25 (ref)			
26 - 34	-4.86 (-15.10 to 5.39)	0.351	
≥35	4.51 (-5.38 to 14.40)	0.370	
IMD quintile (continuous, 1 - 5)	2.85 (0.45 to 5.26)	0.020*	0.022
Carer for children <5y	-8.23 (-18.05 to 1.60)	0.100	0.008
Severe lung disease	-11.30 (-26.11 to 3.51)	0.134	0.006
Neurodivergence	20.24 (2.19 to 38.30)	0.028*	0.019
Complex regimen	10.49 (2.12 to 18.87)	0.014*	0.025
Habit (continuous, 1 - 5)	9.73 (7.17 to 12.30)	<0.001***	0.214

Adjusted R^2 = 0.353. AIC = 1972.90.

AIC = Akaike Information Criterion. IMD = index of multiple deprivation* = p<0.05, ** p<0.01, ***p <0.001.

Whilst caring for children <5 years of age and severe lung disease were both associated with lower adherence, these were not statistically significant when using a p value threshold of 0.05, but were significant when relaxing that threshold to 0.157 in keeping with the AIC-based selection process, as shown in Figure 13 (361). For the purposes of this work, which was to identify important factors, this distinction serves to increase awareness of the potential impact of severe lung disease and children under 5 on adherence.

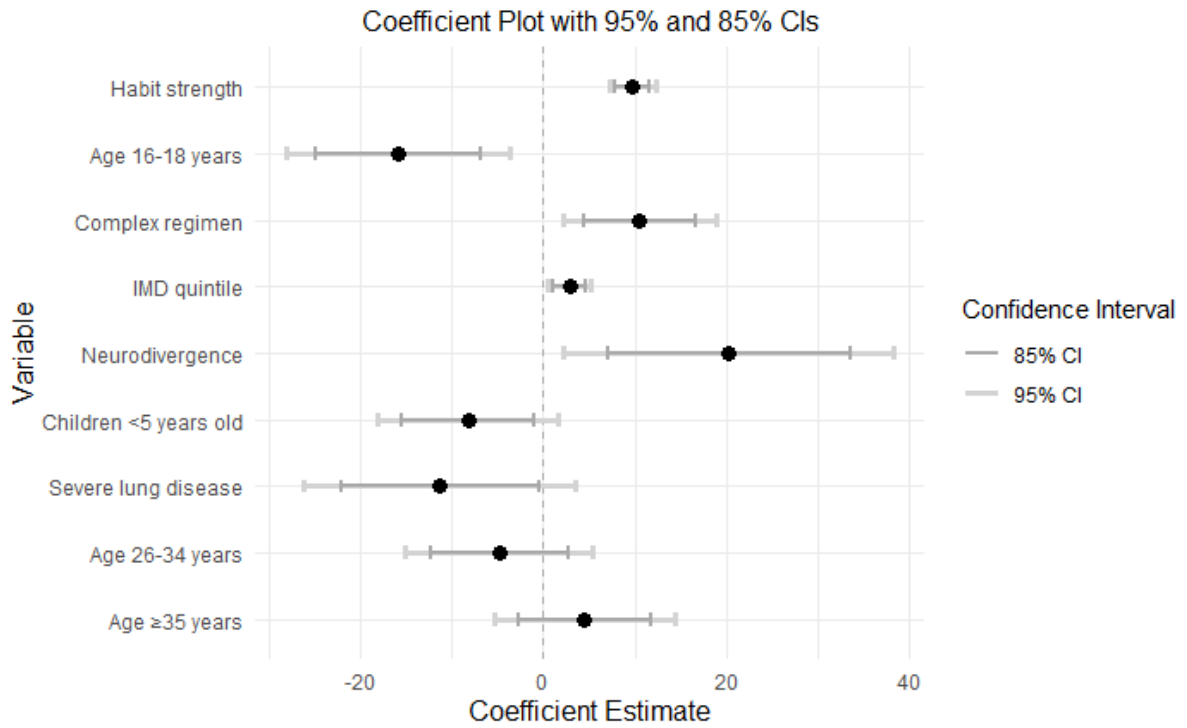

Figure 13: Coefficients for the primary multivariable linear regression model.

Model assumptions

Both continuous variables in the final model (IMD quintile and habit) demonstrated monotonic relationships with the outcome of mean adherence. All other variables were dichotomised, therefore the assumption of linearity was satisfied. Adjusted GVIF values for all variables were below 2 (range 1.00 to 1.11) indicating negligible multicollinearity.

The model residuals followed a normal distribution with a slight positive skew when assessed with a histogram (Figure 14). However, the Q-Q plot of residuals demonstrated deviation at the upper end of theoretical quantile (Figure 15). This is in keeping with the positive skew of the adherence data and may indicate outliers or heteroscedasticity.

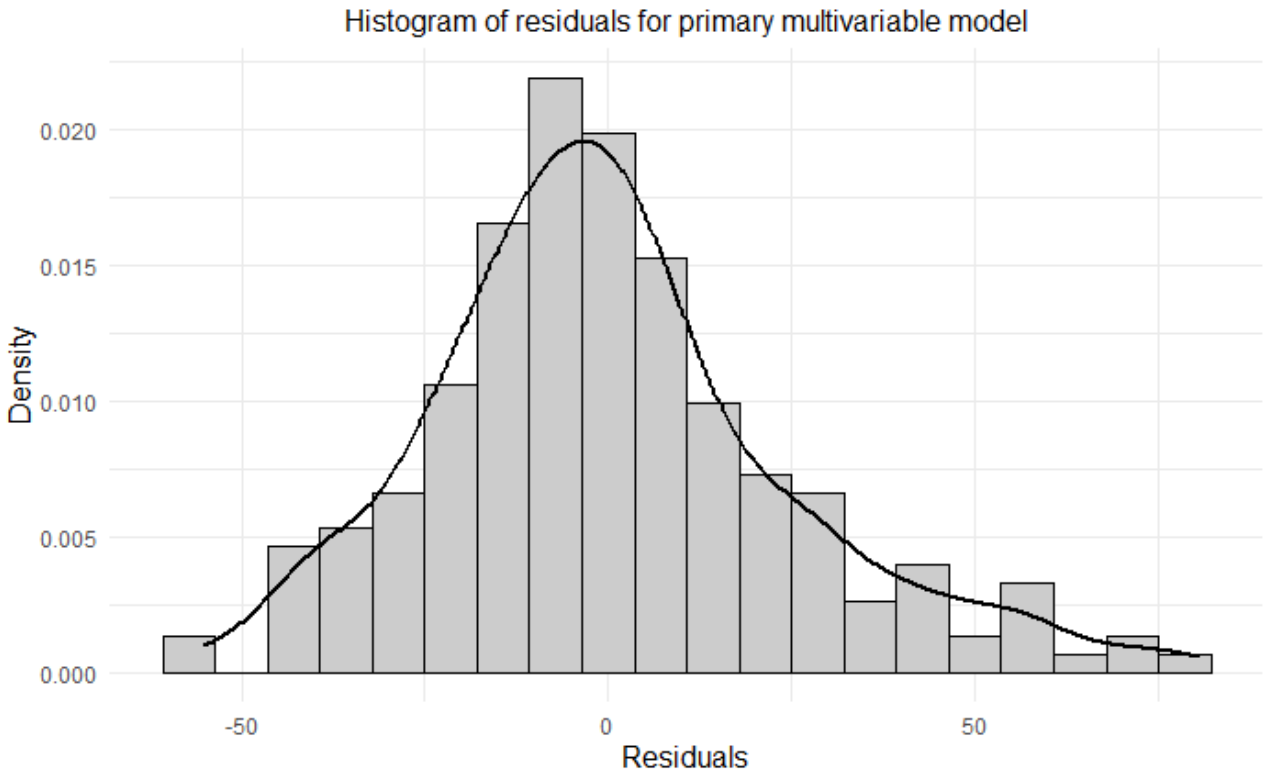

Figure 14: Histogram representing the distribution of residuals for the primary multivariable linear regression model.

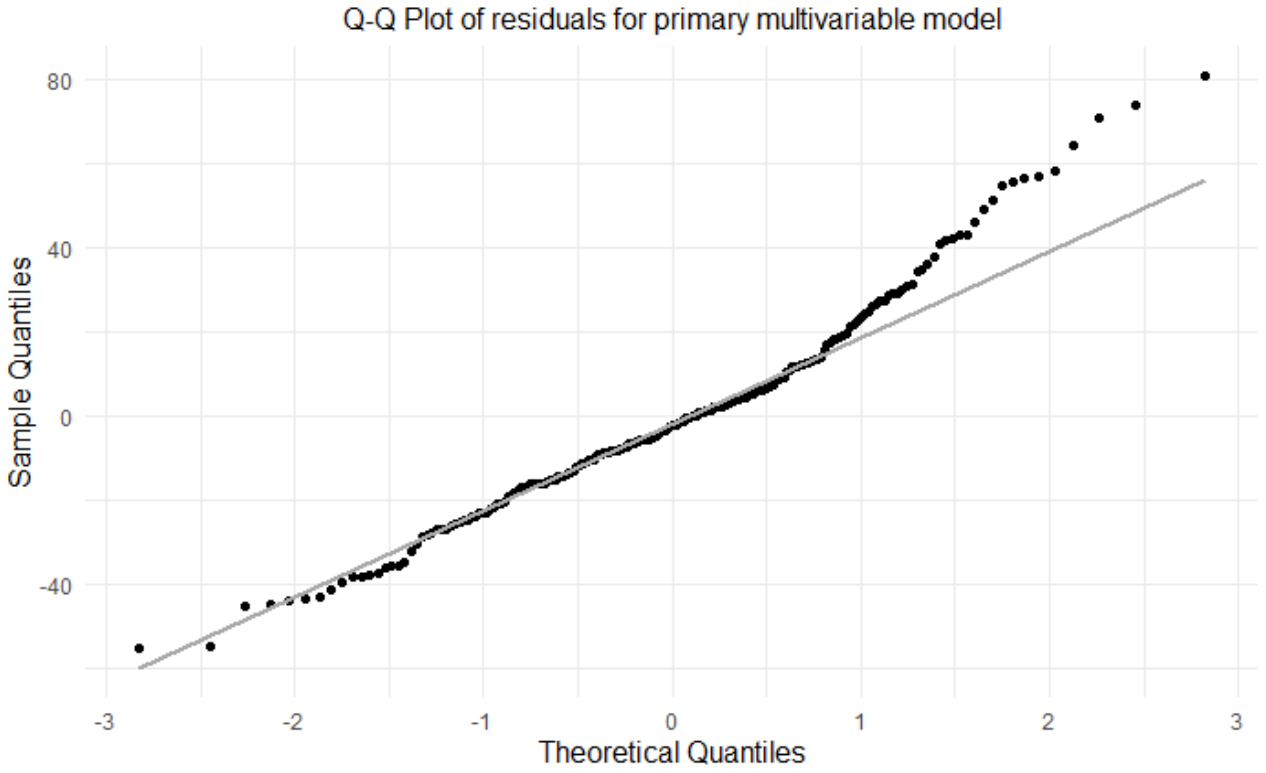

Figure 15: Q-Q plot representing the distribution of residuals for the primary multivariable linear regression model.

There was also evidence of heteroscedasticity in the residuals (Figure 16). Given these findings, the outcome variable was transformed using a logit function as part of the second sensitivity analysis.

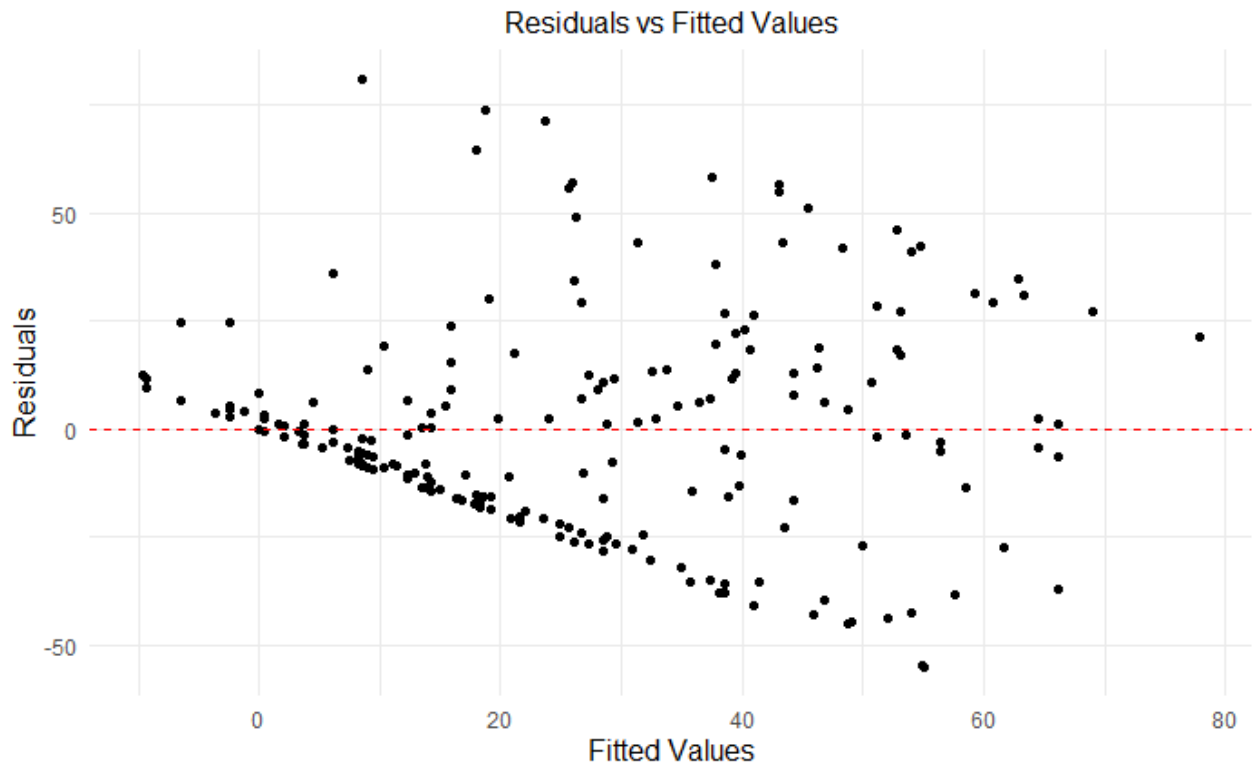

Figure 16: Scatterplot representing fitted values vs residuals for all cases in the primary multivariable linear regression model.

9.3.6 Sensitivity analyses

Sensitivity Analysis 1: Complete case analysis

The rationale for this sensitivity analysis, which involved replicating the primary model using only those with complete objective adherence data covering the entire 12-month period (n=140/211) was to produce coefficients which are unaffected by imputation. In this sensitivity analysis, whilst the direction of association for all variables was consistent with the primary analysis, only neurodivergence (coefficient 27.93, 95% CI 2.83 to 7.53, p = 0.028) and habit (coefficient 10.31, 95% CI 6.98 to 13.65, p<0.001) retained a statistically significant relationship with adherence. The full results are shown in Table 22.

Table 22: Multivariable linear regression model results (complete case sensitivity analysis)

Variable	Estimate (95% CI)	p value	Adjusted partial R^2
Age (years)			0.031
16 - 18	-17.22 (-36.08 to 1.64)	0.073	
19 - 25 (ref)			
26 - 34	-6.62 (-20.24 to 7.01)	0.339	
≥35	4.71 (-8.04 to 17.46)	0.467	
IMD quintile (continuous, 1 - 5)	2.81 (-0.38 to 5.99)	0.084	0.015
Carer for children <5y	-6.30 (-21.74 to 8.14)	0.390	-0.002
Severe lung disease	-11.27 (-30.06 to 7.53)	0.238	0.003
Neurodivergence	27.93 (2.83 to 53.01)	0.029*	0.028
Complex regimen	5.77 (-4.50 to 16.04)	0.268	0.002
Habit (continuous 1 - 5)	10.31 (6.98 to 13.65)	<0.001***	0.216

Adjusted R^2 = 0.308. AIC = 1345.45

AIC = Akaike Information Criterion. BMI = Body mass index, CFTRm = Cystic fibrosis (CF) transmembrane conductance regulator protein (CFTR) modulator, IMD = index of multiple deprivation. * = p<0.05, ** p<0.01, ***p <0.001.

Sensitivity Analysis 2: Linear regression with logit transformation of mean adherence outcome variable

Given the potential heteroscedasticity of residuals in the primary multivariable analysis and the positively skewed adherence outcome data, this sensitivity analysis explored if the original findings were sustained in a model with different assumptions.

Mean percentage adherence was transformed to a proportion and a small value (ἐ = 0.001) was added to ensure no proportions were on the lower boundary value of 0. The maximum adherence in this data set was 99.5%, therefore no adjustments were required at the upper boundary. The resulting adherence proportion was converted to odds, and the log(odds) was taken as the logit transformation. The variables in the primary multivariable model were retained and logit adherence was used as the outcome. Backward selection was not repeated.

In this model, increasing habit (odds ratio [OR] 2.62, 95% CI 2.06 to 3.34, p<0.001) and presence of neurodivergence (OR 6.61, 95% CI 1.19 to 36.70, p = 0.032) were also significantly associated with higher adherence. Caring responsibilities for children <5 years old had a significant negative association with adherence in this sensitivity analysis (OR 0.34, 95% CI 0.13 to 0.86, p = 0.024). The results of the analysis are shown in Table 23.

Table 23: Multivariable linear regression model results (logit transformation sensitivity analysis)

Variable	Odds Ratio (95% CI)	p value
Age (years)		
16 - 18	0.33 (0.10 to 1.05)	0.061
19 - 25 (ref)		
26 - 34	1.04 (0.39 to 2.75)	0.939
≥35	1.82 (0.71 to 4.66)	0.212
IMD quintile (continuous, 1 - 5)	1.24 (0.99 to 1.56)	0.065
Carer for children <5y	0.34 (0.13 to 0.86)	0.024*
Severe lung disease	0.32 (0.08 to 1.30)	0.112
Neurodivergence	6.61 (1.19 to 36.70)	0.032*
Complex regimen	1.69 (0.76 to 3.74)	0.198
Habit (continuous 1 - 5)	2.62 (2.06 to 3.34)	<0.001***

Adjusted Psuedo-R^2 = 0.317. AIC = 981.66

AIC = Akaike Information Criterion. IMD = index of multiple deprivation, $\%FEV_1$ = percentage of predicted forced expiratory volume in 1 second. * = p<0.05, ** p<0.01, ***p <0.001

Following logit transformation, the distribution of residuals in the histogram was unchanged (Figure 17), however there was significantly less deviation from the theoretical normal distribution in the Q-Q plot (Figure 18). Whilst the scatterplot of residuals vs fitted values did not show perfect homoscedasticity (Figure 19), this was likely due to a significant proportion of mean adherence values being 0% (n = 28, 13.3%) and imputed at 2.78% (n = 40, 19.0%). Acknowledging this, the findings from the primary multivariable analysis are considered valid.

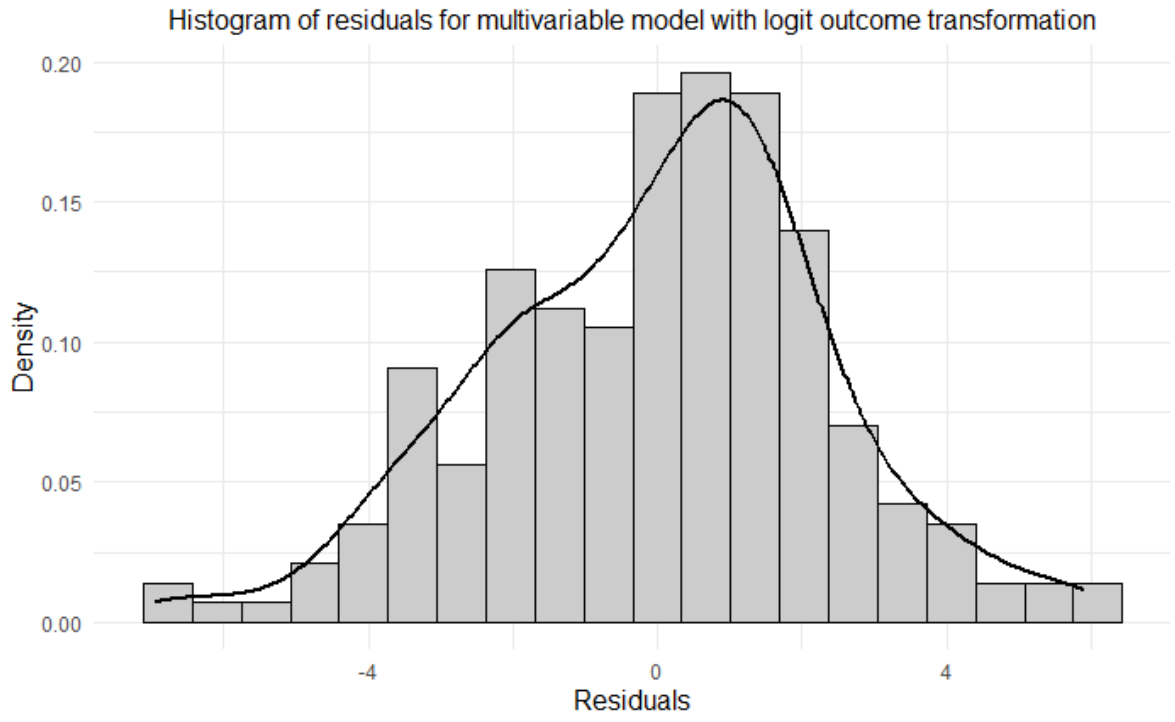

Figure 17: Histogram representing the distribution of residuals for the multivariable linear regression model with logit transformation.

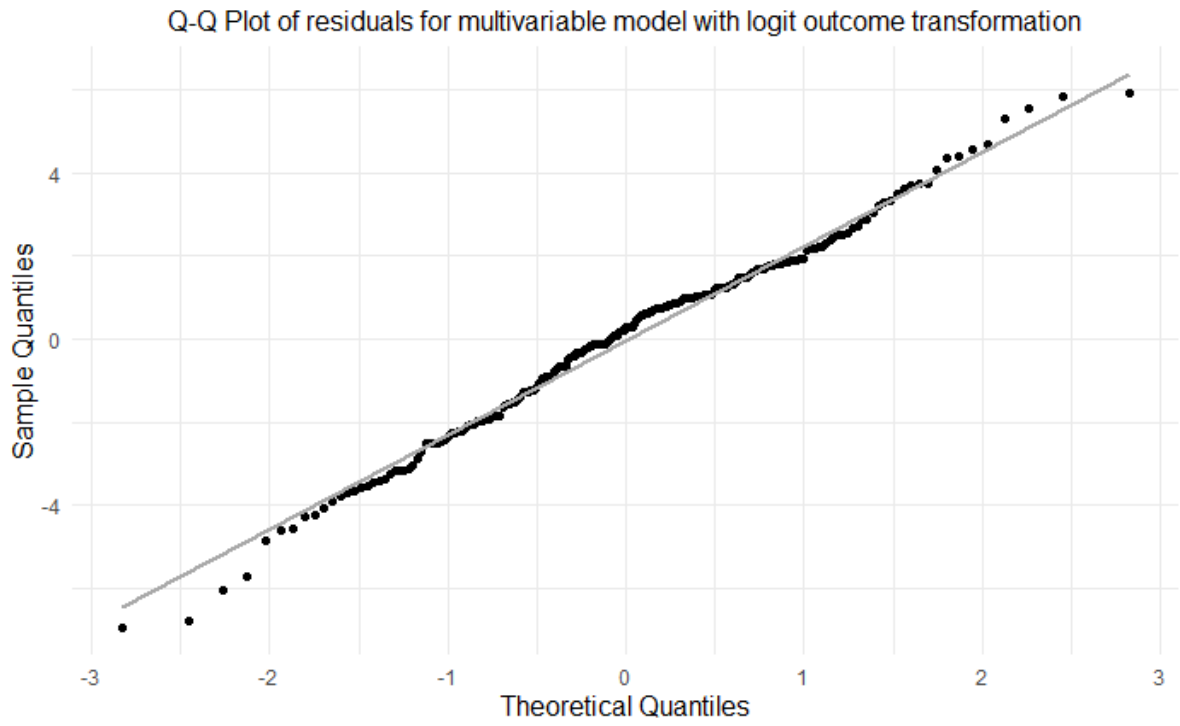

Figure 18: Q-Q plot representing the distribution of residuals for the multivariable linear regression model with logit transformation.

