Symptoms and adherence in adults with Cystic Fibrosis: understanding the complex relationship.

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Candidate Declaration

I hereby declare that:

1. I have not been enrolled for another award of the University, or other academic or professional organisation, whilst undertaking my research degree.

2. None of the material contained in the thesis has been used in any other submission for an academic award.

3.I certify that this thesis is my own work. The use of all published or other sources of material consulted have been properly and fully acknowledged.

4.The work undertaken towards the thesis has been conducted in accordance with the SHU Principles of Integrity in Research and the SHU Research Ethics Policy, and ethics approval has been granted for all research studies in the thesis.

5. The word count of the thesis is 81,956.

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Abstract

Treatment adherence in adults with Cystic Fibrosis (CF) is low. One of the reasons identified for lack of adherence to treatments is that patients may not experience any immediate relief in their symptoms or notice changes as a result of taking their treatment, with many reporting that they do not perceive there to be consequences of non-adherence. To date previous literature has not investigated the impact of presenting symptom and adherence data to participants to illustrate the links. The overarching aim of this thesis was to explore the feasibility and usefulness of self-monitoring and using adherence and symptom feedback data with patients with Cystic Fibrosis.

Within this thesis four studies, which have mixed methodologies, are presented:

Study 1 was a quantitative survey study which recruited members of the general public (n=106) and aimed to investigate how graphical adherence and symptom data should be presented to aid understanding of feedback data. The materials used include the Graph Literacy Scale and a bespoke Cystic Fibrosis Graph Survey. The study found that including a text description made no significant difference to how participants interpreted graphs and participants preferences in terms of format was a double line chart. The findings in relation to graph preferences were utilised in studies 2 and 3 of the thesis when feedback data was presented to participants.

Study 2 included a pilot study and main study. The study aimed to explore the preliminary feasibility of self-monitoring within an N-of-1 study and examining the temporal relationship between treatment adherence and self-monitored symptoms in CF patients. The pilot study was mixed methods and included a N-of-1 study (n=6) and also a qualitative content analysis of interview data with the same participants. Materials used include a symptom questionnaire, Fitbit watches and objective adherence data. Individual symptom and adherence data was presented to participants during their interview.

The findings from the pilot study revealed that self-monitoring design was feasible and acceptable to participants and a number of changes to the design of the main N-of-1 study was made as a result of the findings. The main study consisted of a N-of-1 study (n=19) the symptom questionnaire was modified slightly as a result of the findings from the pilot study. Overall the study concluded that the relationship between symptoms and adherence is unique and individualised.

Study 3 was a qualitative study and included a sample of participants from study 2 (n=13). This study aimed to further develop an understanding of how people recognise the factors which influence their CF symptoms, how these symptoms are influenced by treatment and the value of symptom tracking with patients with Cystic Fibrosis as a long-term tool. Materials used included an interview schedule and feedback data (from the N-of-1 study). The data revealed a total of five themes; the feasibility of symptom tracking, the impact of symptom tracking, clinical applications, understanding the complexity of symptoms and adherence and finally why I take my treatment. These findings offered more insight into the feasibility and usefulness of symptom tracking.

The final study of the thesis (study 4) was a qualitative study which recruited 8 Healthcare Professionals (HCP). Materials used included an interview schedule and a summary of previous findings. The study aimed to further understand health professionals' perceptions of the relationship between treatment adherence and symptom experiences and explore the perceived feasibility and usefulness of using this data as part of clinical management of CF. In total there were 6 themes identified: 'The influence of modulator treatments', 'Empowerment and respect when managing adherence', 'Symptom tracking an additional burden?' 'The unique experience of living with CF', 'Symptom tracking: it has a role for some patients?', 'Contextual issues: the closure of CFHH and 'The practicalities of using symptom tracking data in clinic'.

These findings provided insight into the feasibility and acceptability of symptom tracking in the clinical setting.

The findings from this thesis highlight the complex nature of the relationship between symptoms and objective nebuliser adherence in adults with CF. In relation to symptom tracking, the findings suggest that this could be something which is useful and feasible to some patients living with CF and also HCP's. This thesis offers a unique contribution in that the relationship between symptoms of CF and nebuliser adherence has been investigated using novel N-of-1 methods, the findings of such have been shared with CF patients and professionals.

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Chapter 1 Introduction

1.1 Background to Cystic Fibrosis

Cystic Fibrosis (CF) is a life-limiting, genetic condition, which is caused by mutations in the transmembrane regulator (CFTR) gene, which was first identified in 1989 by Karem and colleagues (Karem et al.,1989). Although it is likely that folklore referred to the poor prognosis associated with the disease “Woe to the child who tastes salty from a kiss on the brow, for he is cursed and soon will die.” (Yu and Sharma, 2022, p.2).

The disease affects over 10,000 people in the UK (CF registry, 2019), causing a thick and sticky mucus to fill the airways and the tubes in the body. As a result of this multiple organs and systems are affected such as the reproductive organs, the liver (Cystic Fibrosis Trust, 2020a) and the pancreas, which prevents nutrients from food entering the digestive system (Cystic Fibrosis Trust, 2020a). In the lungs the build-up of mucus can lead to a range of symptoms including respiratory problems such as coughing and shortness of breath (Sawicki et al., 2008). Recurring bacterial infections within the lungs can cause severe respiratory symptoms (Kiedrowski and Bomberger, 2018). Progression of the disease in the airways ultimately causes respiratory failure (Flume, 2009).

Although the disease affects many areas of the body it is the impact upon the lungs, which often leads to mortality in patients. This is caused by thick mucus in the airways trapping viruses and bacteria which are inhaled when breathing (Bhagirath et al., 2016). Overtime this damages the lungs and causes a decrease in levels of oxygen held by the organ, this then leads to the development of chronic infections (Borriello et al., 2004) and therefore reduced lung function. One example of a chronic infection people with CF may experience is *Pseudomonas Aerguinosa,* commonly named *Pseudomonas.*

Pseudomonas is one of the most common sputum colonisations in patients with Cystic Fibrosis (CF Trust, 2020). In 2020 the CF Trust reported that 31.9% of adults with CF live with chronic *Pseudomonas.* This colonisation causes increased lung infections and is commonly cited as the cause of death in patients with CF (Lyczak et al., 2002). When patients with CF contract *pseudomonas* the pathogen causes inflammation in the lungs and airways, which is caused by the lack of efficient microbial clearance (Bhagirath et al., 2016). As a result of this the lungs become damaged and are unable to protect from the development of further infections; rather the microenvironment within the lungs actually facilitates the development of infection (Bhagirath et al., 2016). *Pseudomonas Aeruginosa* is one of many problematic