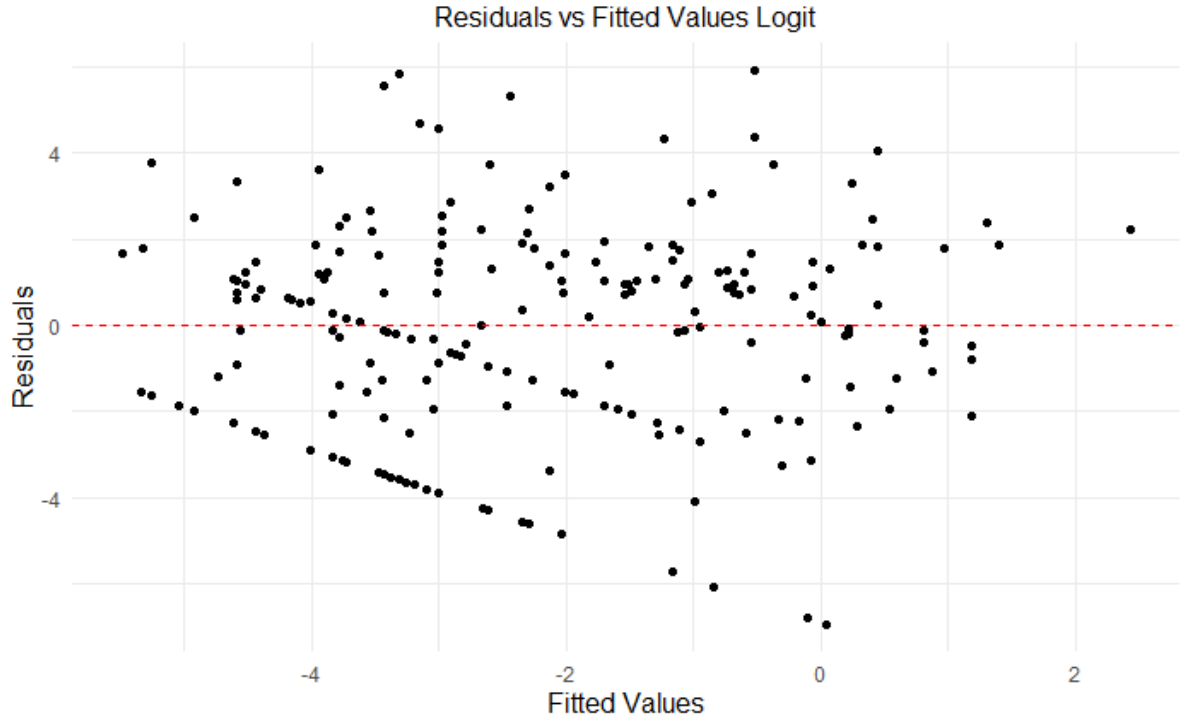

Figure 19: Scatterplot representing fitted values vs residuals for all cases in the multivariable linear regression model with logit transformation

Sensitivity Analysis 3: Analysis of continuous variables in their original form

Seven variables (age, distance to CF centre, BMI, %FEV_1, PHQ-9 score, GAD-7 score and mean number of daily doses prescribed) were considered to exist naturally on a continuous scale but were categorised in the primary analyses. The relationships between the natural, continuous values for these variables and mean adherence are shown in Figure 20. These plots demonstrate that some relationships may be monotonic (e.g. age and BMI) whereas others may not (e.g. GAD-7 and PHQ-9 scores), though the confidence intervals of the locally estimated scatterplot smoothing curves generally support the assumption of monotonicity.

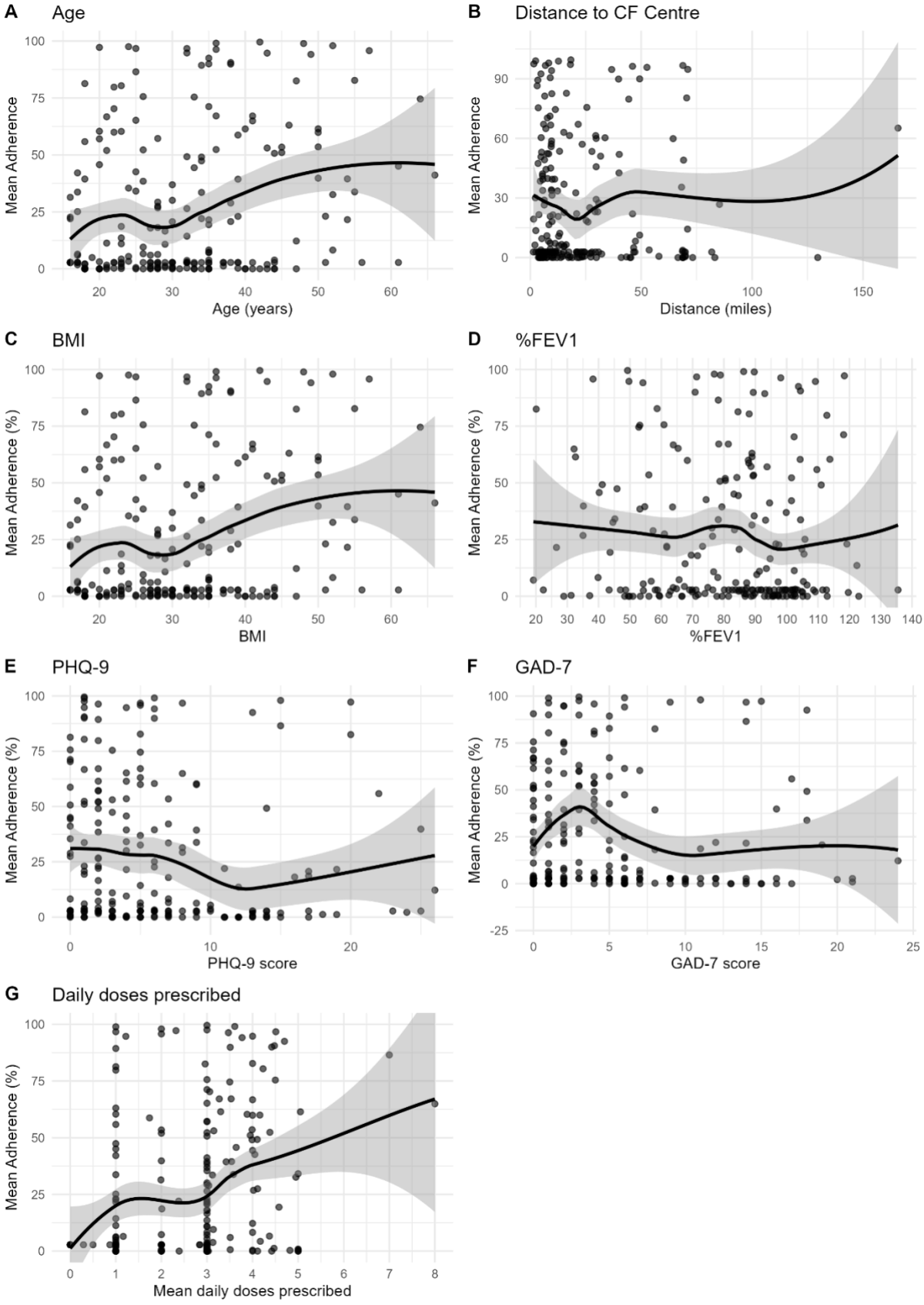

Figure 20: Scatterplots representing relationships between continuous independent variables and mean adherence

The backward selection procedure used in the primary multivariable analysis was repeated, this time treating all seven variables as continuous under the assumption of linearity. The final model retained a similar set of variables to the primary analysis, with the exception of $\%FEV_1$, which was excluded at the final step of the backward selection process. Model fit was comparable, with only marginal differences in AIC (1967.38 vs 1972.90) and adjusted R^2 (0.361 vs 0.353). The model coefficients and partial adjusted R^2 values were comparable to those from the primary multivariable analysis, as shown in Table 24.

Table 24: Results of backward selection multivariable model building in the primary analysis and continuous variable sensitivity analysis

Primary Multivariable Analysis			
Variable	**Estimate (95% CI)**	**p value**	**Adjusted Partial R^2**
Age (years)			0.047
16 - 18	-15.88 (-28.14 to -3.62)	0.011*	
19 - 25 (ref)			
26 - 34	-4.86 (-15.10 to 5.39)	0.351	
≥35	4.51 (-5.38 to 14.40)	0.370	
IMD quintile (continuous, 1 - 5)	2.85 (0.45 to 5.26)	0.020*	0.022
Carer for children <5y	-8.23 (-18.05 to 1.60)	0.100	0.008
Severe lung disease ($\%FEV_1$ <40%)	-11.30 (-26.11 to 3.51)	0.134	0.006
Neurodivergence	20.24 (2.19 to 38.30)	0.028*	0.019
Complex regimen (≥3 doses/day)	10.49 (2.12 to 18.87)	0.014*	0.025
Habit (continuous, 1 - 5)	9.73 (7.17 to 12.30)	<0.001***	0.214
Adjusted R^2 = 0.353. AIC = 1972.90			
Sensitivity Analysis – assuming linearity of continuous variables			
Variable	**Estimate (95% CI)**	**p value**	**Adjusted Partial R^2**
Age	0.62 (0.31 to 0.93)	<0.001***	0.066
IMD quintile (continuous, 1 - 5)	3.01 (0.64 to 5.38)	0.013*	0.025
Carer for children <5y	-9.12 (-18.64 to 0.39)	0.060	0.012
Neurodivergence	23.76 (5.84 to 41.68)	0.010*	0.028
Daily doses prescribed	3.93 (1.40 to 6.45)	0.002**	0.039
Habit (continuous, 1 - 5)	9.48 (7.05 to 11.91)	<0.001***	0.221
Adjusted R^2 = 0.361. AIC = 1967.38			

AIC = Akaike Information Criterion. IMD = index of multiple deprivation* = p<0.05, ** p<0.01, ***p <0.001. Please note that %FEV1 was removed from the sensitivity analysis model in the final step of the backward selection process, when it was treated as a continuous variable.

The original, final primary multivariable model, which included $\%FEV_1$, was then re-modelled, using linear tail-restricted cubic splines to allow for potential non-linearity in age, $\%FEV_1$ and daily doses prescribed. Analysis of variance (ANOVA) was used to test for statistically significant relationships. The direction, magnitude, and statistical significance of effects in this sensitivity analysis were consistent with the primary model, as shown in Table 25.

Table 25: Multivariable linear regression model results (continuous variable sensitivity analysis using cubic splines)

Sensitivity Analysis – using splines to address potential non-linearity			
Variable	**Low, High Range**	**Coefficient (95% CI)**	**p value**
Age (years)	23, 38	9.37 (-0.40 to 19.14)	0.001***
IMD quintile (1 - 5)	1, 4	8.49 (1.13 to 15.84)	0.024*
Carer for children <5y	No, Yes	-10.0 (-20.1 to 0.03)	0.051
%FEV_1	64.3, 97.5	-2.46 (-12.6 to 7.7)	0.311
Neurodivergence	No, Yes	22.4 (4.1 to 40.7)	0.017*
Daily doses prescribed	1.0, 3.3	6.78 (-1.85 to 15.42)	0.014*
Habit (1 - 5)	2, 4	19.4 (14.4 to 24.4)	<0.001***
AIC = 1976.32			

AIC = Akaike Information Criterion. IMD = index of multiple deprivation* = p<0.05, ** p<0.01, ***p <0.001. The "Effect" column represents the estimated difference in per cent adherence between individuals at the low versus high values of each predictor, as indicated in the "Low, High Range" column. For example, an individual aged 38 years would be expected to have adherence 9.37 percentage points higher than someone aged 23 years, holding other covariates constant. P values refer to the overall statistical significance of the spline term, whereas individual coefficients and confidence intervals should not be interpreted in isolation.

The residuals were similar for all three models (the primary multivariable model, the continuous variable sensitivity analysis assuming linearity and the continuous variable sensitivity analysis using cubic splines), as shown in Figure 21. The consistency between models in this sensitivity analysis is reassuring, suggesting that categorisation of the continuous variables did not have a major effect on the findings of the primary multivariable analysis.

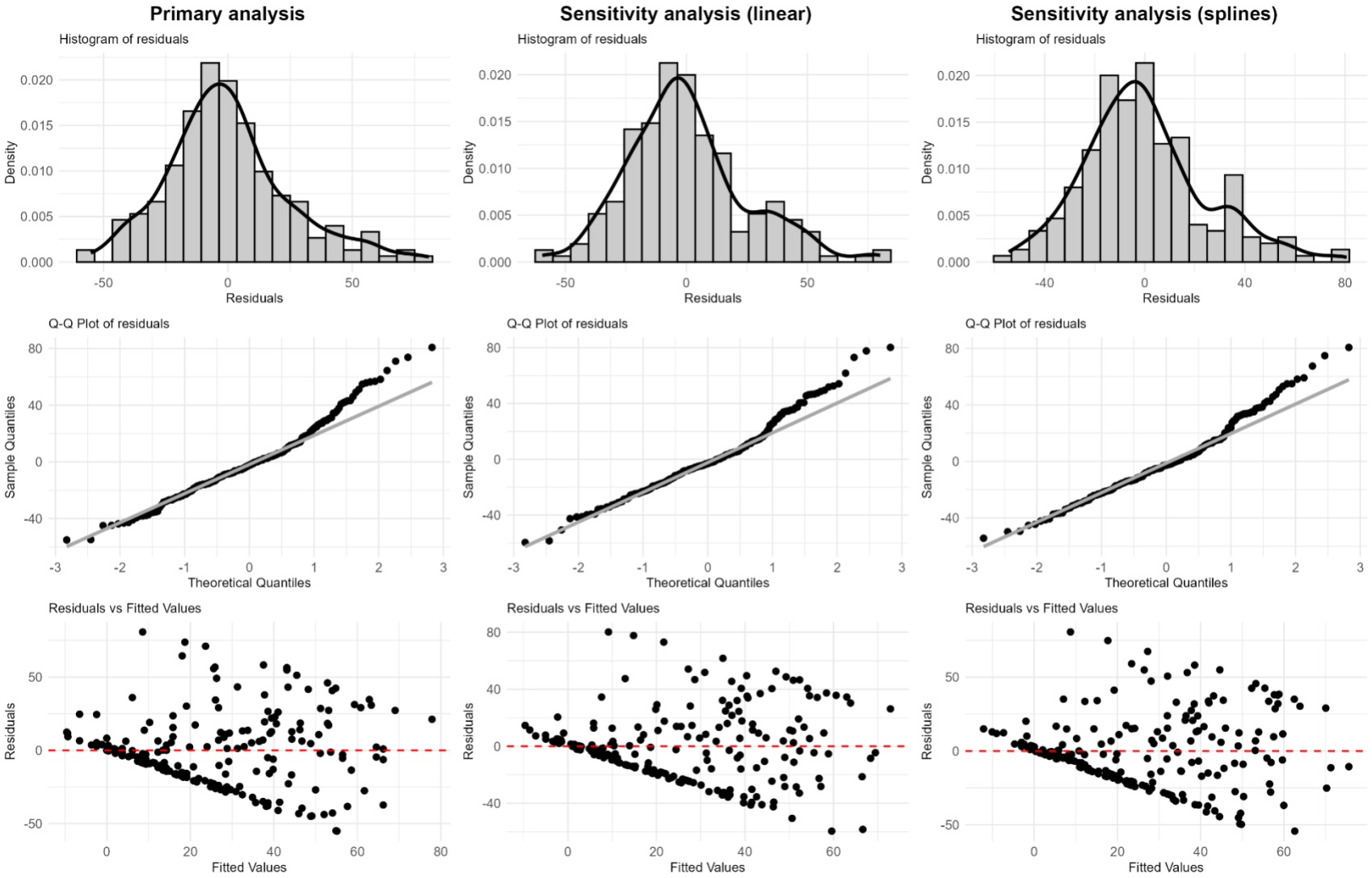

Figure 21: Histograms, Q-Q plots and scatterplots of residuals for primary multivariable models and both continuous variables sensitivity analyses.

9.3.7 Classification and Regression Tree

The three variables with the highest partial adjusted R^2 values in the primary multivariable analysis (Table 21) were included in descending order. For the first partition, habit (adjusted partial R^2 = 0.214) was dichotomised to "absent habit", for those with scores of 1 to 2 (indicating disagreement with the presence of habit for taking inhaled medicines) and "uncertain or reported habit", for those with scores of 3 to 5 (uncertainty or agreement with the presence of habit). Mean adherence for the "absent habit" group was significantly lower at 11.7% (95% CI 7.6 to 15.8%) compared to the "uncertain or reported habit group" of 41.0% (95% CI 34.7 to 47.3, p<0.001).

For the second partition, age category (adjusted partial R^2 = 0.047) was used. As 16-18y was the only category with a significant association with adherence in the primary multivariable analysis, this transformed via dummy coding to a binary variable, denoting age category 16-18y or not. In the "absent habit" subgroup, those who were 16-18y had lower mean adherence of 7.7% (95% CI 1.2 to 14.2) than those over 18y with a mean adherence of 12.3% (95% CI 7.7 to 17.0). In the "uncertain or reported habit group" those who were 16-18y had lower mean adherence of 19.5% (95% CI 7.1 to 31.9) than those over 18y with a mean adherence of 44.6% (95% CI 37.8 to 51.4).

For the third level, the binary variable of a complex inhaled medicines regimen (adjusted partial R^2 = 0.025) was used. There were no participants in the 16-18y age group who were prescribed a complex regimen therefore only those >18y were compared. In the "absent habit" subgroup, mean adherence for those >18y on a complex regimen was higher 27.6% (95% CI 14.0 to 41.3) than those >18y not on a complex regimen at 8.4% (4.1 to 12.6). In the "uncertain or reported habit group" subgroup, mean adherence for those >18y on a complex regimen was higher 49.3% (95% CI 39.7 to 59.0) than those >18y not on a complex regimen at 40.5% (95% CI 31.1 to 49.9). The full results are shown in Figure 22.

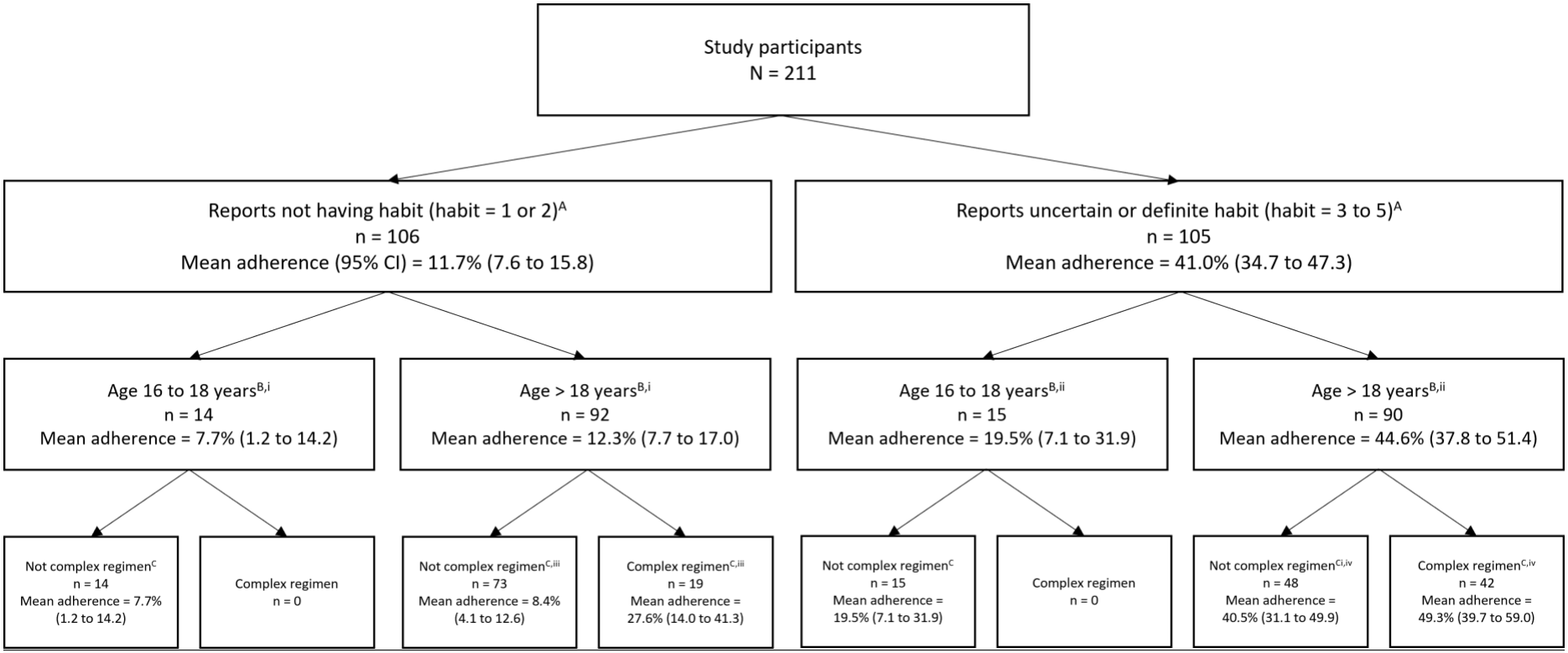

Figure 22: Classification and regression tree with comparison in mean adherence across subgroups.
Hypothesis tests for differences between groups gave the following p values: [A]p=<0.001; [B]p=<0.001; [C]p=<0.001; [i]p=0.685; [ii]p=0.008; [iii]p=0.009; [iv]p=0.24

9.4 Discussion

9.4.1 Main findings

In this analysis, the factors significantly associated with higher adherence to inhaled medicines were self-reported habit, being on a complex inhaled medicines regimen, higher socio-economic status and having a diagnosis of neurodivergence. Being in the 16-18y age category was associated with lower adherence. Having severe lung disease or caring responsibilities for children under 5 years of age were also associated with lower adherence and improved the performance of the final model, though these only reached statistical significance at a threshold of $p<0.15$.

Reassuringly, the results from the primary analysis were similar to those in the sensitivity analyses, particularly in the cases of habit and neurodivergence, which had statistically significant relationships in all three analyses. I am therefore more cautious in concluding that age, socio-economic status, and complex treatment regimens are associated with adherence. However, given that that adherence data are not missing at random, and the confidence in the imputation method, the fact that these significant associations were only found when imputed data were included highlights the importance of imputation to detect significant associations when they exist.

In addition, the results for neurodivergence may be affected by sparse data bias due to the small number of participants with a documented diagnosis of neurodivergence (n=9). This method of identifying neurodivergence is likely to underestimate the true prevalence due to NHS-wide challenges in accessing appropriate diagnostic services (362).

Overall, and considering the results of the classification and regression tree analysis, there are clear differences in adherence according to habit, age, and complex regimen, suggesting that the results from the primary multivariable analyses are valid and not just an artefact of an imperfect regression model.

9.4.2 Contribution to Programme Theory

The main contribution to the Programme Theory from this analysis is empiric support for the importance of habit in affecting adherence to inhaled medicines, as outlined in

several CMOCs (PBM_09b, PBM_10a-f). Additionally, that caring responsibilities for children under 5 was associated with lower adherence supports elements of Programme Theory related to how parenthood (and other competing life responsibilities, such a full-time work, which have become more prevalent for pwCF post-ETI) are barriers to adherence (CMOCs ETI_01, PBM_09b, PBM_10a). Where elements of Programme Theory were challenged by these data include that being prescribed a complex regimen, which one would expect to be more burdensome, was associated with higher adherence (CMOCs ETI_03, PBM_07) and that severe lung disease was associated with lower adherence (CMOCs INH_04). These findings are discussed, in turn, in this section.

The findings related to habit are consistent with previous work from the pre-ETI era demonstrating a significant association between habit and objective adherence to inhaled medicines (187, 279). Previous studies demonstrated this relationship in smaller populations (n=36 and n=61) using data specifically collected for research, whereas this analysis used routinely collected data across an entire Centre population, mitigating the impact of recruitment bias. Importantly, of all variables found to be significantly associated with adherence in the primary multivariable analysis, habit is the only one which is readily modifiable by behaviour change interventions, such as that offered by CFHealthHub (34).

All six treatment-specific factors (necessities, concerns, intention, self-efficacy, habit, and burden) were individually associated with adherence in bivariate analyses. However, in the multivariable model, only habit remained significantly associated. This does not imply that the other factors are unimportant but rather may reflect their interdependence and their sequential role in the formation of adherence habits.

The CFHealthHub intervention, which is explicitly designed to promote habit formation as a mechanism to sustain adherence, provides a useful framework through which to interpret this finding. The intervention operates sequentially: it begins by addressing beliefs about necessity and concerns, with the aim of forming an intention to engage with treatment through reflective motivation. Once sufficient motivation is established, barriers such as high perceived burden are addressed. At this point, fixed cues are introduced, and pwCF are supported to develop action plans for integrating inhaled

medicines into daily life. Feedback from electronic adherence monitoring is used to assess whether these plans are working, with the goal of building self-efficacy. These processes collectively support the development of habit, sustaining adherence through automaticity.

That habit remained the only factor significantly associated with adherence in the multivariable analysis may reflect its role as the culminating outcome of these interrelated psychological processes. Habit may act as a very proximal determinant of adherence, while the other factors may operate more distally, shaping the formation and maintenance of habit. This interpretation aligns with both the Programme Theory, recognising the importance of habit, and established models of behaviour change, which recognise that reflective processes often precede and give way to more automatic, habitual behaviours over time (363).

Tentative comparisons with pwCF in the pre-ETI era can be drawn using the non-intervention arm of the CFHealthHub RCT (n = 303), where similar measures were used to represent the same constructs as in this analysis. In the CFHealthHub RCT, mean objective adherence to inhaled medicines over 52 weeks in the non-intervention arm (n=238) was 39.4% (95% CI 35.3 to 43.6). Mean adherence in my study cohort was 26.4% (95% CI 22.2 to 30.7). Despite differential mean adherence, the baseline necessity and habit scores were comparable, as was the monotonic relationship between habit and adherence, with similar bivariate linear regression coefficients. The full comparison is shown in Table 26.

Table 26: Comparison with CFHealthHub RCT results

Variable	CFHealthHub RCT non-intervention arm (2017-19) N=303*		This analysis (2022-24) N=214	
	N (%)		N (%)	
% Adherence to inhaled medicines, mean (95% CI)	302 (99.7)	36.9% (33.3 to 40.6)	213 (99.5)	26.4% (22.2 to 30.7)
Necessity, mean (SD)	300 (99.0)	4.0 (0.84)	213 (99.5)	4.0 (0.98)
Habit, mean (SD)	300 (99.0)	3.3 (1.32)	213 (99.5)	2.88 (1.46)
% Adherence by habit score, mean (95% CI)				
1	30 (9.9)	20.8% (12.0 to 29.7)	46 (21.5)	6.4% (1.9 to 10.9)
2	62 (20.5)	23.0% (17.1 to 28.9)	60 (28.0)	15.8% (9.3 to 22.2)
3	62 (20.5)	26.5% (19.6 to 33.4)	23 (10.7)	29.6 % (17.3 to 41.9)
4	70 (23.1)	41.8% (35.5 to 49.0)	42 (19.6)	40.3% (30.3 to 50.4)
5	75 (24.8)	59.2% (51.7 to 66.7)	42 (19.6)	48.4% (37.4 to 59.4)
Bivariate linear coefficient for mean adherence by habit score	299 (98.7)	10.60 (8.13 to 13.10) R^2 0.194	211 (98.6)	10.89 (8.34 to 13.44) R^2 0.252

CI = confidence interval. SD = standard deviation. *238 RCT control arm participants had adherence data covering <52 weeks. Of these 53 had >12 months adherence data and 11 had 1 to 12 weeks adherence data. These data were used to impute for the entire 52-week period for these 64 participants and allowed them to be included in this comparison. A single participant had no adherence data and was excluded.

The lower adherence seen in the current study cohort may be explained by the recognised reduction in the use of inhaled medicines in the post-ETI era. Although CFTRm use in the RCT participants was not reported, at the time, fewer than 20% of adults with CF in the UK were prescribed a CFTRm, compared to nearly 90% in the current study cohort (364). Additionally, recruitment bias in the RCT may have contributed to higher adherence, as study participants are typically more engaged and may have a higher baseline adherence than the general population. This is reflected in the baseline mean adherence of 36.9% (95% CI 33.3 to 40.6) compared to 26.4% (22.2 to 30.7) in this cohort. The role of habit within the Programme Theory is discussed in more detail in Chapter 10.

A limitation of this analysis was that the psychological construct of habit was measured by the agreement with a single statement ("Using nebulised treatment is something I do without thinking"), derived from the SRBAI, giving a range from 1 to 5 (lowest habit to highest habit) (340). In the previous studies, habit was measured using all four items from the SRBAI which gives a range of 4 to 20 (187, 279).

Furthermore, as these data were collected as part of routine clinical care, there is the risk of participants reporting higher levels of habit (or indeed any of the treatment-specific factors included in this analysis), knowing these would be seen by their health care providers. Social desirability bias is well recognised in qualitative health research (365). Although these analyses used quantitative measures, the way the data are collected and utilised in clinical consultations creates the potential to be influenced by social desirability bias.

The similarity in regression coefficients for the bivariate analysis of habit and adherence between this analysis (10.89, 95% CI 8.34 to 13.44) and the pre-ETI CFHealthHub RCT (10.99, 95% CI 8.24 to 13.7) suggests that adherence still differs based on habit. While social desirability bias may have led to some over-reporting of habit, it was therefore unlikely to have been a widespread issue.

9.4.3 Additional significant associations

Age

The results for age were slightly unexpected. They are consistent with the recognised non-linearity between age and adherence, however previous work using MPR to measure adherence, suggest that the relationship is U-shaped, in that adherence is lowest in the 19-25y age group (150, 151). Electronically captured data in this analysis show a different relationship, where the 16-18y group have a lower mean adherence than 19-25y (Figure 23).

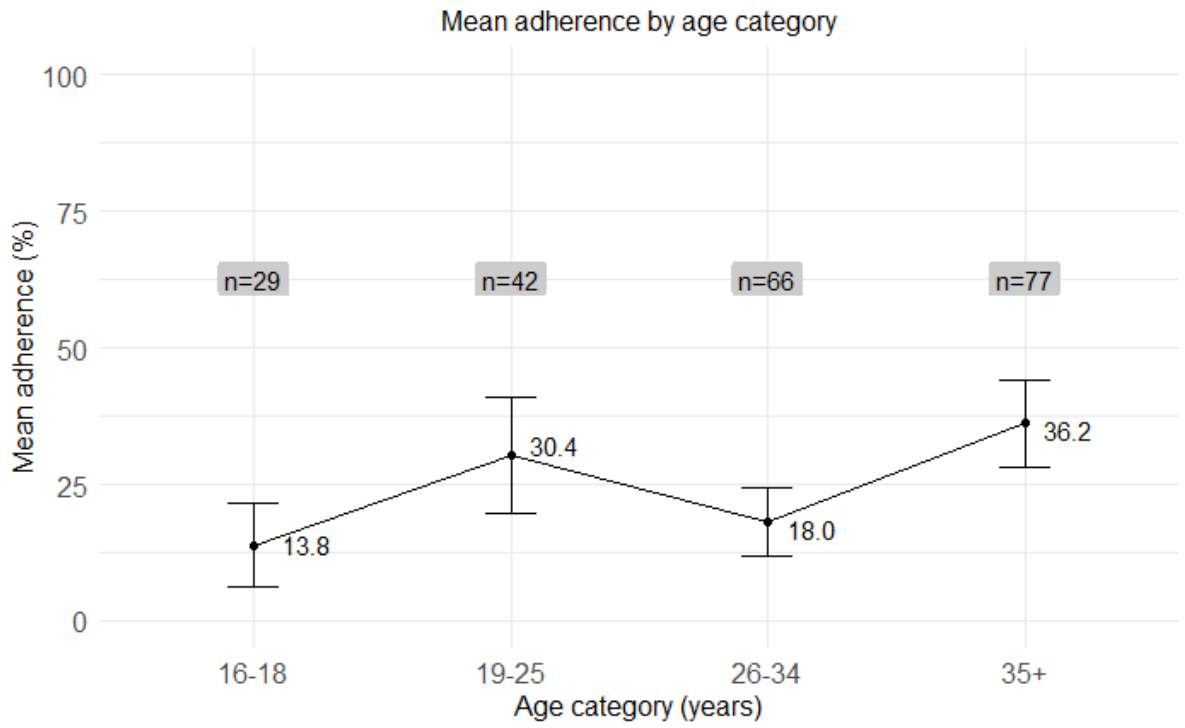

Figure 23: Line plot of mean adherence across age categories.
Error bars represent 95% CI.

Transition from paediatric to adult CF care generally begins around age 13, but the earliest age at which someone typically fully transitions to adult CF care is 16 (122, 366). All members of the 16-18y age group will have transitioned to adult care after the introduction of ETI in 2020, compared to the majority of the 19-25y group, most of whom would have transitioned before 2020.

Despite no meaningful difference in disease severity, measured by mean $\%FEV_1$, between the 16-18y and 19-25y age groups (in that the majority had mild lung disease with $\%FEV_1 \geq 80\%$), the mean number of daily prescribed inhaled medicines doses was significantly lower for those in the 16-18 year age group, as shown in Table 27. Given that pwCF with a $\%FEV_1$ of 95% would typically have similar treatment requirements to those with a $\%FEV_1$ of 87%, this discrepancy may represent a change in the paediatric Centre's approach with reduced use of inhaled medicines.

Table 27: Mean daily prescribed doses and $\%FEV_1$ by age category.

	Mean daily prescribed doses of inhaled medicines (mean, SD)	$\%FEV_1$ (mean, SD)	Adherence (mean, SD)
Age (years)			
16 - 18	1.6 (0.9)	94.8 (12.2)	13.8 (20.2)
19 - 25	2.7 (1.3)	87.0 (22.5)	30.4 (34.0)

$\%FEV_1$ = percentage of predicted forced expiratory volume in 1 second. SD = standard deviation.

In the first few years of transition from paediatric to adult care, a key priority for clinicians is building rapport and relationships, and the Programme Theory identified this as a potentially challenging time for pwCF and clinicians (CMOC PBM_26). Altering established treatment regimens from paediatric Centres, especially with the recognised uncertainty as to optimal treatment in the post-ETI era, risks impeding the relationship-building process. The relatively preserved lung function in the 16-18y age group (mean $\%FEV_1$ = 94.8%) and the sustained benefits of ETI, prescribed to 25 out of 29 individuals (86%) in this group, suggest that there would generally be less clinical urgency to modify existing inhaled medicines regimens or focus on adherence during consultations.

Furthermore, clinicians in this Centre have maintained a consistent approach to inhaled medicines post-ETI, in that withdrawal or reduction is rarely encouraged, whereas real-world data suggests this approach may not be seen across other Centres (309, 367-369). Therefore, the relationships between age and adherence described in this study may not generalise to other regions where there may be less divergence in prescribing practices between adult and paediatric Centres.

An additional consideration relates to the proportion of cases requiring adherence data imputation in each age category. As shown in Table 28, the highest proportion of missing data adherence was in the 16-18y age category (10/29, 34.5%). The single, mean imputation strategy using a value of 2.78% will have drawn the group mean closer to 2.78%. Whilst age was not significantly associated with adherence (p = 0.073) in the complete case sensitivity analysis, the direction and size of the coefficients were similar (-15.88 vs -17.22). This gives confidence that adherence is indeed lower in the 16-18y age category despite the effects of imputation.

Table 28: Missing adherence data across age categories in primary multivariable analysis

Age Group, years	Total cases, n	Cases with missing adherence data, n (%)
16 - 18	29	10 (34.5)
19 - 25	42	3 (7.1)
26 - 34	63	15 (23.9)
≥35	77	11 (14.3)

Acknowledging these caveats, the relationship between age and adherence, whilst still important, appears to have changed following the introduction of ETI. Further study in larger, multi-Centre populations may help a better understanding the relationship between age and adherence in the post-ETI era.

Socio-economic deprivation

This analysis found that adherence increased in line with increasing socio-economic status, defined by IMD quintile (coefficient 2.85, 95% CI 0.45 to 5.26, p = 0.020). A previous CF Registry analysis demonstrated that pwCF from the most deprived areas had worse clinical outcomes, were less likely to be prescribed inhaled medicines and more likely to require IV antibiotics than those in the least deprived areas (292). However, a previous analysis using a smaller sample of the same adult CF Centre cohort in the pre-ETI era (2013 to 2016) found no clear difference in adherence based on IMD quintile (278).

The detection of a significant relationship in my analysis compared to the previous analysis may be influenced by the larger sample size (n = 211 vs 102) and the ability to adjust for more independent variables. Nevertheless, the estimate of a difference in mean adherence between of 11.4 percentage points at extremes of IMD is relatively small, suggesting whilst it is important, it may not be as closely related to adherence as other variables explored in the analysis. Additionally, even for those in the least deprived areas (IMD quintile 5, n = 31), mean adherence is still low at 39.1% (95% CI 26.4 to 51.8).

Caring responsibilities for children under 5 years

In the primary analysis, those with caring responsibilities for children under 5 years o (n = 33, 15.4%) had lower adherence (coefficient -8.3, 95% CI -18.76 to 0.88), though this relationship did not reach the threshold for statistical significance (p = 0.074). Nevertheless, this is consistent with qualitative findings in the survey and focus groups where pwCF reported the competing priorities of childcare as a barrier to adherence (CMOC POBM_09b). Caring responsibilities may affect both the physical capability (i.e.

lack of time) and social capability (i.e. lack of headspace) which influence the behaviour of treatment taking, as per the COM-B model (161). This, alongside other commitments related to work and social priorities, emerged as key factor influencing adherence decisions in the current era.

In 2024, 116 women with CF had successful pregnancies, a doubling from 56 in 2020 (38, 370). With rising fertility in the UK CF population, driven by the effects of restored CFTR protein function in the female reproductive tract and improved health and longevity, this proportion is likely to grow, becoming an increasingly important factor for clinicians and intervention developers to address regarding adherence and health behaviours (371).

Severity of lung disease

Severe lung disease, as defined by a $\%FEV_1$ <40% was associated with lower adherence (coefficient -11.30, 95% CI -26.11 to 3.51), though this was not statistically significant in the primary multivariable analysis (p = 0.134). In contrast, descriptive and bivariate analyses suggested a trend toward higher adherence among those with severe lung disease, albeit not statistically significant. Qualitative findings from the Realist Evaluation so far also found that severe lung disease was a contextual factor which appeared to result in increased perceived necessity of inhaled medicines despite ETI, which, according to the Programme Theory was expected to result in higher adherence, as captured in CMOC INH_04.

This divergence between bivariate and multivariable findings may reflect Simpson's paradox, a situation in which an apparent trend observed in simple analyses is reversed when confounding variables are taken into account, which has been described in similar analyses where continuous variables are categorised (372). The reversal of the direction of association between $\%FEV_1$ and adherence from bivariate to multivariable analysis could also indicate a suppressor effect (373). A suppressor variable is one that enhances the predictive validity of another independent variable by accounting for variance irrelevant to the outcome, potentially obscuring or reversing the apparent direction of effect.

In this case, %FEV1 (as an indicator of severity of lung disease) may share meaningful variance with other variables in the final model, such as age or regimen complexity,

thereby altering its observed association with adherence. Given that %FEV_1 declines over time, participants with severe lung disease are likely to be older (51). As adherence is associated with increased survival, it is plausible that those with severe lung disease may have maintained higher adherence over time (150). However, disease severity could also reflect historic periods of lower adherence or other clinical factors (150).

It may be expected that those who were old enough to develop severe lung disease may have survived to an older age as a result of higher adherence. The mean age was 39.2 years (SD 10.4) in the 13 participants with severe lung disease, compared to a mean age of 31.0 (SD 10.4) in those with mild or moderate lung disease. Those who have severe lung disease and are older may be more likely to require a complex inhaled medicines regimen, though in this sample only 6/13 of those with severe lung disease (46.1%) were indeed prescribed a complex regimen. This underscores the value of multivariable model building and highlights that adjusting for relevant covariates is a methodological strength of this study. Additionally, this complexity when dealing with quantitative data, where multiple interrelated contextual factors (e.g. age, disease severity, treatment complexity) influence adherence, demonstrates the utility of a theory-driven realist approach to evaluation of complex behaviours.

Neurodivergence

These results suggest that those with neurodivergence will, on average, have a 20.24 (95% CI 2.19 to 38.30) percentage point higher adherence than those without, which was statistically significant (p = 0.028). I advise caution in interpreting the strength of this association. Whilst the co-efficient is the largest in the primary multivariable analysis, it also has the widest confidence interval and the lowest adjusted partial R^2 value of all significantly associated variables. Therefore, the result may be at least partially influenced by sparse data bias, where the true strength of associations can be distorted where few data points exist (352).

Of the nine participants with neurodivergence, three had mean adherence of 97 to 99%, three had missing adherence data and therefore imputed 2.78%, and the remaining three had adherence of 0%, 7.3% and 30.1%, respectively. The significant positive relationship and relatively high coefficient is heavily influenced by the three cases with high

adherence. With such few data points, there may be other characteristics of these three individuals, not captured in this analysis, which affected adherence. As discussed earlier, using a documented diagnosis of a neurodivergent condition does not capture the true spectrum of neurodivergence and likely underestimates the prevalence in this cohort. For example, those with milder symptoms or who had not received a formal diagnosis would not have been classified as having neurodivergence.

However, I do not dismiss these findings, as it is plausible that those with neurodivergence may find it easier to build routine and therefore habit, which is significantly associated with adherence. Furthermore, the heterogeneity of neurodivergence makes the binary classification used insensitive for fully exploring the effect on adherence.

Importantly these data do not suggest that the presence of neurodivergence is associated with lower adherence, which contrasts with qualitative data from the Realist Evaluation. Therefore, adherence interventions aimed at mitigating the effects of neurodivergence may be less helpful than those focussing on other factors such as habit.

Complex Regimen

Those prescribed a complex treatment regimen (which was defined as >3 doses of inhaled medicines prescribed daily) had a 10.5 percentage point (95% CI 2.12 to 18.87) higher adherence to inhaled medicines than those prescribed a standard treatment regimen (≤3 doses per day). This is consistent with previous findings in CF from the pre-ETI era, where higher adherence was associated with increasing numbers of inhaled medicines prescribed (151).

In other long-term conditions, such as asthma and acquired immunodeficiency syndrome (AIDS), a complex treatment regimen is associated with lower rather than higher adherence (20, 374) and simplifying treatment regimen, e.g. by reducing the number of daily doses prescribed, has been used to try support adherence (375, 376).

The conceptual relationship between regimen complexity and adherence is that it is mediated by perceived treatment burden. The findings of the Realist Evaluation so far would suggest that, for example, being asked to take 5 doses of medicine per day would

plausibly be more burdensome than 1 dose per day, so it might be expected to be associated with lower adherence.

In this CF Centre, where electronic adherence monitoring is embedded in routine care, when there is a clinical deterioration, the decision to escalate from a standard to complex regimen would likely be informed by adherence to the current regimen. The Centre also has a functioning medicines optimisation process, where medicines waste is actively reduced for those with lower adherence, and as such the likelihood of escalation to a more complex regimen with more daily doses prescribed is low (377). For those with low adherence, treatment failure may well be due to low adherence rather than an inadequate treatment regimen. Therefore, there is less chance of a complex regimen being advised, and instead a focus on adherence support would predominate. This phenomenon has also been described in the management of type 2 diabetes, though the authors attributed this to clinical inertia rather than active focus on adherence and waste reduction (378).

Therefore, those who are prescribed a complex treatment regimen are more likely to already have higher adherence and this relationship may exemplify reverse causation, where it is the higher adherence that has influenced the prescription of a complex regimen. These results may not be generalisable to other CF Centres, particularly those who do not use electronic adherence monitoring, as it may be that they are more likely to respond to clinical deterioration with treatment escalation rather than addressing adherence.

This also highlights the complexity of the concept of burden as a barrier to adherence. A simplistic definition of burden may consider only the number of treatments/doses prescribed, however both this analysis and aforementioned CF study would challenge that definition (151). As shown in Figure 24, the mean perceived burden of inhaled medicines was similar across all ranges of daily doss prescribed.

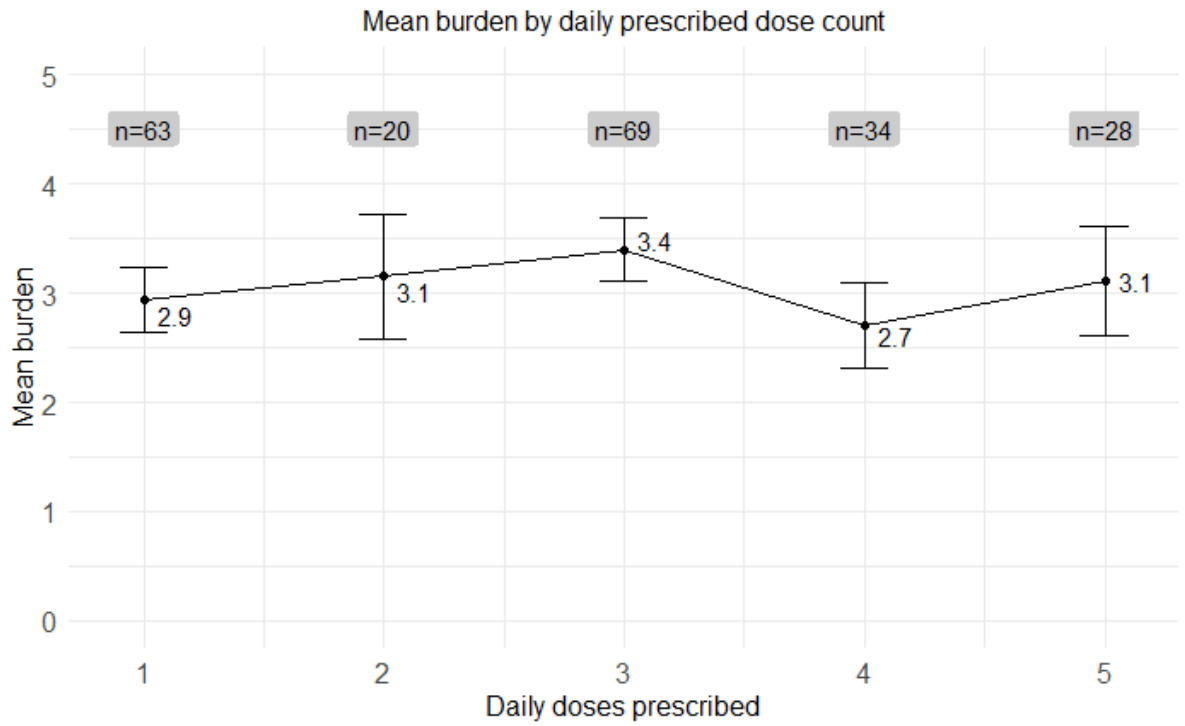

Figure 24: Line plot of mean burden by number of daily doses prescribed.
Error bars represent 95% CI.

The qualitative data collected throughout this study also highlighted the multi-faceted nature of perceived burden, related not only to the number of doses prescribed but also the social/stigmatising aspects of burden and the requirements for nebuliser device setup and maintenance.

9.4.4 Strengths

This analysis had multiple strengths. Whilst convenient, self-reported adherence to inhaled medicines is typically higher than that recorded via electronic data capture and therefore considered less accurate and is prone to being affected by social desirability bias (146, 379, 380). Additionally, whilst MPR and prescription data are may be more accurate measures of adherence than self-report (113, 321), they may still over-estimate true adherence compared to electronic data capture at the time of medicine administration (381, 382). A recent Cochrane review concluded with a recommendation to measure adherence to inhaled medicines in CF using electronic data capture where possible (383). This is the first analysis using electronically captured adherence data to explore determinants of adherence in the post-ETI era.

The imputation strategy allowed inclusion of the entire Centre population in the analysis, which is a key strength of this approach. Alternative study designs, such as research interviews or a questionnaire may have been affected by selection bias, where those who participate in CF research studies are known to be different to those who do not (347-349). By using routinely collected data only, with a robust imputation strategy, the entire Centre cohort could be included, encompassing the full range of adherence and engagement. Whilst the requirement for imputation introduces some uncertainty, the complete-case sensitivity analysis results provided support to conclude that the results of the primary analysis were robust.

9.4.5 Limitations

The outcome measure was the aggregated, mean daily adherence over a 12-month period. For example, on any given day, adherence for a pwCF prescribed 2 doses of inhaled medicines is either 0%, 50% or 100%. In this analysis, these coarse values were aggregated and averaged to give a value on a 0-100% scale representing adherence over the 12-month study period. This means that very different patterns of treatment-taking (e.g. sustained low adherence vs short periods of high adherence followed by periods of no adherence) may be indistinguishable. However, the effects of different levels of adherence on health outcomes, particularly long-term outcomes of interest in CF, such as FEV_1 decline and exacerbation rate, are not instantaneous. The aggregate value used represented a participant's overall exposure to inhaled medicines over the 12-month period, which would be expected to influence outcomes.

A single, mean imputation method was chosen under the assumption that data were not missing at random. With missing adherence data affecting 40 (18.7%) of participants, a substantial portion required imputation. This approach may have underestimated true adherence for those with missing data and, as demonstrated in the scatterplots of residuals vs fitted values, affected the model outputs, though the complete-case sensitivity analysis provided reassurance for the key findings. An alternate approach using multiple imputation, including by chained equations, could be considered in future validation studies, though these are predicated on the assumptions of data missing at

random and may introduce bias when data are missing not at random, as assumed in this case (384).

As discussed, an additional limitation included the low event rate for some variables such as "looked after children" (n=6) and alternate residential circumstances (n=5). This reduced the statistical power of the models to detect true associations and conversely may have inflated true associations, as may have been the case with neurodivergence (n=9), or have led to overfitting.

Using routinely collected data mitigated the impact of selection bias but required utilisation of single questions from validated questionnaires measuring the treatment-specific factors. This may have affected the measurement of these complex psychological constructs. Social desirability bias may have influenced self-report of the treatment-specific factors and there is inherent limitation in reducing such complex factors to a single piece of quantitative data.

This analysis was carried out in a Centre where the CFHealthHub approach to adherence support through habit formation was well-embedded. PwCF may already have been sensitised to thinking about these psychological constructs, which may have improved accuracy of reporting but also means results may not generalise to Centres where this approach is not embedded. A further potential limitation of single-centre study is the generalisability of the study cohort to the UK-wide adult CF population. Reassuringly, whilst the study cohort were slightly younger than the UK average, overall characteristics were broadly similar, as shown in Table 29.

Table 29: Comparison of demographics between study cohort and UK adult CF population

	Study cohort	**UK adult CF population**
Age (years), mean	31.5	34.2
Sex (male), %	51.9	53.9
Ethnicity (White British), %	94.4	94.5
BMI, mean	25.2	24.4
%FEV_1, median (IQR)	84.8 (63.8 to 97.5)	81.4 (62.0 to 96.0)

BMI = body mass index. %FEV_1 = percentage of predicted forced expiratory volume in 1 second. IQR = interquartile range.

Whilst there are advantages to using of real-world data, such as wider inclusion of participants within a population, there are also recognised limitations in the lack of granularity compared to research data (385). Data quality can be affected by the

methods through which it is collected, for example there was reliance on accurately coded diagnoses of CFRD and neurodiversity in the EMR. To mitigate this, stringent definitions were used and only those variables which we believed would be accurately and objectively coded were included.

9.5 Conclusions

This analysis used quantitative data to answer the third research question (*"What factors are associated with adherence to inhaled medicines for pwCF in the post-ETI era?")*. These findings support the inclusion of habit as an important determinant of adherence in the Programme Theory and is consistent with pre-ETI studies. Additional treatment-specific factors such as perceived necessity and treatment burden also had significant associations with adherence in bivariate analysis. These results demonstrated how age, complex treatment regimens, socio-economic status and neurodivergence had statistically significant associations with adherence, which supported other aspects of Programme Theory developed in the Realist Evaluation. These may also be considered importance contextual factors for future Realist study. A detailed discussion of the findings of the entire study follows in Chapter 10.

Of all factors significantly associated with adherence in the primary multivariable analysis, habit is the only readily modifiable factor with RCT-level evidence for a habit formation intervention (34). This analysis supports continuing to consider habit formation an appropriate strategy for supporting adherence in CF which may also generalise to other long-term conditions.

10. Discussion

10.1 Introduction

This study has examined the impact of ETI and the COVID-19 pandemic on perspectives and behaviours surrounding inhaled medicines and models of care within CF. Through qualitative interviews with clinicians, the first research question ("*How have ETI and the COVID-19 pandemic shaped perspectives of CF clinicians on inhaled medicines and the demands on their services?*") was answered. Building on insights from the clinician interviews, the second research question ("*How have ETI and the COVID-19 pandemic shaped the experiences and care needs/preferences of pwCF?*") was answered through a national survey and focus groups with pwCF. Insights from these qualitative data collected from both clinicians and pwCF provided some insights into the answer for the third research question ("*What factors are associated with adherence to inhaled medicines for pwCF in the post-ETI era?*"). A cross-sectional regression analysis, quantitatively tested feasible determinants of adherence, revealing five factors significantly associated with adherence to inhaled medicines in a multivariable regression analysis.

Using the aforementioned data, this study developed an explanatory theory addressing how these important contextual changes have shaped the perception of the role of inhaled medicines for both pwCF and clinicians, the evolving care needs and preferences of pwCF, and the implications for UK specialist adult CF services. In this chapter, I discuss the findings of this Realist Evaluation, paying particular attention to the generative mechanisms which are theorised to be driving varying outcomes the real world.

10.2 Key points

The following list of key points presents the key findings in this study. Each is discussed in more detail throughout this chapter.

1) Habit remains strongly associated with adherence but is highly context-sensitive and may be easily disrupted.

2) The presence of symptoms and whether treatments provide noticeable impacts influences adherence.
3) Many pwCF want to rationalise their inhaled medicines regimen with a hope to reduce overall treatment burden, in light of ETI-driven improvements. They may do this autonomously if it is not supported by their care providers.
4) Where there is uncertainty as to the role of inhaled medicines, CF clinicians value objective data (e.g. lung function and published evidence) whereas pwCF value subjective data (e.g. symptom burden) in determining its role. This epistemological dissonance strains the therapeutic relationship.
5) PwCF have evolving care needs and preferences for care delivery. Virtual care has a clear role in certain cases, however abrupt changes to a long-established care model can result in feelings of abandonment in other cases. A personalised approach is required.

10.2.1 The role and nature of habit

In the pre-ETI era, habit and routine had a strong relationship with adherence to inhaled medicines (187, 279). As a result, the CFHealthHub intervention utilised habit formation to improve adherence, as demonstrated in the CFHealthHub RCT (34). This study demonstrated that habit remains an important consideration in determining adherence to inhaled medicines in the post-ETI era. This finding directly answered the third research question (*"What factors are associated with adherence to inhaled medicines for pwCF in the post-ETI era?")*. However, this study revealed a range of complexities surrounding the formation, maintenance, and resilience of habits that warrant careful consideration by those seeking to use this mechanism to support long-term adherence. As illustrated in CMOCs PBM_10a to PBM_10f, habits manifest in diverse forms.

The method and setting in which a habit is established, as well as the degree to which it becomes embedded, significantly influence its capacity to withstand dynamic contextual changes to sustain adherence. The highly context-sensitive nature of cue-dependent habit has drawn criticism, as has the over-reliance on habit for long-term behaviour change interventions (386, 387). Previous work concurs with the finding of this

study, in that there is intra-person variability in how important a role habit plays in sustaining behaviour (388).

In line with the CFHealthHub intervention and informed by the COM-B model of behaviour change, supporting adherence to inhaled medicines begins with motivation, specifically by addressing the perceived necessities and concerns of pwCF regarding their prescribed regimen of inhaled medicines. Hospital admissions may provide a valuable opportunity to initiate habit formation, as the heightened salience of CF during acute episodes of illness increases the perceived health threat and thereby perceived necessity, giving rise to motivation to take treatment. Additionally, the structured clinical environment may help to alleviate concerns or mitigate barriers, increasing the capability and opportunity for treatment-taking.

However, when habits are formed primarily in response to the salience of an exacerbation or the routines imposed by the hospital setting, they may not be sustained upon discharge, as they fail to transfer effectively into an individual's typical routine. This failure may lead to emotional responses such as guilt or shame, which may, in turn, either motivate pwCF to re-engage with adherence support or, as was described by pwCF in this study, undermine their motivation further, leading to reduced self-efficacy and sustained low adherence.

Acknowledging the context-sensitive nature of habit, supporting adherence through home-based interventions and by aligning treatment-taking with stable routines outside the hospital setting can foster habits that are more likely to be sustained in everyday life. However, no routine remains entirely stable over time. Anticipated disruptions, such as holiday travel, pose a threat to the continuity of habitual adherence. At these times, automatic motivation involving habitual processes may no longer be enough to sustain adherence, and instead pwCF are required to engaged in reflective motivation, where decisions to take treatment must be taken more deliberately (161).

For some pwCF, where treatment-taking is deeply embedded in their identity and they have a clear intention to maintain adherence, they achieve this by actively adapting their holiday routines and resourced to incorporate capability and opportunity for treatment-taking. In contrast, when required to reflect on treatment-taking in the face of disruption,

others perceive a brief interruption in treatment as low risk, particularly when weighed against the practical burden of transporting and administering inhaled medicines while travelling. In such cases, individuals may make a conscious decision to temporarily pause treatment.

When pre-existing habits are well-embedded and necessity beliefs for treatment are strong, treatment-taking tends to be effortlessly re-integrated into the existing routine upon return. However, for pwCF with lower necessity beliefs or ongoing challenges in maintaining routine adherence, such interruptions may give rise to a more permissive mindset, whereby holidays are construed as a break from treatment itself. This may result in greater difficulty re-establishing prior habits of treatment-taking once routine life resumes.

Notably, and consistent with the aforementioned critique of over-reliance on habit formation as a mechanism for supporting adherence, one focus group participant (pwCF_07) described a deeply embedded, identity-based habit of inhaled medicine use, characterised by minimal perceived burden and consistently high adherence. However, following initiation of ETI, the marked improvement in symptoms prompted a re-evaluation of the necessity of inhaled medicines, ultimately leading to discontinuation. In this case, both subjective experiences and objective health indicators remained stable following cessation, reinforcing his decision to continue without inhaled medicines. This case illustrates that even highly ingrained habits, including those tied to personal identity, may be disrupted when perceptions of necessity change, particularly when these are validated through lived experience (286).

10.2.2 Symptoms and noticeable effects drive adherence

This analysis identified that symptom burden, current perceived health state and whether inhaled medicines have a noticeable impact were key factors which pwCF considered to influence adherence to inhaled medicines, answering the third research question (*"What factors are associated with adherence to inhaled medicines for pwCF in the post-ETI era?"*). This finding is consistent with previous studies in CF (280, 389).

Many pwCF experience unprecedented improvements in health and well-being from ETI, which has given rise to restored wellness as a key mechanism driving behaviour in the post-ETI era, where improvements in health have led pwCF to re-evaluate the necessity of established treatments such as inhaled medicines, especially when they are considered burdensome. This was captured across several CMOCs, including ETI_02d and PBM_05a,06,09a,10f,12,16,19 and directly relates to the second research question (*"How have ETI and the COVID-19 pandemic shaped the experiences and care needs/preferences of pwCF?"*), in that changing clinical features of CF have impacted needs and preferences of pwCF.

Inhaled mucolytics thin and aid clearance of mucus. Therefore, it is understandable that their necessity is questioned in the context of pwCF with low or absent sputum production, as captured from a pwCF perspective in CMOC PBM_12 and a clinician perspective in CMOC INH_04. This rational uncertainty, as described in my study by both clinicians and pwCF, is consistent with findings of a USA-based survey exploring the same issue (390).

There appears to be less uncertainty regarding the sustained necessity for inhaled antibiotics, compared to mucolytics, in the post-ETI era. Concerns about untreated and persistent chronic *Pseudomonas* infection was cited by pwCF and clinicians throughout this study as a reason for continuing inhaled medicines post-ETI. This was captured from a pwCF perspective in CMOCs PBM_02,12,18, and a clinician perspective in CMOC INH_05.

However, the accurate detection of pathogens, in particular *Pseudomonas*, is more challenging in the post-ETI era, due to a reduction in sputum sampling, Established methods for defining chronic *Pseudomonas* infection use either the proportion of samples with *Pseudomonas* growth over a defined time period (the Leeds criteria (391)) or a combination of pseudomonas serology, strain typing and clinical context (the CFHealthHub criteria (316)).

With the reduction in sputum production post-ETI, clinicians are now becoming increasingly reliant on cough swabs to detect *Pseudomonas*, which have a lower sensitivity than sputum samples (392, 393). In 2023, The CF Trust reported the proportion

of adults with CF meeting the criteria for chronic *Pseudomonas* infection (as defined by the number of positive samples over 12 months) as 13.6%, a reduction from 41.0% in 2019 (38, 364). This dramatic decrease may reflect the reduced sensitivity of sample-based criteria, rather than a true reduction in the presence of chronic *Pseudomonas* infection in pwCF. This concerns leads some clinicians to recommend more intensive testing for *Pseudomonas*, as captured in CMOC INH_05.

Recognising these uncertainties, post-ETI therapeutic rationalisation trials have focussed specifically on withdrawal of mucolytics rather than antibiotics (116, 217). To date, only one randomised trial (SIMPLIFY) has compared the effects of stopping versus continuing mucolytics for pwCF taking ETI (116). There was no difference in lung function between those who were randomised to stop or continue inhaled medicines.

However, SIMPLIFY was a short trial (6 weeks) and included pwCF with near-normal lung function (mean %FEV_1 = 96.9). Whilst the results are encouraging, the study does not consider the potential long-term impacts of discontinuing mucolytics on outcomes such as life expectancy or exacerbation rate, and therefore clinicians are advised to use this evidence with caution (79, 117). Additionally, a sub-study within SIMPLFY, which recruited pwCF with lower lung function (%FEV_1 40 to 59%) demonstrated decreased lung function for those discontinuing but increased lung function for those continuing mucolytics, though these differences were not statistically significant (394). It is important to note that, in the pivotal RCT for ETI, all pre-existing treatment, including inhaled medicines were continued (105).

However, as was clear in my study, in the real-world, decisions to reduce or withdraw inhaled medicines are being made by pwCF with greater value being placed on lived experience and symptom burden than the published evidence base. This was captured in CMOCs ETI_02d, PBM_05b,12. This is also reflected in the 24-week follow-up period for SIMPLIFY, where up to a third of study participants did not restart the withdrawn medicine after the study period ended, prior to any results being published (369).

This highlights one of the key contextual challenges of the post-ETI era. Clinicians caring for pwCF must balance both recognition of the burden of treatment for pwCF with the probabilistic long-term health benefits of maintaining high adherence, informed by

professional experience and the published evidence base. This is the foundation upon which shared decision-making is based, in that there is the recognition that medical evidence and clinician recommendations have a role, yet the perspectives of pwCF must also be respected and considered.

This challenge is widely recognised in the context of prescription medicines for long-term conditions, where the rationale for treatment is long-term (not short-term) benefit. For example, in individuals with atrial fibrillation (AF), oral anticoagulation lowers the long-term risk of stroke. However, those who start oral anticoagulation may not experience immediate benefits and may actually encounter side effects (395). Despite this, the rationale for treatment is the reduction in the risk of stroke in the long-term. Decisions which pwCF make around treatment taking, when considering long-term outcomes (such a prolonged life) are similarly probabilistic (396). Keyte *et al*. remarked that this apparent shift towards pwCF relying on restored wellness to inform decisions around treatment taking is consistent with a lay perception of health, but risks being inaccurate, and may even be influenced by factual misunderstandings (397).

Another complexity arising from symptom-driven approaches to treatment relates to a change in the experience and perception of exacerbations in pwCF taking ETI. Whilst a universal definition of pulmonary exacerbations has always been lacking, as identified in a recent scoping review, there is general agreement that they consist of an increase in symptoms (e.g. cough, breathlessness or sputum production) accompanied by a reduction in lung function (275). The increase in symptoms, along with decrease in objective measures of lung function makes exacerbation salient to both pwCF and clinicians (390). Treatment of pulmonary exacerbations typically includes initiating courses of oral or intravenous antibiotics, consideration of admission to hospital and focussed chest physiotherapy alongside inhaled medicines (79, 398).

Clinicians and pwCF in this study agreed that, post-ETI, there may be no change in symptoms despite a drop in lung function, which would typically constitute a recognised exacerbation, as captured in CMOCs PEX_01,03. This may both falsely reassure pwCF and clinicians that a change in treatment, for example a short course of oral or intravenous antibiotics, targeted chest physiotherapy or a focussed period of adherence

support, is not required. This finding related to both the first (*"How have ETI and the COVID-19 pandemic shaped perspectives of CF clinicians on inhaled medicines and the demands on their services?"*) and second research questions (*"How have ETI and the COVID-19 pandemic shaped the experiences and care needs/preferences of pwCF?"*), in that demands on CF services have changed as a result of changing care needs for pwCF.

These findings are consistent with a recent study of CF clinicians based in the USA, where they recognised that exacerbations were now subtle, often do not lead to pwCF seeking care due to lack of recognition, less worrying for clinicians and treated less aggressively than in the pre-ETI era (276). Therefore, when relying on pre-ETI indicators of exacerbation, such as increases in cough, to expecting similar outcomes and treatment recommendations is unrealistic. In the context of so much uncertainty, there is a requirement for further research into defining and managing pulmonary exacerbations in the post-ETI era (276).

10.2.3 Approaches to therapeutic rationalisation

Perceived treatment burden has long been cited as a significant barrier to adherence for pwCF, incorporating a direct infringement on daily activities (182). Previous work has highlighted how pwCF may feel burdened by the requirement or expectation to adhere to treatment regimens whilst balancing this with efforts to live a "normal" life (281). Participants in my study provided greater insight into this, by highlighting how the possibility for a "normal" life, including features such as full-time work, parenthood, marriage, and social opportunities, has been enabled by the improvements in health offered by ETI. One participant even demonstrated a quite extreme transformation in terms of his fitness and exercise capability, indicating he was now fitter than his friends who don't have CF.

In light of restored wellness, treatment burden is perceived differently. As outlined in the Health Belief Model, decisions around health behaviours, such as adherence to treatment, are contingent on a balance between perceived health threat, cues to action and an assessment of barriers and benefits of treatment (274). When the perceived health threat and cues to action are lower, as I have found is the case for many pwCF in

the post-ETI era, the threshold of benefit required to overcome the barrier of burden is higher, leading to lower adherence. This is consistent with previous studies which identified barriers as a Health Belief Model construct significantly associated with adherence to inhaled medicines (399). This is captured in CMOC ETI_04 and also in relation to delayed detection of pulmonary exacerbations in CMOC PEX_01. For many pwCF, the perceived benefits have reduced to the point where the effort required to overcome treatment burden to maintain daily adherence to inhaled medicines is no longer considered worthwhile. This directly answered the second research question (*"How have ETI and the COVID-19 pandemic shaped the experiences and care needs/preferences of pwCF?"*) and demonstrated how care preferences and perspectives on inhaled medicines have changed since the introduction of ETI.

Whilst it is natural for clinicians to aspire to support all pwCF to maintain high adherence, a personalised approach may include efforts to determine what level of adherence allows pwCF to enjoy their life as a whole, as captured in CMOC PBM_26 (281). This is consistent with a recent discrete choice experiment study where pwCF indicated they were prepared to trade-off reductions in lung function and additional life expectancy to reduce treatment burden (265). This was also reported by pwCF_13 in my study, who advised he would trade a degree of lung function for the ability to discontinue inhaled mucolytics.

Trading long-term, probabilistic benefits for immediate, more prominent burden reduction, however, may be a manifestation of temporal discounting bias, as captured in CMOCs ETI_02d and PBM_03 (400). Clinicians should consider this, alongside the information needs of pwCF when engaging in informed discussions as part of shared decision-making.

Interestingly, my findings suggest that one reason for pwCF considering inhaled medicines as equally as or more important than pre-ETI is to sustain the benefits of ETI into older age. This suggests those who take this longer-view of the benefits may have higher adherence or at least sustain the perceived necessity of inhaled medicines in the post-ETI era, as captured in CMOCs ETI_02d, 03 and PBM_03.

Whilst it was beyond the scope of this work to make definitive recommendations regarding therapeutic rationalisation, it is important for pwCF and clinicians to be aware of the complex decision-making process which is ongoing across the CF population. With an appreciation of the psychological and behavioural mechanisms that are driving decisions I hope to inform better two-way dialogues between pwCF and clinicians.

In recognising the uncertain role of inhaled medicines for pwCF on ETI, especially in those with little or no symptoms and improvements/stability in objective health measures, these data suggest clinicians typically remain conservative and hesitant in recommending changes to established, evidence-based treatment regimens such as daily inhaled medicines, as captured in CMOCs INH_01,04-07. Conversely, pwCF may prefer to respond differently and advocate for changes and treatment reduction, as captured in CMOCs PBM_01,03,05a,06,09a,12,13a,14 and INH_03,06-08.

This discordance has also been described in two other post-ETI studies of both children and adults with CF (264, 397). It can be unsettling for clinicians, when treatment withdrawal is seen to undermine the professional duty to protect and promote health (401). In particular, clinicians interviewed in my study cited evidence of severe/structural lung disease and confirmed chronic *Pseudomonas* infection as key contextual factors where they would consider the role of inhaled medicines to be absolutely maintained to prevent deterioration.

A large national survey from the USA including pwCF and clinicians overwhelmingly indicated that trials of therapeutic rationalisation should be considered in the context of ETI (390). Clinicians in my study cited a lack of published evidence to support withdrawal of medicines for pwCF on ETI as a reason why to not support this strategy. Additionally, clinicians reported fearing the uncertain consequences of de-prescribing. PwCF and clinicians in my study doubted the external validity of large population-based trials to inform these decisions. Similar perspectives were reported in a recent study, where CF clinicians in Australia were interviewed about the barriers and enablers of “de-prescribing” post-ETI (402).

In my study, several participants expressed a desire to experiment with their own treatment, with some reporting firsthand experiences of doing so, which aligns with the

findings of other post-ETI studies (264, 389, 402). This gives rise to another key mechanism that appears to be driving behaviour in the post-ETI era. Autonomy reclamation is a motivational mechanism where pwCF who feel well seek to reclaim control over their healthcare, driven by a renewed hope for normality and a desire to reduce medical intrusion, as captured in CMOCs ETI_01, PBM_01 and INH_06-07. This manifests as autonomous decisions to engage in therapeutic rationalisation, where treatment regimens are reduced with or without the knowledge or approval of clinicians. Previous work recognised that children with CF also demonstrate reclaimed autonomy and engage with therapeutic rationalisation, in the context of restored wellness post-ETI (264).

This rationalisation includes features of symptom-driven adherence, where pwCF have periods of high adherence prompted by increases in symptoms, which are not sustained post-recovery, as captured in CMOCs PBM_10b and PBM_15. Some participants also described how they consider inhaled medicines as a treatment best reserved for times of ill health, a view which been described in previously in CF, and was captured in CMOC PBM_05a (264, 279, 403). Clinical guidelines recommend inhaled medicines as long-term maintenance treatment and there is no clinical evidence to support the efficacy of "as required" regimens (54). The only exception would be the first detection of *Pseudomonas* infection, when a 3-month eradication course of inhaled antibiotics might be prescribed (48, 54). However, eradication is often unsuccessful, leading to chronic *Pseudomonas* infection where long-term antibiotic treatment is indicated (49). Importantly, clinicians should consider that the absence of evidence in the scientific literature may not play a significant role in the decisions that pwCF make regarding treatment, and hold much less weight than perceived necessity, burden and current health status (404).

While such self-directed experimentation may align with principles of patient-centred care and autonomy, particularly in respecting the preferences of pwCF for reducing treatment burden, it also presents an ethical challenge for clinicians, particularly concerning the principles of non-maleficence and beneficence. Clinical frameworks, such as the PLUTO framework described earlier in this thesis, may help in this situation,

where clinical parameters are frequently monitored and considered against contemporaneous levels of adherence to treatment (221).

In light the transformative effects of ETI, a consequence of autonomy reclamation, from the perspective of CF clinicians, appears to be professional disempowerment**,** a normative mechanism resulting from disruption to professional authority, as captured in CMOCs INH_01-03. Clinicians interviewed in this study reported feeling less confident in making treatment recommendations due to the absence of an evidence base, particularly as they observe patients actively engaging in therapeutic rationalisation. Some clinicians responded to this by increasing the adoption of shared decision-making, advocating for close monitoring to identify deteriorations rather than continuing to advocate the use of inhaled medicines, especially when the therapeutic rationale was either unclear to the clinician or not accepted by pwCF, as captured in CMOCs ETI_03, INH_01, and INH_04.

At this point, I consider the definition of adherence, and how this term could be problematic when attributing value judgements or aspirations to "higher adherence." As discussed in Chapter 2, adherence can be defined of as "*the extent to which the patient's behaviour matches the prescriber's recommendations" (18)*. If the prescriber is unsure what to prescribe in order to give the person they're caring for the best outcomes, then to use "adherence" to the prescribed regimen as a marker of quality of care may be problematic. This not an exclusive post-ETI phenomenon. This definition of adherence is inherently linked to the regimen that is prescribed, rather than the regimen which is proven to be efficacious, and has been a contentious point throughout the journey of CFHealthHub (345, 354). Whilst it is beyond the scope of this work to define optimal therapeutic regimens, it continues to be an important consideration when it comes to making recommendations about addressing adherence to inhaled medicines in the post-ETI era.

10.2.4 Epistemological dissonance between pwCF and clinicians

Epistemological dissonance, another key mechanism found in this study, appeared to be driving some tension and disagreement between pwCF and clinicians relating to health indicators, as captured in CMOCs ETI_02b and INH_02. Epistemological

dissonance is a cognitive-relational mechanism, resulting from disagreement between how “knowledge,” or in this case “optimal health,” can be accurately determined. This work demonstrated how PwCF and clinicians prioritise different types of evidence when assessing health status and treatment need. PwCF seem to value subjective health indicators, such as symptoms and overall wellness to determine the health status and thus the necessity for treatment, whereas clinicians value objective indicators, such as lung function, more highly. This dissonance is captured in CMOCs ETI_02b,d, PBM_05a-b,12 and relates to all three research questions.

When there is concordance between these indicators, there appears to be less conflict and more agreement on the rationale for increasing or initiating treatment, which is captured in CMOC ETI_02e and is consistent with another post-ETI study (390). However, when there is discordance between subjective and objective health measures, as there increasingly is in the post-ETI era, there is disagreement and discomfort resulting in variation in treatment recommendations and behaviours.

Work in other long-term conditions has shown that better relationships between clinicians and people with long-term conditions leads to higher adherence (405). Additionally, the quality of communication and trust, which are feature of these relationships appear to play be important significant role ingredients of such relationships (406, 407). This is consistent with my finding that, for some people who considered inhaled medicines equally or more important than pre-CFTRm, this was driven by the fact that their clinicians recommended that it remained important, even when they reported not understanding that rationale. In a setting where uncertainty exists for pwCF, it is reasonable that the advice of a trusted clinician who communicates well may encourage a certain behaviour, as captured in CMOC PBM_05b. Recognising that this is important, the fact that multiple clinicians interviewed in Chapter 4 also reported uncertainty about what to advise pwCF regarding inhaled medicines could understandably lead to lower adherence.

Epistemology in health care has evolved over recent decades, moving from objective primacy (e.g. blood test results) to an incorporation of subjective information (e.g. self-reported quality of life measures) as evidence of health and benefit (or harm) (408). This

is philosophically consistent with adoption of shared decision-making and considering the health consultation as meeting between experts: the clinician(s); and the patient. My findings provide evidence that, when there is uncertainty regarding optimal treatment and epistemological dissonance, the result is a highly variable, complex therapeutic landscape.

10.2.5 Changing models of care

Recent work from the CF Foundation and European CF Society (ECFS) recognises many of the complexities identified in this study, as captured in the statement: "*Unsurprisingly, pwCF whose health has improved or even stabilized on IVA or ETI are reappraising the value proposition of subscribing to a time-honored care model adopted prior to the advent of transformative CFTR modulator therapies*" which reflected the opinions of participants in my study (409). Key potential complexities identified in a recent study include: an increased number of adults with CF requiring care; more adults with CF working full-time and raising children presenting a barrier to attending appointments; a longer length of life with CF-related comorbidities (e.g. liver disease, diabetes); and co-morbidities related to aging (e.g. hypertension)(263).

That ETI was released at the start of the COVID-19 pandemic emerged as an important contextual factor, as captured in CMOC ETI_01. In 2020, CF Centres worldwide were required to rapidly adopt telehealth and remote monitoring practices to comply with lockdown and social distancing measures, while maintaining continuity of multi-disciplinary care. This change occurred despite limited prior experience and was generally regarded as positive (410, 411).

Whilst some Centres, such as the Centre where I worked clinically, have reinstated the historic CF care model, where all routine outpatient appointments are conducted in person, this appears to be atypical in the current era. Most other Centres appear to have adopted a hybrid approach, where some care is delivered in-person and other care is delivered virtually. Participants indicated that they favoured this approach, especially at times of good health, as virtual appointments can be easier to schedule alongside other commitments, as captured in CMOCs PBE_01 and VRT_01,08. This approach is

recommended and guidance on optimal use is included in the most recent 2024 ECFS Standards of Care (118).

In response to the second research question *("How have ETI and the COVID-19 pandemic shaped the experiences and care needs/preferences of pwCF?"*), a key change in care needs is the transition from acute to chronic and preventative care. With reduced reliance on acute interventions, such as inpatient treatment for exacerbations, following ETI, there is now greater emphasis on long-term, preventative support. Improvements in respiratory health and life expectancy have further moved care priorities toward issues more commonly seen in the general population, including healthy weight management and cardiovascular risk reduction. This evolving care landscape also addresses the first research question (*"How have ETI and the COVID-19 pandemic shaped perspectives of CF clinicians on inhaled medicines and the demands on their services?"*), reflecting changing demands on CF care providers.

In this study, CF clinicians expressed discomfort in addressing these emerging issues, citing limited experience and confidence. Likewise, pwCF described how they turned to their CF team for support with non-CF issues. Some reported their needs were met, whereas others described a lack of appropriate support, as captured in CMOCs ROL_01-02,04-05.

This evolving landscape has been acknowledged by the CF Foundation, which recognises current gaps in clinician expertise and advocates for development of collaborative relationships with "essential partners", such as mental health care providers and liver specialists, alongside "trained and trusted" colleagues in other disciplines such as geriatrics, rheumatology and cardiology, to support the delivery of comprehensive care where the core CF team may lack the requisite knowledge or experience (412).

Whilst there is clearly widespread, inter-continental optimism about changing the CF care model in response to ETI, this study highlighted the risk of felt abandonment, a key mechanism which should give pause to CF care providers and advocacy groups who may be working towards widespread expansion of such changes at pace. Most pwCF are diagnosed at birth, as part of newborn screening, and as such frequent interactions with

CF care teams at paediatric and adult Centres is an important part of their lives. This study demonstrated the strength of relationships between pwCF and their care providers, with it being considered “familial” in some cases. Whilst some pwCF and clinicians may be keen to rapidly leverage the impact of ETI and change care models, the data clearly show how this can lead to feelings of abandonment and isolation for pwCF, as captured in CMOCs VRT_09-10. This supports the absolute requirement for personalised approaches to care, which consider the preferences and needs of all pwCF under the care of specialist Centres as individuals and offer services which meet those needs.

A survey study of CF care providers in the USA during the COVID-19 pandemic revealed a general satisfaction with remote care and a clear preference for a hybrid model of remote/in-person care to be delivered (413). This study also called for future work to help inform optimal hybrid models of care. My study allowed triangulation of these clinician perspectives with the perspectives of pwCF, which generally aligned regarding implementation of hybrid models of care. My study highlighted, however, that it is likely that the same specific model will not be suitable for everyone, and care providers should consider how they can take a personalised approach for each pwCF, based on their needs and preferences.

For example, one focus group participant was satisfied with virtual appointments to discuss issues related to her CF-related diabetes (CFRD), but not for other CF-related health issues. Successful optimisation of virtual diabetes care was reported during the COVID-19 pandemic, which was facilitated by the widespread availability and trust in the accuracy of continuous glucose monitoring systems (414). However, when it comes to monitoring respiratory health, there is uncertainty as to the accuracy of home spirometry, as described in this study and supported by the other studies (415-418). Consequently, the 2024 ECFS Standards of Care recognise that home spirometry monitoring is feasible but must be used with caution (118). This may explain how, for pwCF, a virtual approach to CFRD management may be considered more appropriate than respiratory management.

10.3 Strengths

This study was strengthened by its mixed-methods design, which incorporated interviews with clinicians, a national survey, in-depth focus groups and a cross-sectional regression analysis. This allowed for breadth and depth in understanding the evolving experiences and needs of both pwCF and clinicians in the post-ETI era.

The inclusion and direct comparison of perspectives from both pwCF and clinicians enabled theory testing and refinement across sources. For instance, where clinician perspectives formed initial hypotheses about the reasoning and behaviour of pwCF, these were tested and developed using the accounts of pwCF themselves. This constant, iterative, comparative process enhanced the explanatory power and trustworthiness of the findings.

This was the first study which recruited via the CFHealthHub consent to future research mailing list, which allowed invitations to be sent to over 1400 pwCF. The reach of this mailing list greatly surpassed the 354 addresses included in the CF Trust's research interest mailing list, illustrating how the integration of forward-looking consent processes within long-term studies and learning health systems can enhance broader research engagement. Following this study, another doctoral researcher in CF was inspired to use the same approach to recruitment.

10.4 Limitations

Several broad limitations should be considered when interpreting the findings of this study, alongside those discussed in preceding chapters. Across all components of the study, sampling was primarily opportunistic rather than theoretical or purposive. This approach facilitated recruitment at scale, particularly for the survey and focus groups, but limited the ability to test specific elements of theory or to ensure representation of diverse contexts or outcomes across the full spectrum of experience and engagement.

Additionally, with recruitment of both clinicians and pwCF being primarily achieved thorough the CFHealthHub learning health system, the findings may not generalise to settings where CFHealthHub was not adopted. Future work may look to further develop the Programme Theory with those across wider contexts, especially now the

CFHealthHub programme has ended. Nonetheless, variation in reported perspectives and behaviours was found across all phases of data collecting, providing reassurance that an appropriate range of contexts and outcomes were explored, and resulting mechanisms are accurate reflections of reality.

Due to the impending closure of the CFHealthHub programme during this study, it was not possible to purposively sample pwCF with different levels of adherence, as measured objectively through CFHealthHub. A lack of objective adherence data prevented direct linkage of perspectives and reported behaviours to objective adherence outcomes. This sampling method could have enhanced the explanatory power of the realist analysis and should be considered in validating the Programme Theory in future work. Similarly, future work may benefit from using longitudinal adherence data to explore how adherence changes over time in response to clinical symptoms. Other studies using objective adherence to data to quantitatively explore the relationship between FEV_1 outcomes and adherence to inhaled medicines for pwCF, including NEEMO, are ongoing (218). The findings of this Realist Evaluation may help contextualise these quantitative findings going forward.

A limitation common to doctoral research is that data collection and analyses was primarily done by myself as an individual, and as such be subject to the influence of my own experiences and beliefs, as described in section 3.4 (Reflexivity). Mitigations included the keeping of a reflexive journal and discussion of key aspects of theory development with the research supervisors.

Finally, my identity as a clinician-researcher and known association with CFHealthHub may have introduced response bias, particularly in the interviews with fellow clinicians. Participants may have been inclined to align their responses with perceived expectations or to avoid expressing critical views. Some evidence of this was observed, including changes in tone or hesitancy following the sharing of less favourable opinions related to CFHealthHub. While rapport was generally strong and several participants did express critical perspectives, these dynamics may have influenced the data collected. A more distanced interviewer, or a broader research team conducting interviews, might have mitigated this risk. However, my position as a clinician working in this area afforded me

a tacit understanding of professional culture and language, and facilitated discussions between experts, rather than positioning myself as a neutral interviewer, which is consistent with the philosophy of realist interviewing (256).

These limitations reflect the resource constraints of doctoral study and the complexities of working as an embedded researcher. Despite these limitations, the use of multiple methods of data collection from a range of respondents, alongside realist approaches to analysis enabled the development of context-sensitive Programme Theory for CF care in the post-ETI era and allowed me to answer the three research questions set out at the start of this study.

10.5 Conclusions

This Realist Evaluation identified key mechanisms which are shaping the lived experience of CF and care delivery in the post-ETI era. Restored wellness has led pwCF to reclaim autonomy and seek to reduce long-standing treatment burden through therapeutic rationalisation. The uncertainty of the landscape has led to epistemological dissonance, where there is a new and unfamiliar discordance between subjective and objective health indicators. The resulting uncertainty leads some clinicians to feel professionally disempowered, which can manifest as inconsistent treatment recommendations or adoption of shared decision-making, where the lived experience of CF is considered alongside the best medical evidence and clinical judgement to make treatment recommendations.

The adoption of new models, with a more flexible and multi-modal approach to accessing CF care has been liberating for some, especially those enjoying good health with the ability to advocate their needs. Conversely, others have experienced feelings of abandonment, likely compounded by the isolating nature of CF as a condition across the life course.

Taken together, these findings reflect the emergence of a complex therapeutic landscape, in which established assumptions about adherence, authority, and care provision are being reconsidered. The mechanisms uncovered in this study demonstrate the contingent nature of adherence to inhaled medicines in the post-ETI era, shaped not

only by restored wellness but also by changing identities, motivations, and expectations. Importantly, these changes are not experienced uniformly, instead, they are mediated by contextual factors and individual narratives. This points to the continued relevance of nuanced, theory-driven approaches to understanding thoughts and behaviours in long-term condition care, such as CF.

11. Conclusions

11.1 Introduction

This final chapter brings together the findings of this study, which provided insights into how CF care has been shaped by ETI and puts forward recommendations for care providers as they adapt to these changes. As discussed in Chapter 1, the motivation behind this study was to explore the impact of a transformational medicine (ETI) in a long-term condition (CF) with findings that may somewhat generalise to other conditions.

11.2 Answering the research questions

Research Question 1

> "How have ETI and the COVID-19 pandemic shaped perspectives of CF clinicians on inhaled medicines and the demands on their services?"

Chapters 4 to 6 detailed interviews with clinicians from multiple UK adult CF centres, which revealed emergent uncertainty about the role of inhaled medicines for pwCF prescribed ETI. For pwCF experiencing marked symptom improvement, particularly a reduced or absent sputum burden, the justification for continuing mucolytics has become less compelling. However, in specific contexts, such as chronic *Pseudomonas* infection or established severe structural lung disease, the rationale for maintaining inhaled medicines, particularly antibiotics, remains stronger.

Improvements in the classical manifestations of CF, namely respiratory and pancreatic disease, among those taking ETI have brought other clinical concerns to the fore. These include mental health, liver and musculoskeletal issues, as well as age-related comorbidities, such as cardiovascular disease. CF clinicians are increasingly required to manage these less familiar issues, which can lead to clinical discomfort and uncertainty.

There is reduced demand for both inpatient and outpatient administration of IV antibiotics, due to reduction in the rate and severity of pulmonary exacerbations. This has led to changing responsibilities for certain disciplines, e.g. specialist nurses assuming responsibility for co-morbidity screening and blood test monitoring. This has

the potential to free up capacity to deliver more holistic care to pwCF with higher health care needs.

ETI-driven improvements in health, along with digital acceleration driven by the COVID-19 pandemic have led to the widespread, yet variable, adoption of hybrid face-to-face/virtual models of care. These have helped reduce the burden of attending face-to-face appointments for pwCF, but clinicians are concerned about the quality of care that can be provided virtually and the negative impact this modality can have on therapeutic relationship-building.

Research Question 2

> "How have ETI and the COVID-19 pandemic shaped the experiences and care needs/preferences of pwCF?"

Chapters 4 to 6 revealed some insights, albeit from the clinician perspective, into how some pwCF, particularly those who feel well, are expressing a preference for a more "light-touch" model of care, where there is reduced medical intrusion, achieved through, for example, adopting virtual consultations.

In Chapters 7 and 8, theories derived from the clinician interviews were directly tested with pwCF. Health improvements associated with ETI have altered views on the necessity of historically burdensome, though comprehensive, models of care and treatment regimens. A reduction in sputum production and limited perceived benefit have diminished the rationale for continuing inhaled medicines. Several pwCF reported a desire to trial the withdrawal of inhaled medicines to assess individual impact but felt clinicians would be unsupportive of this approach, leading some to conceal autonomous changes.

Emerging care needs for pwCF increasingly involve age-related comorbidities, yet many feel these are inadequately addressed within current models of care. Uncertainty persists around whether responsibility for these issues lies within primary or secondary care services, leaving pwCF under-served and caught between systems.

In terms of care preferences, virtual care offers the potential to reduce travel burden and medical intrusion, supporting a lifestyle more aligned with that of the general population.

This is particularly valued as opportunities for full-time employment and parenthood expand alongside improved health. However, some pwCF view certain concerns as poorly suited to remote consultation, and rapid shifts in care models risk evoking feelings of abandonment.

Research Question 3

> "What factors are associated with adherence to inhaled medicines for pwCF in the post-ETI era?"

Qualitative findings from Chapters 4 to 8 identified several factors influencing adherence to inhaled medicines among pwCF, including perceived health status, noticeable effects of medicines, habit and routine, competing priorities, relationships with care providers, and perceived treatment burden. In Chapter 9, quantitative analysis using objective real-world adherence data from a whole-centre cohort demonstrated that habit had the strongest association with adherence. Other significant factors included age, socioeconomic status, neurodivergence, and treatment complexity; however, these are less amenable to intervention. In contrast, habit formation can be actively supported through clinician-delivered interventions, such as the CFHealthHub intervention.

11.3 Summary of key mechanisms

The Realist Evaluation allowed exploration of context both within and external to a functioning learning health system which was ultimately abandoned, likely in part due to the impact of ETI on the perception of the role of inhaled medicines. The realist approach allowed me to identify six key mechanisms driving thoughts and behaviours for clinicians and pwCF. It is important to emphasise that these mechanisms appear to be activated in some pwCF and clinicians in response to some contextual factors. These mechanisms do not intend to explain the thoughts and behaviours of all pwCF and clinicians.

Restored wellness

A cognitive mechanism where improvements in health lead pwCF to reassess the necessity of established, burdensome aspects of care, such as inhaled medicines and frequent appointments.

Autonomy reclamation

A motivational mechanism where pwCF with restored wellness seek to reclaim control over their healthcare, driven by a renewed hope for normality and a desire to reduce medical intrusion.

Therapeutic rationalisation

An agentic mechanism, where pwCF begin evaluating and adjusting their own treatment regimens in light of restored wellness, aiming to reduce burden and align care with their new lived reality. This includes features of event-contingent adherence, where pwCF have periods of high adherence, prompted by increases in symptoms or exacerbations which are not sustained post-resolution.

Professional disempowerment

A normative mechanism resulting from disruption to professional authority, resulting from restored wellness, autonomy reclamation and therapeutic rationalisation. Clinicians feel less confident in making treatment recommendations due to the absence of an evidence base, particularly as they observe pwCF actively engaging in autonomous therapeutic rationalisation.

Epistemological dissonance

A cognitive-relational mechanism in which pwCF and clinicians prioritise different types of evidence when assessing treatment need, with pwCF often valuing subjective wellness and clinicians relying on objective indicators. Misalignment of subjective and objective health indicators can lead to disagreement, discomfort, and variation in treatment recommendations and behaviours.

Felt abandonment

An emotional-relational mechanism in which rollout of virtual care and remote monitoring is experienced by pwCF not as liberating but as a loss of connection and support, with the potential for harm, particularly when changes are implemented broadly and without individual tailoring. This is grounded in the isolating experience of living with CF and the strength of the therapeutic relationship built with CF clinicians over the life course.

11.3 Implications for care in the post-ETI era

ETI represents the most significant advance in improving both the quality and length of life for pwCF to date, and optimism is therefore an appropriate, and warranted, response. Whilst real-world evidence regarding the medium to long-term impacts of therapeutic rationalisation are awaited, many pwCF, driven by restored wellness, wish to explore the possibility of treatment withdrawal. Whilst clinicians, driven by professional duty and inherent risk-aversion, may struggle to recommend these approaches, pwCF, with a reclaimed sense of autonomy are making these decisions regardless, valuing lived experience over the wait for evidence. Clinicians who are aware of this may consider taking an open approach to pwCF who make these decisions, to encourage them to engage with careful monitoring in cases of treatment withdrawal, as an embodiment of shared decision-making.

Clinicians also need to consider how care models need to change in the post-ETI era. The emergence of issues indirectly related to CF, and more akin to those experienced by the general population, necessitates upskilling within the CF MDT or closer collaboration with professional colleagues, to ensure that the needs of pwCF are met going forwards. Finally, this work has highlighted the requirement for personalised care, both in terms of treatment recommendations but also care delivery, and the extent to which virtual and in-person appointments are balanced. As this study demonstrated, there is significant variation in the experiences of virtual care, and as such a flexible, personalised approach should provide the optimal care experience for pwCF.

11.4 Recommendations for clinical practice and future research

The following recommendations were constructed from a review of the evidence presented in this thesis, alongside the existing data and my personal interpretations. They are intended to support CF care providers who are experiencing uncertainty in the post-ETI era and other key stakeholders who are considering developments of the CF care model.

Recommendation 1: Initiation of adherence support during admission

Clinicians should make considered use of hospital admissions as opportunities to discuss the ongoing role for inhaled medicines in maintaining health. The connection between adherence and health is often more salient to pwCF during acute illness.

Recommendation 2: Continuation of adherence support post-admission

Increased adherence to inhaled medicines achieved during hospital admission may not be sustained post-discharge. Ongoing, individualised adherence support is likely to be required.

Recommendation 3: Re-education around recognising exacerbations

The clinical presentation of chest infections and pulmonary exacerbations may be less distinct or more difficult to recognise in pwCF taking ETI. This evolving symptom profile may necessitate re-education for both clinicians and pwCF, with a focus on identifying individualised warning signs and early indicators of clinical deterioration.

Recommendation 4: Integration of subjective and objective health indicators

Many pwCF place greater emphasis on subjective experiences of wellbeing than on objective clinical markers. As a result, pwCF who feel well despite a reduction in lung function, may be reluctant to increase their treatment burden. Ensuring that treatment discussions reflect both clinical evidence and the lived experience for each pwCF is essential for supporting informed decision-making and sustained engagement with care.

Recommendation 5: Adoption of shared decision-making

Many pwCF are experiencing improved health post-ETI, enabling them to pursue a wider range of life opportunities. As a result, engaging with burdensome legacy treatments or aspects of the pre-ETI care model may become more difficult, with health-related activities increasingly de-prioritised. Adopting a shared decision-making approach to care delivery, underpinned by open, non-judgemental exploration of the perspectives of

pwCF can strengthen therapeutic relationships and support sustained engagement with care.

Recommendation 6: Personalised trials of therapeutic rationalisation

Some pwCF may wish to trial the withdrawal of certain treatments in order to find a personally acceptable balance between health and treatment burden. Clinicians should seek to engage constructively with pwCF pursuing this approach, recognising that such trials may occur autonomously. Collaborative planning, including agreed monitoring schedules, can support safe trials while maintaining trust. Although the possibility of clinical deterioration may be difficult to accept, this process can also provide valuable insight for pwCF into the role and necessity of specific treatments. Frameworks such as PLUTO may assist multidisciplinary teams and pwCF in navigating these decisions, balancing respect for autonomy with professional responsibilities to provide evidence-based care.

Recommendation 7: Risk of felt abandonment with changing care models

Clinicians should remain attentive to the relational and psychosocial value of regular, in-person contact for some pwCF particularly those who have come to rely on strong, enduring relationships with their care team over the life course. Abrupt reductions in the frequency or format of contact may lead to feelings of abandonment or disconnection. Any changes to the model of care should therefore be introduced sensitively, with clear communication and appropriate alternatives in place to maintain continuity and trust.

Recommendation 8: Personalised approach to care models

Clinicians should adopt a tailored approach to the delivery of care, balancing virtual and face-to-face appointments, based on a shared decision-making process that acknowledges the priorities and practical requirements of both care teams and pwCF. Preferences for care delivery will vary, and services should aim to offer flexible arrangements that reflect individual needs. A predominantly virtual or pwCF-initiated model may be appropriate for individuals who demonstrate high levels of treatment-related knowledge, self-efficacy, and trust in their care team. A pragmatic model, already

in use at some Centres, involves an in-person Annual Review, with other appointments delivered according to the preference of pwCF and clinical need.

Recommendation 9: Reconfiguration of CF care services

As pwCF live longer, age-related health concerns such as cardiovascular risk factor and cancer risk monitoring are becoming increasingly relevant. However, uncertainty remains regarding where responsibility for the management of these issues lies between specialist CF services and primary care. This ambiguity can leave pwCF feeling unsupported or caught between services. Specialist CF Centres should consider developing local protocols for the proactive identification and management of these co-morbidities, either within the CF service or through structured collaboration with primary care providers.

Recommendation 10: Requirement for holistic care

A reduction in acute care demands on specialist CF services post-ETI offers provides an opportunity to adopt a more holistic and equitable approach to care. Care providers should consider how this may enhance their capacity to deliver in-depth, specialist CF care to those who need it, while also collaborating with other specialist colleagues to address emerging non-respiratory concerns. This will ensure that the complex, multi-faceted needs of pwCF are effectively met through coordinated, person-centred care.

11.5 Contribution to knowledge

This thesis provides a context-sensitive understanding of CF care in the post-ETI era. By adopting a realist approach, key mechanisms driving behaviour in this context were identified, theorised, and described, drawing on a diverse range of information sources across the CF community. A large amount of complex, mixed-methods data has been summarised and synthesised into an accessible theoretical framework to understand the effects of ETI on pwCF and specialist CF care services. As the first Realist Evaluation conducted in CF, this study uniquely explored the relationship between context and outcome this study and demonstrated the need to think differently in the post-ETI era with a refined, tested Programme Theory capturing a range of experiences. The refined

CMOC index (Table 14) provides tested (and further testable) hypotheses to guide future service developments.

The findings demonstrated how the CF model of care must adapt to meet the evolving needs of pwCF and provided recommendations for practice. This demonstrates the utility of Realist Evaluation to explore the effects of significant contextual changes on health service delivery which could be replicated in other disease areas.

Additionally, the PLUTO framework, introduced earlier in the thesis, provides a practical tool for clinicians and pwCF to collaboratively design individualised treatment trials as part of shared decision-making. This framework allows for the tailored exploration of therapeutic rationalisation, supporting more personalised care strategies and would benefit from further evaluation in routine clinical care.

This study also contributed to the broader field of long-term condition care. The regression analysis revealed that habit, as a modifiable and teachable attribute, plays a crucial role in medicines adherence, and as such may be a more appropriate (and achievable) target for intervention, compared to strategies related to less modifiable determinants of adherence, such as socio-economic and health-related factors. The qualitative findings also offer valuable insights into both the strength and context-sensitive nature of habit, which could inform interventions aimed at supporting adherence in other long-term conditions.

Appendices

Appendix 1: Topic guide for clinician interviews (Chapter 4)

Clinician Interviews topic guide

Opening questions

1. Please could you briefly describe your current role within your CF Centre?
2. How long have you been working in CF?

Context questions

3. What are your thoughts about CF care in the post-ETI era?

   Probe: Could you indicate the most important things in the post-ETI era? This could be their aspirations for pwCF, perceived importance of clinical outcome measures, scepticism about treatment, remote care, burden reduction, adherence/access to Kaftrio,

4. What are your thoughts on CFTR modulators?

   Probe: What aspects of CF care have changed because of CFTRm

   Probe: Do you feel any differently about ETI than you do about ivacaftor

5. How has ETI changed the way you deliver CF care?

   Note: Worth considering if these changes are due to Covid or ETI

6. How do you think ETI has changed PwCF's views on care, and why do you think that is?

   Probe: What care they do/don't want?

   Probe: How they want to receive it?

Complexity questions

7. What do you feel your team is trying to achieve when seeing pwCF in clinic?

   Note: this could vary significantly based on role within MDT

   Probe: Is there any uncertainty about how you're making decisions?

8. How do you determine if you are giving good care to people with CF now?

   Probe: If doesn't mention FEV_1/BMI; then I ask do any clinical measures (FEV_1/BMI) feature into this?

   Probe: How do you set targets for FEV_1?

   Probe: If they don't mention adherence; then I ask, and what are your current thoughts on adherence (modulators, oral, inhaled etc.)

9. What do you consider the important uncertainties around optimal delivery of CF care?

    Probe: If they mention inhaled therapy uncertainties, then ask how do they think we might resolve that uncertainty?

    Probe: SIMPLIFY/HERO2/STORM/NEEMO studies

    Probe: How likely do you think they are to resolve this

    Probe: Is there something else they are doing locally to resolve the uncertainty?

10. What role do you see for nebulised therapy in CF care now?

    Probe: Does whether someone is on ETI or not change your opinion on this

Implementation questions

11. What would you say is the role of CFHealthHub (CFHH) now?

    Probe: Has the role of CFHH changed in the post-ETI era?

12. How is CFHealthHub currently used in your Centre?

13. What do you think of PLUTO, as a clinical framework in routine care?

    Probe: How would PLUTO help with routine care? Does PLUTO encourage any changes in behaviour from how you are currently delivering care?

14. What do you think of PLUTO in terms of contributing to completing NEEMO?

    Probe: If they haven't thought about this, worth saying that PLUTO is designed to give personalised care and complete NEEMO

15. Does PLUTO change how you think about the current role of CFHealthHub?

Final questions

16. Has this conversation led to any changes in the way you think about this topic?

17. What else do you think it is important to consider in the post-ETI era?

Appendix 2: Final codebook for thematic analysis (Chapter 4)

Research Objective 1: Changes since ETI

Admissions fewer
Aging CF population increasing
    Cardiovascular risk
    CF-related Diabetes
    Potential for cancers
Appointment frequency
    Individualised decisions on length of follow-up
    Maintaining frequency
    Reducing frequency
Benefits being withdrawn
Challenges of extended life expectancy
Changing clinician roles
Changing relationships with pwCF
Clinicians more relaxed and less worried about pwCF
COVID-19
ETI impact different to other CFTRm
    Clinical impact
    Eligibility for ETI
GI Symptoms improved
Glycaemic control improved
Variable Engagement with spirometry
    PwCF do complete it
    PwCF not completing home spirometry
IVs fewer
Life expectancy increased
Liver issues
Lung function improvements
Mental Health
More well people
Non-resp issues revealed
PwCF behaviour
    Attendance related to well-ness
    CF is now less important or worrying to pwCF
    Less attendances
    More likely to take advice on treatment if symptomatic
    Other treatment reduction
    PwCF are more busy and have better opportunities
    Prefer remote attendance
    Reluctance to start new treatments
    They feel well so reduce treatments
    Voted with their feet
Pregnancy
QoL increases
Reduced need for Lung Transplant

Remote care
Sputum less
Symptom and exacerbation perception
Weight
    Weight gain - negative
    Weight gain- positive
Whole MDT Consultations

Research Objective 2: Thoughts on inhaled medicines
Antibiotics should be continued if Pseudomonas is still isolated.
Concern about inaccurate trial results
Equally as important as ever
Increase use of dry powder inhalers
Nebs are less important to the pwCF
PwCF stop nebs without talking to the MDT
Reduced use post-ETI
Risk of wasting potential of ETI
Role for those not on CFTRm
Scope for reducing nebs
    Antibiotic reduction
    Mucolytic reduction
Uncertainty as to the role

Research Objective 3: Thoughts on CFHealthHub
Allows holistic assessment
Changed the way we discuss adherence
Clinician Engagement
    Engagement stimulated by clinical deterioration
    Reasons for reduced engagement
        CFHealthHub is not effective
        PwCF more well
        Reduced urgency for deterioration
    Unchanged
    Variable engagement between MDT members
Community
Culture of discussing adherence more generally
Different post-RCT
Identify those with falling adherence sooner
Importance of leaders
PwCF disengagement
Power or importance of objective adherence data
Recruitment to CFHH reduced post-Kaftrio
Research potential within CFHH
Technical issues are a frustration
Unable to deliver intervention

Research Objective 4: Thoughts on PLUTO

- Barriers to local implementation
  - Adherence is less important
  - Clinician time pressure
  - Confirming responsibility for PLUTO display
  - Data in different places
  - Different consultants preferences
  - DNA Rate as a deterrent for pre-clinic prep
  - FEV1 decline of 1%
    - Natural lung function variability
    - Uncertainty as to 1% threshold
  - Inaccurate FEV1 and Weight readings
  - Insufficient data
  - It's nothing new
  - Lack of a single clinic note for the whole MDT
  - Lack of agreement on Target FEV1
  - Lack of time to convene
  - Lone champion for CFHH
  - Measuring CFTRm adherence
  - Money
  - Negativity
  - Omits PwCFs perspective
  - The changes required
  - Too structured
  - Virtual clinics
  - Weight stability
- Changes needed
  - Agreement as to target FEV1
  - Changes to clinical structures, staff roles, staff mix
  - FEV1 measurement standardisation
  - Remove the 1% FEV1 threshold
- Facilitators of local implementation
  - Culture of valuing adherence
  - Making PLUTO visible
  - New staff members
  - PLUTO allows individualised care
  - Similarity to existing processes
  - Simplicity of PLUTO
  - Uses familiar data already collected
- General thoughts
  - Benefits or not of physically seeing the framework
  - Formalisation
  - Helps clinicians use adherence data
  - Helps frame discussions with pwCF
  - Helps with the reset of target FEV1
  - Keeping adherence on the agenda
  - Mitigates staff changeover and helps junior staff

- PLUTO is good
- PLUTO may bias you toward increasing treatment
- Useful for non-doctor MDT members
- We are doing it anyway
- Importance of FEV1 monitoring

Additional themes

Balancing burden with treatment optimisation
Deterioration harder to recognise post-Kaftrio
Disadvantages of remote care
Don't forget those not on CFTRm
FEV1 reset
FEV1 terminology i.e. target or baseline
Hard for pwCF to think decades ahead
How lung function data are used
Importance of having objective data to justify treatment
Importance of relationships
Improvements from Kaftrio not being sustained
Personalised or Individualised care
Scepticism
Uncertainty
- Clinician uncertainty
- PwCF uncertainty

Variation
- Clinician Variation
- PwCF variation

Wish we had CFTRm in the past

Current complexities

How much treatment is enough
Microbiology and Sputum
Optimal MDT composition
What are they trying to achieve in clinic
- Assessment of health stability
- Clinical parameter monitoring
- Keep well for as long as possible
- Monitor for Kaftrio side effects
- Support self-management
- The best for that individual
- Unsure

Appendix 3: CMOC index for Initial Programme Theory (Chapter 5)

Theory ID	Title	CMOC
ETI has had a transformative impact on CF		
ETI_01	The transformative effects of ETI have led to reduced emphasis on non-ETI treatments	The introduction of ETI during the emotionally intense period of the COVID-19 pandemic, coupled with its widespread availability and significant clinical benefits (C) meant that both clinicians and pwCF perceived ETI as a transformative solution and are optimistic that it may "fix" the problems associated with CF (M: reasoning) resulting in pwCF leading lives more akin to that of the general population (O1) with a reduced emphasis on adherence to non-ETI treatments such as inhaled medicines (O2) and increased opportunity for relationships and work (O3)
ETI_02a	Clinicians value subjective reports of improvement over traditional objective measures and therefore reduce monitoring and treatment	When clinicians observe significant health improvements in pwCF post-ETI (C1) they come to view pwCF as more clinically stable and less vulnerable (M1: reasoning). As a result, they may place greater weight on subjective reports even when objective measures show decline (M2: reasoning) which leads them doubt the accuracy of objective measures that conflict with the subjective report (O1) and adjustment of their clinical thresholds and deliver less intensive monitoring and treatments (O2).
ETI_02b	Clinicians value objective measures of improvement over subjective reports and therefore recommend continuing existing treatments	When clinicians observe discordance between objective indicators (e.g. lung function) and self-reports of wellness (C1), some clinicians continue to value objective health indicators as a more reliable indicator of health status (M1: response). Although this decline may be contested by pwCF, who do not perceive themselves as unwell (M2: reasoning), clinicians maintain their trust in the validity of objective measures (M3: reasoning). As a result, they recommend continuation or reintroduction of treatment based on the objective clinical data (O1), while also scheduling reviews to monitor changes over time and reassess treatment needs (O2).
ETI_02c	When subjective and objective measures both indicate a good health state, clinicians place less emphasis on adherence support	When pwCF feel subjectively well and this aligns with stable objective health measures (e.g. FEV_1) (C), clinicians reason that current adherence must be effective in maintaining stability (M1: reasoning), reducing perceived need to probe adherence or encourage change (M2: response) resulting in de-prioritisation of discussions around adherence (O).
ETI_03	PwCF may wish to trade-off optimal health outcomes by reducing treatment burden leading to shared decision-making	Some clinicians believe pwCF benefit most from ETI when it's added to, rather than replaces, existing treatments (C). However, when pwCF feel significantly better, they may question the need to continue older regimens (M1: reasoning) and may want to trade-off the optimal clinical outcome with burden reduction (M2: response). This can make it harder for clinicians to support pwCF to maintain high adherence which may require different strategies to communicate long-term benefit (O1). Conversely, an acceptance of this may encourage adoption of shared decision-making regarding treatment (O2)

Mental Health implications for pwCF related to ETI		
MH_01	PwCF prescribed ETI are anxious about secondary inefficacy	For pwCF who's health improves significantly after years of illness (C), fears about the permanence of these improvements can create anticipatory grief and a fragile hope (M: reasoning) leading to emotional distress and worsening mental health (O).
MH_02	PwCF who are not prescribed ETI, either through ineligibility or intolerance, may feel excluded	PwCF who are ineligible for ETI (C1) and pwCF who have experienced significant health improvements from ETI and then have to discontinue ETI due to side-effects (C2) may experience feelings of exclusion (M1: response) or loss (M2: response) leading to emotional distress and worsening mental health (O)
MH_03	PwCF may be distressed after experiencing an exacerbation whilst prescribed ETI, requiring clinicians to reassure and set expectations	PwCF who have experienced significant health improvements from ETI and consider themselves "cured (C1). They may interpret an unexpected exacerbation as evidence that ETI has stopped working, which shatters their perception of ETI as a cure/effective treatment (M: reasoning) resulting in emotional distress and a sharing this with clinicians (O2). Clinicians who have these conversations with pwCF (C2) reflect on communication strategies when initiating ETI (M1: response) then actively and explicitly set expectations that ETI may reduce but does not eliminate exacerbations for everyone (M2: response) meaning pwCF adjust their expectations (M3: response) and are less distressed by the development of exacerbation (O2)
MH_04	PwCF now have to contend with an unanticipated, increased life expectancy for which they may not be prepared.	Increased life expectancy following ETI has created a new reality for many pwCF who made significant life decisions based on the expectation of a shortened lifespan (C1). Now facing a longer, healthier future (C2), some experience anxiety and regret about not having pursued long-term goals like careers or financial planning (M: reasoning). This mismatch between past decisions and current possibilities/expectations contributes to increased psychological distress (O).
MH_05	There is uncertainty as to whether deteriorations in mental health post-ETI are side-effects or responses to changing circumstances	When pwCF experience a deterioration in mental health since starting ETI (C1) and perceive this as a side-effect of ETI (C2 and M1: reasoning), adherence to ETI may reduce (O1) because the negative effects of the psychological distress outweigh the perceived benefit of ETI (M2: reasoning). The uncertainty around the aetiology of deteriorations in mental health for those taking ETI (C3) makes it difficult for clinicians to know if they are providing the most appropriate care (M3: response) and they consider research in this area important (O2).
The changing nature of pulmonary exacerbations		
PEX_01	Pulmonary exacerbations present differently post-ETI, leading to delayed recognition and treatments	PwCF who are prescribed ETI and experience fewer or no symptoms, even when there is an acute decline in lung function (C1). They are therefore less likely to recognise when they are having an exacerbation (M1: response) meaning clinicians cannot rely on pwCF reporting exacerbations (M2: reasoning) increasing the reliance on objective measures such as lung function (M3: response). This increased the risk of delayed intervention (O1) and deterioration to more severe, acute clinical conditions, such as pneumonia (O2).

PEX_02	Post-ETI, pulmonary exacerbations can be managed with oral antibiotics rather than hospital admission for IV antibiotics.	PwCF who are prescribed ETI experience milder exacerbations and/or an improved resilience to infection (C), meaning oral antibiotics are increasingly seen as effective at resolving symptoms without the need to escalate to IV treatment (M1: resource/reasoning), meaning fewer pwCF therefore require admissions for IV antibiotics (O).
PEX_03	Discordance between symptoms and lung function result in uncertainty about when to recommend treatment for suspected exacerbations	PwCF prescribed ETI experience a discordance between subjective symptoms and changes in objective lung function (C). This creates uncertainty for clinicians (M1: response), who were accustomed to interpreting changes in FEV_1 as a reliable marker for infection or deterioration (M2: resource). Clinicians therefore adapt their clinical reasoning and decision-making processes (M3: response), which can lead uncertainty into optimal care delivery, for example when to recommend treatment with antibiotics (O).
Changes in the ways pwCF now engage with clinicians		
PBE_01	When pwCF are well, their preferences for care delivery change, requiring adoption of personalised approaches.	When PwCF perceive themselves as well and/or this view is shared by clinicians (C1), pwCF and/or clinicians may view continuation of routine appointments or monitoring (M1: resource) as unnecessary or, for pwCF specifically, forgettable and inconvenient (M2: response), especially when faced with competing responsibilities (M3: reasoning). This may lead to reduced attendance or disengagement with some aspects of care (O1). Clinicians, observing reduced attendance (C2/O1), may be prompted to embrace shared decision-making approaches to agree personalised follow-up intervals (M4: response), which allows pwCF to have input into the frequency and nature of their appointments (O2).
PBE_02	Virtual appointments may improve engagement for pwCF who face barriers to attending in-person appointments	For pwCF with milder disease who may have difficulty attending face-to-face appointments (C), the option to attend appointments virtually (M1: resource) increases their ability and willingness to engage with care (M2: response), ensuring continued access to specialist CF care (O).
Changes in the ways pwCF now engage with non-ETI treatments		
PBM_01	Autonomous treatment reduction by pwCF post-ETI may conflict with clinicians' perspectives that treatment should be continued, straining the therapeutic relationship.	PwCF who feel well better after starting ETI (C) may view ETI as a cure (M1: reasoning), reducing the perceived need for other treatments (M2: reasoning). This fosters greater autonomy (M3: response) and, in some cases, leads them to independently stop inhaled medicines (O1). Some openly discuss this with clinicians, while others do not (O2). In reclaiming autonomy (M2: response) pwCF may place more value on informal or selective sources of evidence, while overlooking their limitations (M4: reasoning, confirmation bias) which reinforces their decisions to reduce treatment (O3). Meanwhile, clinicians who are aware of the limitations of trial evidence and cautious about its interpretation (C2) may experience concern or frustration when pwCF cite incomplete or oversimplified interpretations of data (M5: reasoning). They anticipate challenges in communicating nuance and correcting misinterpretations (O4), especially when pwCF are confident in their own information

		sources (C3). This tension requires clinicians to balance the duty to support informed choice with the desire to maintain rapport and trust (M6: reasoning), which may strain the therapeutic relationship (O5).
PBM_02	PwCF may conceal low adherence prompting clinicians to explore this sensitively or objectively. In certain cases, such as pseudomonas infection, clinicians feel more strongly about pwCF maintaining adherence to inhaled medicines	PwCF who feel pressure to demonstrate adherence (C1) may conceal low adherence (O1) due to fear of judgment (M1: reasoning), prompting clinicians aware of this risk to probe gently and use CFHealthHub to support adherence (M2: resource). However, if pwCF remain stable despite low adherence but have evidence of persistent Pseudomonas infection (C2), clinicians may hesitate to reduce treatment intensity (O2) due to perceived risk of sub optimally treated infection (M3: reasoning).
PBM_03	When lung function declines without worsening symptoms, it is difficult for clinicians to advocate for increasing adherence.	When pwCF discontinue other treatments post-ETI and experience a decline in lung function (C), clinicians may struggle to persuade them to restart treatment (O1). This is because pwCF who still feel well despite this decline (C2) and view their current health as "good enough" compared to their pre-ETI baseline, consider restarting treatment as unjustified (M1: reasoning). Clinicians may try to encourage re-engagement by highlighting previous peak lung function readings and framing continued treatment as key to long-term wellbeing (M2: response), but younger adults may not connect with these future-oriented arguments due to temporal discounting bias (M3: reasoning, retroduction). Therefore, some pwCF choose not to restart treatment (O2), and clinicians may then negotiate a new, lower but stable health target (O3) to maintain engagement (M4: reasoning).
PBM_04	Childhood experiences impact adherence behaviours in adulthood	PwCF who have experienced medical trauma in childhood (C) may have low adherence to inhaled medicines (O) due to the development of psychological barriers, which can be perceived by clinicians as illogical (M: reasoning)
PBM_05	PwCF value subjective health indicators over trial evidence regarding the need for inhaled medicines.	When pwCF are uncertain about the value of inhaled medicines for them (C), some pwCF trust personal experience, such as the fact they feel well and asymptomatic despite not taking inhaled medicines over clinical trial evidence (M1: response), leading to lower adherence (O1). Conversely, those who perceive symptoms as CF-related (C) may see greater value in inhaled medicines (M2: reasoning) and be more receptive to clinician advice (M3: response), increasing adherence (O2).
PBM_06	PwCF who have fewer symptoms post-ETI consider inhaled medicines ineffective or unnecessary	When pwCF no longer experience clear symptoms or exacerbations due to ETI (C1), and where the benefits of inhaled medicines are not immediately noticeable (C2) or even new side-effects emerge (C3), pwCF may consider inhaled medicines ineffective (M1: reasoning, retroduction) or unnecessary (M2: reasoning, retroduction), leading to reduced adherence (O1). Clinicians who historically justified these treatments by citing symptom relief or exacerbation prevention (C4) now find these

		arguments less persuasive for pwCF (M4: reasoning), leading to challenges in sustaining engagement with prescribed treatment (O2).
PBM_07	When treatments are burdensome and have no noticeable effect, adherence will be lower.	When pwCF are prescribed treatment every day (C) treatments which are perceived as more burdensome (M1: reasoning) are less likely to be taken as prescribed (O). This is exacerbated when the more burdensome treatments have a lower perceived effect, for example due to pwCF not noticing a difference when it is taken (M2: reasoning).
PBM_08	PwCF who experience restored wellness post-ETI reduce other treatments to enjoy a period of normality with low treatment burden	PwCF who perceived historically high treatment burden (C1) and notice a health significant improvement in health post-ETI (C2) may choose to reduce or stop other treatments (O) reasoning that, although they may require them again in the future they have the opportunity to experience a rare period of subjective wellness and reduced treatment burden (M2: reasoning).
PBM_09a	PwCF who had low adherence to inhaled medicines pre-ETI continue to have low adherence	PwCF who had low adherence to inhaled medicines before starting ETI and have had a significant improvement in symptoms post-ETI (C) are sceptical about the need for inhaled medicines (M: reasoning) which perpetuates low adherence (O, retroduction)
PBM_09b	Despite high pre-ETI adherence, significant lifestyle changes can lead to lower adherence	PwCF who had high adherence to inhaled medicines before starting ETI (C) continue to have high adherence (O1) unless there has been a significant change to their life, such as parenthood (C2) in which case the requirement to balance this responsibility (M: response) leads them to reduce adherence (O2)
PBM_10	Hospital admissions are a key resource for offering adherence support due to increase disease salience and supportive external scaffolds	When pwCF are admitted to hospital for treatment (C) clinicians can use this opportunity to discuss the role of inhaled medicines (M1: resource) as link between pre-admission adherence and the need for hospitalisation becomes more salient (M2: reasoning). This increases engagement with adherence support (M3: response) and increases adherence post-discharge (O1)
Clinician uncertainty about optimal use of inhaled medicines		
INH_01	Uncertainty about the role of inhaled medicines post-ETI leads to reduced clinician confidence and	Where ETI has led to uncertainty and disagreement between clinicians and pwCF about the necessity of established treatment regimens such as inhaled medicines (C), clinicians experience a loss of confidence in giving firm recommendations (M1: response). Reflection on previous certainty leads to adoption of strategies to manage this uncertainty, including openly sharing it with pwCF (M2: response), and shifting to a learning mindset (M3: response). This

	adoption of shared decision-making	leads to inconsistent advice across the team (O1) but a shift towards shared decision-making and collaborative relationships with pwCF (O2).
INH_02	When maintained subjective wellness conflicts with deteriorating objective health measures pwCF may be reluctant to increase treatment taking. Clinicians look to published evidence to help construct persuasive arguments in favour of treatment.	When pwCF experience declining lung function but are reluctant to restart or continue treatments (C1), clinicians use adherence and lung function data (M1: resource) to illustrate trends and build persuasive explanations for continuing treatments (M2: reasoning). However, when pwCF report feeling well despite lung function decline (C2), clinicians may place more weight on subjective reports of wellness (M3: response), leading to reduced confidence in advising treatment escalated (M4: reasoning). Clinicians value trial-based evidence to support their recommendations and reduce reliance on personal judgment (M5: resource/reasoning). Access to such evidence increases clinicians' confidence in communicating their advice (M6: reasoning), making pwCF more likely to accept treatment recommendations (O1). As this evidence is lacking (C3), pwCF who would previously have been advised to escalate treatment based on declining lung function (C4) may continue with existing regimens or lower adherence levels (O2).
INH_03	When pwCF autonomously stop inhaled medicines, clinicians recommend close monitoring of health indicators	In the event that pwCF stop inhaled medicines of their own accord (C) then clinicians may change their approach from recommending re-initiation of the previous treatment regimen to negotiating a monitoring strategy to detect any deterioration or harm resulting from treatment reduction (M1 - response). For this strategy to be successful (O1) it is important for the pwCF to adhere to the monitoring regimen (M2 – response), so the clinician has the information they need to make clinical recommendations (M3 – resource). Clinicians may respond to the deterioration by having increased confidence in recommending initiation of treatment (M4 – reasoning).
INH_04	Reduced sputum production post-ETI leads to the uncertainty regarding the necessity of inhaled mucolytics to be questioned. In some cases, clinicians engage in shared decision-making but in others, where the indication for treatment is stronger, they do not advocate for treatment reduction	When pwCF have a significant reduction or cessation of sputum production post-ETI (C1) clinicians and pwCF re-evaluate the necessity of existing treatments, such as inhaled mucolytics and chest physiotherapy (M1: reasoning). The longstanding normative use of these treatments in CF (C2) makes clinicians feel uncomfortable about reducing or withdrawing them (M2: response, retroduction). This uncertainty leads to inconsistent recommendations (O1) but encourages clinicians to adopt shared decision-making, considering the preferences of pwCF and the holistic clinical picture (O2). However, in certain cases, such as pwCF with severe, established CF lung disease (C3) clinicians experience less uncertainty regarding the role of established CF treatments, as the severity of the disease reinforces the clinical rationale for high levels of treatment (M3: reasoning) Therefore, clinicians are less inclined to agree to reductions in treatment regimen (O3)
INH_05	Reduced microbiological sample testing in the post-ETI era leads to uncertainty	When pwCF have a significant reduction or cessation of sputum production post-ETI less microbiological result data are available (C1), so clinicians rely on less sensitive cough swabs to detect *Pseudomonas* (M1: resource). This means clinicians are uncertain about the true microbiological status of the lungs (O1) which also increases uncertainty regarding inhaled

	about *Pseudomonas* status. Most clinicians therefore recommend continuing inhaled antibiotics and investigation more intensively.	antibiotics (O2). Some clinicians may respond to this uncertainty by continuing to advocate for the use of inhaled antibiotics (O3) due to the requirement for firm evidence to go against established treatment guidelines in a professional capacity (M2: reasoning). Alternatively, they may also respond by testing for *Pseudomonas* more intensively (M3: response), such as through induced sputum or bronchoscopy, and if all those results are negative over a number of years (C3) then they may consider reducing or withdrawing inhaled antibiotics (O4).
INH_06	When pwCF disagree with clinicians who are certain of the need for inhaled medicines post-ETI, it is considered maladaptive, but they accept the pwCF's autonomy to maintain the therapeutic relationship	When clinicians are confident that pwCF starting ETI should continue all inhaled medicines (C1) they consider it their duty to emphasise this to pwCF (M1: reasoning) doing so through education (M2: response), supported by published evidence (M3: resource). When pwCF decide to reduce or discontinue medicine despite this guidance (C2) clinicians accept their autonomy (M3: response) but interpret this as maladaptive or misinformed (M4: reasoning) which can lead to subtle strains in the professional relationship (O1, abduction). However, clinicians also recognise that respecting autonomy (M4: response) even when decisions seem unwise (C3) improves rapport and strengthens the professional relationship (M5: reasoning, retroduction), which may help maintain long-term engagement in care (O2).
INH_07	Clinicians are more comfortable with reduction of inhaled mucolytics than antibiotics	Where pwCF are determined to reduce the use of inhaled medicines post-ETI (C) clinicians, while respecting autonomy (M1: response), may respond pragmatically and advise changes to the regimen which still involve the sustained use of antibiotics in particular (O1) as there is less uncertainty as to their role compared to other inhaled medicines (M2: reasoning)
Clinician-led prioritisation of focus in outpatient appointments		
CLP_01	Clinicians prioritise issues for discussion at consultations based on resource constraints and individual needs	When clinicians prioritise aims for consultations based on the immediate needs of the pwCF and the time constraints of the clinic (C), these decisions are influenced by both the limited time available and the cognitive burden on pwCF (M: reasoning). Consequently, less pressing aspects of care may be deprioritised, potentially leaving important issues unaddressed (O).
CLP_02	Engaging with CFHealthHub changes the way clinicians discuss adherence, adopting a more open, non-judgemental discussion to	Engagement with the principles and actions of CFHealthHub (C) increases clinicians understanding of the challenges of adherence (M1: resource) leading to the adoption of more empathetic discussions (M2: response). This increases pwCF's comfort in discussing their adherence, though some pwCF may still withhold full honesty (O). Additionally, being part of CFHealthHub (C) may influence clinicians towards wanting pwCF to continue all existing treatments (M3: response) as they are invested in the concept that adherence to inhaled medicines is important and worth supporting (M4: reasoning,

	foster the therapeutic relationship.	retroduction) resulting in a reluctance to advise pwCF who are taking ETI to reduce other treatments or lend their support to this strategy when pwCF suggest it or enact it autonomously (O)
The changing roles and requirements of the CF MDT		
ROL_01	The prominence of non-respiratory issues leads to clinician discomfort due limited experience and confidence in these areas	As respiratory health in pwCF has improved due to ETI (C1), non-respiratory issues, such as mental health, lifestyle challenges have become more prominent (O1 and C1). Clinicians, who are more comfortable advising on respiratory issues (C3), are facing the uncertainties of role expansion (M1: reasoning), as they are required to address a broader range of health needs for the pwCF under there care, meaning their work has become more complex and unpredictable (O2).
ROL_02	Reduced acute care needs of pwCF have shifted specialist CF nurses' roles towards administrative rather than clinical tasks	A reduction in the volume of direct care tasks required, driven by health improvements from ETI (C) means that nurses are redirected towards other tasks such as replenishing routine outpatient prescriptions (O)
ROL_03	Engaging with pwCF about issues beyond their illness builds stronger therapeutic relationships and increases satisfaction	In CF clinics where clinicians have long-term, ongoing relationships with pwCF and take time to engage with them about life beyond their illness (C), the continuity of care and personal interest shown by clinicians fosters trust and allows pwCF to feel seen and valued beyond their medical condition (M1: reasoning, reproduction) leading to stronger therapeutic relationships, improved communication, and may enhance engagement with treatment (O1, retroduction). This also increases clinician satisfaction (O2) as they witness the positive impact of their care on the lives of pwCF (M2: resource)
ROL_04	Reduced frequency of appointments weakens the therapeutic relationship, meaning some pertinent health issues may not be discussed	In the post-modulator era, pwCF are generally more well, attend clinic less often, and also have reduced requirement for ad hoc between-clinic appointments (C1). This is also the case during the transition from paediatric to adult CF care (C2). With fewer appointments, clinicians have less opportunity to build or maintain strong relationships (M1: resource) and may feel less familiar with pwCF and their families (M2: response) and are concerned about pwCF will not feel able to raise appropriate issues with them (M: response). As a result, clinicians place greater emphasis on keeping communication channels open to maintain trust and ensure timely contact through clinical consultations (O).
ROL_05	CF teams must adapt to meet evolving care needs of pwCF post-ETI	Increased longevity in the CF population due to ETI will expose pwCF to previously rare co-morbidities, such as cancer and cardiovascular disease (C). This will require CF care teams to adapt current models of care (M1: response) in order to meet these demands and provide holistic care for pwCF (O)
The role of and challenges associated with virtual care and remote monitoring		
VRT_01	There is variation in preferences for virtual care	When clinicians and pwCF both find virtual care effective (C1), clinicians may feel that reverting to in-person-only care is unnecessary, leading to the continued use and normalisation of virtual appointments (M1: resource). However, there

	vs in-person care, meaning personalised approaches are needed	remains variation in preferences for fully remote care versus hybrid models (C2), depending on individual needs and the context of their care (M2: reasoning). Some pwCF may prefer remote care (O1) as they find it more convenient (M3: reasoning), while others prefer in-person consultations (O1).
VRT_02	Adopting remote care can lead to inadequacy of health data collection, making it difficult for clinicians to make treatment recommendations	For pwCF who are reluctant to engage with monitoring or testing requirements (C1), as they find this burdensome or unnecessary (M1: reasoning), virtual care offers greater flexibility to delay or avoid these requirements (M2: resource), reducing adherence to monitoring requirements (O1). This can leave clinicians with limited data (O2), making it harder to make informed recommendations during remote consultations (M3: response), leading them to revert to recommending in-person care (O3). Additionally, remote consultations may allow intentional or non-intentional concealment of symptoms (e.g. sputum production) (M4: response) which would be detected on physical examination during in-person consultations. This scepticism of how reality is portrayed or identified during a virtual consultation (M5: response) leads to clinician discomfort in adoption of remote care (O4). Furthermore, some clinicians miss the personal, one-on-one communication possible during in-person appointments (M6: reasoning), which can reduce the quality of care (O5).
VRT_03	Hybrid virtual and in-person care models can streamline care and reduce travel burden but may prohibit pwCF from discussing specific health issues	In Centres where a hybrid model for remote and in-person appointments is adopted (C1), consultations with multiple MDT members at the same time (M1: resource) for clinically "straightforward" pwCF (C2) can streamline care by reducing repetition (M2: reasoning). However, this structure requires pwCF to request individual consultations if needed and clinicians are concerned that they may not voice this need (O1) either by not realising it is an option (M2: reasoning) or not feeling they have the agency to make this request (M3: reasoning). Flexibility within hybrid models, such as allowing pwCF to choose between virtual or in-person appointments (M4: resource), can improve satisfaction (O2), particularly for those who face barriers, such as long travel distances or having to take time off work (C3)
VRT_04	Concerns about home spirometry accuracy leads clinicians to rely on alternative health indicators, especially when perceived risk is low, or revert to in-person spirometry	Where there is variation between home and hospital spirometry readings for pwCF (C1), clinicians apply judgement to assess the reliability of home measurements on a case-by-case basis (M1: response). In cases when the home spirometry readings are considered inaccurate (C2) and the clinician has clinical concerns about that pwCF (C3), they recommend hospital spirometry (M2: resource), as there is perceived need for accurate measurement is higher (M3: reasoning). However, if the pwCF appears clinically well (C3), clinicians may still discount the home readings suggesting FEV_1 decline (M4: response) but choose not to advise hospital spirometry (O2), accepting a degree of diagnostic uncertainty due to the lower perceived clinical risk of having inaccurate lung function data (M5: reasoning). for pwCF who appear clinically well (C3). The discordance between home and hospital spirometry readings (C1) can lead to pwCF to discontinue home monitoring (O3) due to feelings of frustration (M6: response).
VRT_05	Clinicians tailor the balance between remote and in-person appointments based on individual risk assessments	When implementing a tailored model of hybrid care delivery (C1) clinicians will assess the risk (M1: response) of each pwCF and those who are deemed high risk (C2) will be preferentially offered in-person appointments due to reduce the risk of "missing" important things during remote appointments (M2: reasoning)

VRT_06	Recognising the risk of missing key pieces of information during remote appointments, clinicians may recommend a certain number of in-person appointments per year	In Centres where both remote and in-person appointments are utilised (C1) and clinicians recognise things can be missed during remote appointments that would less likely be missed during in-person appointments (C2) clinicians may adapt to recommending at least one or two appointments per year, including the Annual Review, are in-person (O), to both align with the preferences of the pwCF for access to remote care (M1: reasoning) and mitigate the clinical risk associated with aspects of care being missed or overlooked in remote appointments (M2: reasoning)
VRT_07	Virtual care can increase capacity for CF Centres, which is important as adult CF caseloads increase	As caseload for adult CF Centres increases (C), adoption of virtual care (M1: resource) enables clinicians to meet this increasing demand efficiently (M2: reasoning). This supports equitable distribution of care across a large caseload (M3: resource) ensuring that all adults with CF have access to specialist CF care (O).
VRT_08	A long-standing therapeutic relationship, built through years of in-person appointments can help improve the experience of remote appointments	When pwCF and clinicians have a long-standing therapeutic relationship (C), developed through years of in-person interactions (M1: resource), both clinicians and pwCF find virtual consultations more acceptable and effective (M2: reasoning), resulting in improved engagement and care delivery (O, retroduction).
Clinician engagement with CFHealthHub programme		
ENG_01	A lack of CFHealthHub data available for clinicians across a Centre leads to disengagement with CFHealthHub	Where fewer pwCF actively share adherence data or data are unavailable due to technical issues (C) and clinicians perceive a reduced need for intervention (O) due to ETI-related improvements in lung function (M1: reasoning), clinicians feel that adherence discussions won't change pwCF behaviour (M2: reasoning), and become frustrated with incomplete data (M3: response), leading to a decline in engagement with CFHealthHub for adherence monitoring (O)."
The delivery of adherence support for inhaled medicines to pwCF		
SUP_01	Objective adherence data increases clinicians' confidence in discussing adherence in an open and honest way	When clinicians use CFHealthHub for adherence monitoring and support (C), and in particular deliver interventions in the home of the pwCF (C2) they gain a better understanding of the context and adherence patterns of the pwCF they are supporting, allowing for more tailored interventions (M1: resource). Discussing objective adherence data helps clinicians feel confident (M2: response) in engaging pwCF in open, honest conversations about adherence (M3: response), reducing recall errors and emotional discomfort that may come from self-reporting (M4: response, retroduction), which ultimately leads to improved adherence discussions about all treatments, not just inhaled medicines (O1).

SUP_02	Clinicians adapt the CFHealthHub intervention when supporting adherence, which may make it less effective	When pwCF cannot access the CFHealthHub digital platform (C1), clinicians may use their own login details to access the system (M1: response), but this reduces the full benefits of personalised, documented planning and goal setting (M2: response), thus limiting the intervention's potential to increase adherence (O1). Additionally, when pwCF are feeling well (C2), they may engage less with specific resources on the CFHealthHub digital platform, perceiving them as less important (M3: reasoning, retroduction) such as educational components, reducing the fidelity with which the intervention is delivered (O2).
SUP_03	The absence of CFHealthHub Interventionist may promote inter-disciplinary delivery of adherence support but the support delivered is with less fidelity	In Centres without a dedicated CFHealthHub Interventionist (C1), adherence support may be less consistently delivered (O1), as responsibility for adherence support is distributed across the team (M2: resource) rather than sitting with an individual. Whilst this may support adoption within the wider team (O1) as it is not seen as the business of a single individual but a shared responsibility (M3: reasoning) it can lead to missed opportunities for adherence support (O2) where clinicians lack the specific skills or training to deliver the intervention with fidelity (M4: reasoning). However, when a trained Interventionist is available (C2), they have sufficient training, experience, and theoretical knowledge to deliver adherence support to pwCF with fidelity (M5: resource), making the intervention more effective (O3).
SUP_04	It is harder to recruit pwCF to CFHealthHub post-ETI as adherence to inhaled medicines is deprioritised	PwCF who have prior experience using CFHealthHub (C1) or are not prescribed ETI (C2) tend to engage more with CFHealthHub (O1). In contrast, newer users, especially who joined around the time of being prescribed ETI (C3) may see adherence support as less important for them (M1: reasoning, retroduction), resulting in difficulties for clinicians to persuade them to engage with CFHealthHub (O1).
SUP_05	A shared responsibility for considering adherence across the MDT, along with a referral process to the CFHealthHub Interventionist leads to widespread adherence support of differing intensities being offered to pwCF	In Centres where various MDT members have been trained in motivational interviewing and are confident in supporting routine adherence conversations (C1), and where a system exists that allows clinicians to refer to the CFHealthHub Interventionist (C2), clinicians have autonomy to triage adherence support needs (M1: reasoning, retroduction) and feel assured that more complex cases can be escalated appropriately (M2: resource, retroduction), leading to referrals to the CFHealthHub Interventionist being reserved for pwCF requiring more detailed or intensive adherence support (O1).
Implementing CFHealthHub into routine care		
IMP_01	Embedding CFHealthHub data review into routine workflows leads to regular and co-ordinated	When CFHealthHub is embedded into routine workflows (C1), such as standardised pre-clinic preparation or weekly meetings (M1: resource), adherence data are used more consistently (O1), enabling clinicians to assess risk (O2) and prioritise adherence support for pwCF who are likely to benefit from it (O3). Regular discussions within the MDT about adherence (M2: resource) ensure a coordinated approach (O4), preventing pwCF feeling overwhelmed (M3: reasoning) and

	consideration of adherence support	promoting efficient use of resources (M4: resource), which results in more streamlined and targeted adherence support (O5).”
IMP_02	When CFHealthHub data review and adherence support are seen as the Interventionist’s responsibility, their absence can result in these activities being overlooked	Where a site had a dedicated CFHealthHub Interventionist (C1), their absence (C2) can lead to reduced utilisation of both the CFHealthHub digital platform and the adherence support intervention (O1) because the Interventionist acted as a champion, keeping adherence data visible and adherence support prioritised (M1: resource). By playing a leading role in chasing and ensuring adherence data sharing with the MDT (M2: response), more adherence data is available to clinicians (O2). However, should access to CFHealthHub data be seen as a shared responsibility within the team (M3: reasoning) others take responsibility for accessing and sharing CFHealthHub data (O3) when the Interventionist is absent (C2). When more adherence data is available (C3), clinicians perceive CFHealthHub as more useful and worthwhile (M4: reasoning), which in turn sustains the use of CFHealthHub (O4).
IMP_03	When resources are limited, clinicians adapt CFHealthHub intervention delivery to ensure that adherence support is available for those who need it	In Centres where resource constraints prohibit the ideal implementation of CFHealthHub (e.g. face-to-face support for all pwCF) (C), clinicians adapt the delivery of adherence support (e.g. using virtual appointments, documenting outside the CFHealthHub digital platform) (M1: resource) to enable provision of adherence support (O), underpinned by a utilitarian rationalisation that, although suboptimal, this is the most pragmatic and equitable use of limited resource to maintain provision among the caseload (M2: reasoning).

Appendix 4: Topic guide for Physiotherapist group interview (Chapter 6)

Interview with Physio team topic guide

Make it clear that this is not about trying to reach a consensus, I expect there to be diversity amongst the group and that's what I want to understand.

Opening question
I am interested in talking about inhaled therapy adherence support with you. We've got 30 minutes. We'll use 2 minutes just to have a think about what topics within this do **you think** are important for us to talk about?

If they don't come back with anything then I can say "well, I have a few thoughts on this".

- How does adherence support fit into your role?
- How do we, as a team, offer adherence support
    - Identification of those needing it
    - Offering it to those who need it
    - Delivering it to those who need it
    - Can you tell me a bit about your experiences in offering/delivering adherence support?
        - How do these experiences impact how you work?
    - What helps that process in each of the domains of the journey (identification, offering, delivering)
    - What gets in the way of that process?

I could offer this as a structure. Is there anything you think is more important outside of these?

Other prompting questions?

- What do they see as the role of inhaled therapy these days? Is it linked to life expectancy?
- What is their role?
- Regarding pre-clinic MDT meeting data sharing, what is their role?

Try to explore what may lead to different outcomes for different people, for example:

Outcome 1: Offering a pwCF who may benefit from adherence support, adherence support.
Outcome 2: Not of offering a pwCF who may benefit from adherence support, adherence support.

Appendix 5: Topic guide for CFHealthHub Interventionist interview (Chapter 6)

Interview with CF Interventionist topic guide

Opening question

I am interested in talking about inhaled therapy adherence support with you. We've got 30 minutes. We'll use 1 minutes just to have a think about what topics within this do **you think** are important for us to talk about?

Other prompting questions?

- How does adherence support with you differ to adherence support with other team members?
- How are people flagged for your attention?
- Do you find that pwCF are interested in spending that time with you to do the full intervention?
- Whose responsibility is it to do the technical troubleshooting?

Appendix 6: Topic guide for Realist focus groups (Chapter 8)

Realist focus groups topic guide

Quick intro

Who are you, where are you from, can you use one word to sum up your weekend.

Brief overview of the structure

Part 1: How things have changed for you over the past few years
Part 2: Times when medicine use might increase or decrease
Break
Part 3: The demands or burden of treatment taking
Part 4: How you interact with your CF Care team

Ground Rules

- Confidentiality
    - Can we agree to keep everything that's discussed in this room.
    - Take away learning but leave behind details such as who said what
    - For me, when I produce my thesis from this focus group, any quote I use from this meeting will be anonymous
    - The meeting is recorded for the purposes of transcription only. We will delete the recording once the text has been transcribed.
- Respect
    - Everyone's contribution is valid here so please feel you can be honest. We know that everyone's life, circumstances and thoughts are difference. It may be that you don't agree with something someone has said and that is ok. All viewpoints are valid.
    - In fact, it's that disagreement as much as the agreement that we are looking to explore this work. Why do people feel a certain way and others feels differently. We are not looking at right and wrong
- Contributions
    - This is your chance to get your voice heard in this work, please contribute as much as you feel able
    - We will use the hand-raise function to try and reduce the talking over people, and also give us the chance to say "you're on mute" – we all know that no virtual meeting is complete without it
    - If you would prefer to put things in the chat, instead of interrupting/raising hands then that is fine and myself or Steve will read it out and start the discussion.

Is there anything else that anyone wanted to ensure before we started.

Complete demographic questionnaire (link to URL)

Part 1 – How have things generally changed with CF over the past few years since Kaftrio? (30 mins)

As a follow on from the icebreaker, who is on Kaftrio or not and for those who are on Kaftrio, how has that changed your approach to treatment and interacting with your care team?

Broadly understand how people are thinking re: health and nebs

Some people think that your health, i.e. how you are feeling at that time, or even if your health improves, or in fact deteriorated has an impact on how you use inhaled medicines or medicines in general. Would you agree with that?
Are there situations where that would or wouldn't be the case? Please feel free to give examples.
Is that always true, are there times when they might not apply.
What makes you feel that way?
General wellness (mental health framed as wellness) – how does that interact with the way you feel about treatment taking.

Part 2 – When might medication use increase or decrease (30 mins)

Let's look at situations where you might increase or decrease medication. Some people fluctuate and vary their use of medication whereas some people might find that isn't the case. It would be interesting to know the situations that might lead to that.

- Attitudes and use when health improve.
- Attitudes and use when health deteriorates.

Break (10 mins)

Part 3 – Burden (30 mins)

Thinking how you balance the demands of taking treatment with the rest of your life, has that changed over the past few years?

Part 4 – Interaction with the clinical team (30 mins)

How has the way you interact with your team changed.
How has that made you feel?
Are there any times when this has been a good change, or a bad change

Appendix 7: Declaration of Generative AI usage in this thesis

Declaration

I confirm that no content created by generative AI technologies has been presented as my own work.

Acknowledge

I acknowledge the use of generative AI for the following purposes:

- to generate materials for background research and self-study in the drafting of this assessment.
- to generate materials that were included within my final assessment in modified form.

Describe

In this study, I used ChatGPT, a language model developed by OpenAI, to assist in generating, refining, and troubleshooting code. Specifically, ChatGPT was used for:

1) Code Generation: Generating initial drafts of code based on described functionality.
2) Code Refinement: Refining and optimising existing code for better performance and readability
3) Troubleshooting: Identifying and fixing errors or bugs within the code.

ChatGPT was also used to provide brief overviews of concepts related to my work, which I used to structure further study using other sources. ChatGPT was also used to support revisions of my written work to improve readability, logical flow and reduce repetition.

Evidence

Example 1: Generating code for specific data manipulation or testing

Generative AI system: ChatGPT

Prompt: in R, in my df eligible_data I want to calculate the proportion who are in levels 1:15 for $Q12

Output: To calculate the proportion of respondents in levels 1:15 for the variable Q12 in your eligible_data dataset, you can use the following code in R:

```
# Calculate the frequency of each level in Q12
level_counts <- table(eligible_data$Q12)

# Filter for levels 1 to 15 and calculate proportions
level_proportions <- prop.table(level_counts[names(level_counts) %in% 1:15])

# Print the proportions
print(level_proportions)
```

Explanation:
1. table(eligible_data$Q12): Creates a frequency table for all levels in Q12.
2. names(level_counts) %in% 1:15: Filters the levels to include only those in the range 1 to 15.
3. prop.table(): Converts the filtered counts to proportions.

If Q12 contains non-numeric levels (e.g., factors or strings), you might need to ensure numeric conversion first:

```
eligible_data$Q12 <- as.numeric(as.character(eligible_data$Q12))
```

Then, rerun the code above.

Prompt: can I also produce a total count of $Q12 %in% 1:15

Output: to count the total number of rows in eligible_data where $Q12 is in the range 1 to 15, you can use the following R code:

```
# Total count of Q12 values in 1:15
total_count <- sum(eligible_data$Q12 %in% 1:15)
# Print the total count
print(total_count)
```

Explanation:
1. eligible_data$Q12 %in% 1:15: Checks if each value in Q12 is within the range 1 to 15, returning a logical vector.
2. sum(): Adds up the TRUE values (treated as 1), giving the total count.

This gives you the count of observations where Q12 is between 1 and 15 (inclusive).

Example 2: Generating code for specific data output plots

Generative AI system: ChatGPT

Prompt: Could i add a label to this code giving me "n=count" for each of the bars? (NB I posted here the full code of a plot using `ggplot2::ggplot`)

Output: To calculate the proportion of respondents in levels 1:15 for the variable Q12 in your eligible_data dataset, you can use the following code in R:

```
# Create the ggplot
ggplot(missing_df, aes(x = Variable, y = ProportionMissing)) +
  # Create a bar plot with 'Variable' on the x-axis and 'ProportionMissing'
on the y-axis
  geom_bar(stat = "identity", fill = "grey80") +
  # Flip the coordinates for better readability (horizontal bars)
  coord_flip() +
  # Add titles and labels to the axes
  labs(
    title = "Proportion of Missing Data by Variable",
    x = "Variable",
    y = "Proportion Missing"
  ) +
  # Use a minimal theme for the plot
  theme_minimal() +
  # Set y-axis limits to be between 0 and 1 (proportion range)
  ylim(c(0, 1)) +
  # Adjust the appearance of y-axis labels (font size)
  theme(
      axis.text.y = element_text(size = 12),
      axis.text.x = element_text(size = 12),
      axis.title = element_text(size = 14),
      plot.title = element_text(size = 16, hjust = 0.5)
      )

rm(missing_df)
```

To add labels displaying "n = count" for each bar in your ggplot, you can use geom_text() with an additional data.frame containing counts of missing values for each variable. Here's how you can adjust your code:

- Calculate counts: Add a column in your data that stores the counts of missing values for each variable.
- Modify the plot: Use geom_text() to place the labels on the bars.

Here's the updated code:

```
# Calculate counts of missing values
missing_df <- missing_df %>%
  mutate(Count = round(ProportionMissing * TotalObservations))  # Assuming
TotalObservations exists
```

Prompt: this is my current Geom Label code

```
geom_label(
    aes(label = paste0("n=", n)),
    hjust = 0, vjust = -3.2, color = "black",
    fill = "grey80", label.size = NA  # Gray background with no border
  )
```

The justification on the box as a whole is correct, i just want to additionally centrally justify the text in the box

Output:
```
# Create the ggplot
ggplot(missing_df, aes(x = Variable, y = ProportionMissing)) +
  geom_bar(stat = "identity", fill = "grey80") +
  geom_text(aes(label = paste0("n = ", Count)),
            hjust = -0.2,  # Adjust position
            size = 4) +    # Text size
  coord_flip() +
  labs(
    title = "Proportion of Missing Data by Variable",
    x = "Variable",
    y = "Proportion Missing"
  ) +
  theme_minimal() +
  ylim(c(0, 1)) +
  theme(
      axis.text.y = element_text(size = 12),
      axis.text.x = element_text(size = 12),
      axis.title = element_text(size = 14),
      plot.title = element_text(size = 16, hjust = 0.5))
```

Key Points:

- Labels with counts: The paste0("n = ", Count) generates the desired text for each bar.
- Positioning: Adjust the hjust and size values in geom_text() to fine-tune the label placement relative to the bars.

If you don't already have a count column, calculate it using your dataset logic. For further details on adding labels, check guides like Cedric Scherer or R-bloggers for similar examples.

Example 3: Help creating acronym for Programme Theory naming structure

Generative AI system: ChatGPT

Prompt: I am trying to assign my CMOCs relevant identifier with a 3-letter acronym determined by their group. For example, CMOCs related to PLUTO are called PLU_01, PLU_02 etc. can you suggest 3 letter codes for patient behaviour around inhaled medicines and Patient behaviour around contacting care providers

Output: Great system! Here are my suggestions for your three-letter acronyms:

- Patient behavior around inhaled medicines → PBM (Patient Behaviour - Medicines)
    - Example: PBM_01, PBM_02, etc.
- Patient behavior around contacting care providers → PBC (Patient Behaviour - Contact)
    - Example: PBC_01, PBC_02, etc.

These are concise, intuitive, and align with your existing structure. Let me know if you'd like alternative options!

Example 4: Improving the clarity of CMOCs

Generative AI system: ChatGPT

Context of AI usage: Having read a piece of qualitative data, I have analysed it to extract what I think are relevant aspects of context mechanism and outcome. I used GenAI as a proofreader to assess the structure and organisation of the CMOC text and if it is understandable. This is consistent with recommendation from the University of Sheffield on the use of generative AI in essays and reports, proofreading subsection (https://www.sheffield.ac.uk/study-skills/digital/generative-ai/essays-reports).

Prompt: I am undertaking a Realist Evaluation, as described by Ray Pawson, and am constructing a CMO configuration to describe findings from my data. Can you please provide feedback on the readability and construction of this CMOC and if it is understandable. "When pwCF are considered clinically "straightforward" (C), the MDT will see them as a group (M) which works well for pwCF who are well (C) because they experience less repetition that seeing different MDT members sequentially (M). However, for pwCF who actually wanted to speak to a specific MDT member individually (C) they are required to request this directly (O) but may not feel like that is an option to them (M), when a group consultation has been allocated (M). This limits opportunities for one-to-one conversation between pwCF and clinicians (C) which are opportunities to glean important information which means things may now be missed (O)"

Output: Your CMOC is well-structured and captures an important dynamic, but the readability can be improved with clearer sentence structure and logical flow. Below is my feedback and a refined version:

Feedback on Readability and Construction:

1. **Sentence Structure & Flow:**
    - Some sentences are quite long and contain multiple **contexts (C)** or **mechanisms (M)** in one place, making it harder to follow. Breaking them up slightly will improve clarity.
2. **Logical Progression:**
    - The CMOC jumps between different groups of pwCF (those who are well vs. those who want one-on-one care). Making this distinction clearer upfront will enhance readability.
3. **Clarifying Mechanisms & Outcomes:**
    - The link between some mechanisms and outcomes could be more explicit, especially around why pwCF may feel unable to request one-on-one time and how this affects care.

Refined CMOC for Better Readability:

When people with CF (pwCF) are considered clinically "straightforward" (C), the MDT sees them as a group rather than individually (M). This approach works well for those who are well (C), as it reduces repetition from seeing different MDT members separately (M). However, for pwCF who wish to speak to a specific MDT member one-on-one (C), they must request this directly (O). When a group consultation has already been allocated, some may feel that individual requests are not an option (M). This limits opportunities for

one-to-one discussions (C), where important information might otherwise be shared, increasing the risk of missing key clinical details (O).
Key Improvements:
✅ **More structured progression:** The CMOC now clearly distinguishes between different patient experiences.
✅ **More readable sentence structure:** Sentences are shorter, making the logic easier to follow.
✅ **More explicit links between M and O:** The reasoning behind why opportunities for important information are missed is clearer.
Would this version work better for you? 😊

Use of the output: I considered the suggestions and used this to refine the CMOC from my own original CMOC, incorporating suggestions I felt were appropriate and did enhance the readability/understandability of the CMOC but ignoring aspects which were uninformative. This was my final CMOC having taken on board the response from ChatGPT. This aligns with the University of Sheffield recommendation that you "*should not forget to fact-check any new ideas that emerge from this process and make sure you have identified reliable academic sources that can support them*" (https://www.sheffield.ac.uk/study-skills/digital/generative-ai/essays-reports#planning-and-structuring)

"When pwCF are considered clinically "straightforward" (C), appointments may be delivered with multiple MDT members at the same time, rather than seeing members separately and sequentially (M). This can work well for pwCF who are "well" (C) by reducing the repetition of discussing similar issues with different MDT members separately (M). However, this may then require pwCF who want to speak to an individual MDT member separately (C) to request this specifically (O). If they do not feel this option is available for them (M) then they may not make this request (O) which limits the opportunities for on-to-one discussions (O), increasing the risk of important clinical information being missed (O)"

Example 5: Improving the clarity of CMOCs

Generative AI system: ChatGPT

Context of AI usage: This aligns with recommendation from the University of Sheffield that “GenAI may be able to help you to articulate your own ideas and formulate your thinking by acting in the capacity of a 'critical friend'” (https://www.sheffield.ac.uk/study-skills/digital/generative-ai/assessment#acknowledge,-describe,-evidence)

Prompt: I am undertaking a Realist Evaluation, as described by Ray Pawson, and am constructing a CMO configuration to describe findings from my data. Can you please provide feedback on the readability and construction of this CMOC and if it is understandable. “PwCF who are already experienced in using CFHH (C) or not prescribed ETI (C) appear more engaged with CFHealthHub (O) than those who joined later and/or are prescribed ETI (C) as they are not “on board” with adherence support (M)"

Output: Your CMOC captures the key ideas from the evidence well, but the wording could be made clearer and more structured. Here’s a refined version:

Revised CMOC (SUP_04_v02):
PwCF who have prior experience using CFHealthHub (C) or are not prescribed ETI (C) tend to engage more with the platform (O). In contrast, newer users or those prescribed ETI (C) may not see adherence support as equally relevant (M), making it harder to get them "on board" (O).
Feedback:

- The original CMOC had multiple **contexts (C)** mixed together—I've separated them more clearly.
- The **mechanism (M)**—why engagement differs—could be expanded. You mention that the importance of adherence was lower for newer patients, so perhaps adding **"because adherence support feels less relevant to them"** could clarify this.
- The **outcome (O)**—reduced engagement—was a bit vague, so I made it more explicit.

Use of the output: I considered the suggestions and used this to refine the CMOC. By looking at the refinements alongside the source data myself, I edited the CMOC for accuracy but also highlighted where abduction was required to hypothesis on the mechanism, which was not grounded in the source data.

“PwCF who have prior experience using CFHealthHub (C) or are not prescribed ETI (C) tend to engage more with CFHealthHub (O). In contrast, newer users, especially who joined around the time of being prescribed ETI (C) may see adherence support as less important for them (M - abduction), making it harder to get them "on board" (O).”

Example 6: Background learning about mechanism typology

Generative AI system: ChatGPT

Context: After identifying the key mechanisms uncovered in my research, I wanted to classify them by type of mechanism, as I had seen in other realist studies. I wanted to learn about the different types of mechanisms that may be revealed in a realist study so I could target further reading to correctly categorise the mechanisms I had identified. I used ChatGPT to help generate an initial list to get me started, before searching for other literature clarifying the specifics of each mechanism. This aligned with the Uni of Sheffield's recommendation that GenAI may be used to guide initial learning but then students should consider "Critical analysis of outputs, fact checking and further research" (https://www.sheffield.ac.uk/study-skills/digital/generative-ai/critical).

Prompt: Please outline and describe common mechanism types which may be revealed in a Realist Evaluation

Output: In realist evaluation, **mechanisms** refer to the processes or factors that explain how and why an intervention works (or doesn't work) in a particular context. These mechanisms are typically not directly observable, but can be inferred from people's responses and actions. Mechanisms are activated by resources (such as the intervention) and are influenced by the context in which the intervention is applied. Below are **common mechanism types** that may emerge in realist evaluations:

1. Cognitive Mechanisms
Description: These mechanisms are related to people's mental processes, beliefs, knowledge, and perceptions. They explain how people make sense of and interpret an intervention or experience, influencing their behaviors and responses.
Examples:
• A person may believe that a treatment is effective because they perceive improvement, even if there's no clinical evidence.
• A patient's understanding of their disease and treatment may affect their adherence to prescribed therapies.
Relevance in Realist Evaluation: These mechanisms help explain how people's **understanding** and **perceptions** of the intervention shape their actions.

2. Agentic Mechanisms
Description: Agentic mechanisms are related to people's **autonomy**, **decision-making**, and **self-efficacy**. These mechanisms focus on the individual's capacity to take control of their health, make decisions, and act based on their personal agency.
Examples:
• A patient might decide to adjust their treatment regimen based on how they feel, rather than strictly following a clinician's instructions.
• A person with a chronic condition may choose to adopt a healthier lifestyle based on their perceived control over the situation.
Relevance in Realist Evaluation: These mechanisms highlight the role of **personal agency** in how individuals respond to an intervention or care model.

3. Emotional-Relational Mechanisms
Description: These mechanisms involve **emotional responses** and **interpersonal relationships** that can influence behavior. Emotional-relational mechanisms explain how trust, fear, connection, or a lack of emotional support may shape responses to an intervention.
Examples:
• A patient feels abandoned by their healthcare provider when care transitions to remote services, leading to decreased engagement.
• A clinician may feel empathy and emotional connection with a patient, motivating them to offer more personalized care.
Relevance in Realist Evaluation: These mechanisms are critical in understanding the **human and relational** factors that influence outcomes, especially in healthcare settings.

4. Normative Mechanisms
Description: Normative mechanisms involve **social rules**, **cultural norms**, and **professional expectations**. These mechanisms describe how people's behavior is influenced by their perception of what is socially or professionally expected of them.
Examples:
• A clinician may hesitate to adjust a treatment plan without clear evidence due to professional norms about evidence-based practice.
• Patients may follow treatment recommendations because they trust medical authority or because it aligns with cultural values.
Relevance in Realist Evaluation: These mechanisms help explain how **social norms** or **professional guidelines** influence behavior and decisions.

5. Motivational Mechanisms
Description: Motivational mechanisms are related to **goals**, **desires**, and **incentives** that drive individuals to act. These mechanisms are particularly important in understanding what motivates people to engage with an intervention or adopt certain behaviors.
Examples:
• A patient's desire for independence motivates them to reduce medication use or adopt self-management strategies.
• A health professional might be motivated by the desire to provide the best care, driving their engagement with the latest medical technologies.
Relevance in Realist Evaluation: These mechanisms clarify the **incentives** or **desires** that propel individuals to take specific actions or adopt new behaviors.

6. Social-Relational Mechanisms
Description: These mechanisms involve **social influences**, such as peer pressure, group norms, and relationships within a network. Social-relational mechanisms explain how interactions with others can shape people's behavior.
Examples:
• A patient might change their treatment adherence based on recommendations or behavior observed in a peer group (e.g., support groups).
• A person might reduce their healthcare visits due to social norms encouraging minimal reliance on the healthcare system.

Relevance in Realist Evaluation: These mechanisms focus on how **interpersonal relationships** and **social networks** influence individual behavior.

7. Cultural-Symbolic Mechanisms
Description: Cultural-symbolic mechanisms refer to the **meaning** people attribute to their experiences, often shaped by culture, identity, and shared values. These mechanisms are concerned with how people interpret their roles or actions through the lens of culture and identity.
Examples:
• A person may see their participation in a health program as a way to assert their **identity** and self-worth.
• Healthcare interventions may be accepted or rejected based on cultural views of illness, wellness, and treatment.
Relevance in Realist Evaluation: These mechanisms explain how **cultural meanings** and **symbolic understandings** influence individual responses to interventions.

8. Structural Mechanisms
Description: Structural mechanisms involve the **organization** of services, **systems** of support, or **resources** available to individuals. These mechanisms explain how the larger system or structure in which an intervention is embedded can influence its effectiveness.
Examples:
• A healthcare system's capacity to provide access to medications or support services may determine whether a treatment succeeds or fails.
• Organizational rules and policies might limit a clinician's ability to customize treatment plans for individual patients.
Relevance in Realist Evaluation: These mechanisms highlight how the **structural context** (e.g., system design, resource availability) affects outcomes.

9. Contextual Mechanisms
Description: Contextual mechanisms focus on how the **specific context** in which an intervention takes place influences the outcomes. This includes environmental, social, and institutional factors that either enable or hinder the intervention's impact.
Examples:
• The socio-economic status of a community may influence how well a health intervention is received or how accessible it is.
• A healthcare system's infrastructure (e.g., digital access for remote care) may determine the success of a telehealth intervention.
Relevance in Realist Evaluation: Contextual mechanisms help explain why an intervention works in some settings and not in others, underscoring the importance of **tailoring interventions to specific contexts**.

How to Identify and Use Mechanisms
In realist evaluation, identifying mechanisms involves analyzing how and why people's behaviors change in response to interventions. By identifying the relevant mechanisms and their activation under different contexts, researchers can uncover why an intervention works in some settings but not in others. These insights can then be used to refine interventions and make them more effective across diverse contexts.

Example 7: Supporting naming of key mechanisms

Generative AI system: ChatGPT

Context of AI usage: The output of realist evaluation is to present middle-range programme theories that explain why a programme is achieving its outcomes, by uncovering hidden causative mechanisms that are triggered by, or interact, with features of context. To help structure and articulate the key findings of a Realist Evaluation, these theories are sometimes named, similar to naming themes in a thematic analysis. I had identified the relevant mechanisms produced as part of the results of my work but was struggling to creatively and accurately name them, and felt this was a task that GenAI could support me in, as a positive use of AI.

Prompt: I am wanting to choose a name to describe this "mechanism" that I have unearthed during my realist evaluation. It describes: a motivational mechanism where people with CF who feel well, having experienced improved subjective health post-ETI, seek to reclaim control over their healthcare, driven by a renewed hope for normality and a desire to reduce medical intrusion. Could you suggest some names for this mechanism, including the concept of autonomy?

*Output***:** Absolutely, that's a rich and nuanced mechanism you're describing—deeply rooted in subjective transformation and agency. Since you want to highlight autonomy and the motivational shift in individuals with CF post-ETI, here are a few name ideas that balance conceptual clarity with emotional and psychological depth:

🔷 **Name Suggestions:**

1. **Restorative Autonomy**
   Captures the sense of autonomy being reclaimed or restored as health improves.
2. **Empowered Withdrawal**
   Highlights the pull away from medical systems, not from defiance but from empowerment.
3. **Hope-Driven Autonomy**
   Emphasizes hope as the engine behind the pursuit of self-governance.
4. **Autonomy Reclamation**
   Straightforward and focused—suggests a taking back of control.
5. **Liberation Through Wellness**
   Evokes the idea that feeling well brings a sense of liberation from medical dependency.
6. **The Normalcy Pursuit Mechanism**
   Centers the desire for normal life as a driver for distancing from clinical oversight.
7. **Agency Reawakening**
   Reflects an internal psychological shift—a reawakening of one's sense of control.
8. **The Detachment Drive**
   Focuses on the motivational aspect to detach from healthcare oversight, sparked by feeling better.

9. **Therapeutic Autonomy Effect**
   Describes autonomy as a therapeutic by-product of effective treatment (ETI).
10. **Post-Intervention Autonomy Shift**
    Places the mechanism temporally and emphasizes the shift post-ETI.

Would you like something more metaphorical or poetic? Or are you aiming for something that would sit comfortably in academic writing (e.g., in a realist evaluation or journal article)? I can tailor the suggestions to that vibe too.

Use of output: From these suggestions, I felt autonomy reclamation seemed to concisely and accurately reflect the mechanism I described in my prompt. I checked the definition of the word reclamation using an online dictionary and was satisfied that "to reclaim" defined as "to regain possession of**"** was an accurate descriptive of the mechanism and used it in my thesis. I consider this a positive use of AI, and is consistent with the recommendation that "*GenAI may be able to help you to articulate your own ideas*" from TUOS guidance for use of GenAI in assessment (https://www.sheffield.ac.uk/study-skills/digital/generative-ai/assessment#using-ai)

Abbreviations

AIC	Akaike Information Criterion
BMQ	Beliefs about Medicines Questionnaire
BMI	Body mass index
CI	Confidence interval
COM-B	Capability Opportunity Motivation – Behaviour model
COVID-19	Coronavirus disease 2019
CO	Context-Outcome
CM	Context-Mechanism
CMOC	Context-Mechanism-Outcome configuration
CF	Cystic fibrosis
CFHH	CFHealthHub
CFRD	CF-related diabetes
CFTR	CF transmembrane conductance regulator gene
CFTRm	CFTR protein modulator
CQC	Care Quality Commissions
CQUIN	NHS Commissioning for Quality and Innovation scheme
DNase	Dornase alfa
ECFS	European CF Society
EMBRACE	Easy Medicine for Burden Reduction and Care Enhancement
EMR	Electronic Medical Record
ETI	Elexacaftor/tezacaftor/ivacaftor
FEV_1	Forced expiratory volume in 1 second
% FEV_1	Percentage of predicted FEV_1
GAD-7	Generalised anxiety disorder-7 questionnaire
GSCE	General Certificate of Secondary Education
GLI	Global Lung Initiative
GP	General Practitioner
GVIF	Generalised Variance Inflation Factor
HbA1c	Glycosylated haemoglobin
ID	Identification
IMD	Index of Multiple Deprivation
IRAS	Integrated Research Application System
IPT	Initial Programme Theory
IQR	Inter-quartile range
IV	Intravenous
LUM/IVA	Lumacaftor/ivacaftor
MDT	Multi-disciplinary team
MO	Mechanism-Outcome
MPR	Medication Possession Ratio
MRC	Medical Research Council
MSK	Musculoskeletal
NA	Not applicable
NASSS	Non-adoption, Abandonment, Scale-up, Spread and Sustainability
NEEMO	National Efficacy-Effectiveness CFTR Modulator Optimisation
NHS	National Health Service

NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
OR	Odds Ratio
PEP	Positive expiratory pressure
PGfAR	Programme Grant for Applied Research
PHQ-9	Patient Health Questionniare-9
PLUTO	Personalised data-Linkage to Understand Treatment Optimisation
PwCF	People with cystic fibrosis
QIPP	Quality, Innovation, Productivity and Prevention
RCT	Randomised controlled trial
SD	Standard deviation
SRBAI	Self-Report Behavioural Automaticity Index
STH	Sheffield Teaching Hospitals NHS Foundation Trust
TEZ/IVA	Tezacaftor/ivacaftor
TUoS	The University of Sheffield
UK	United Kingdom
USA	United States of America

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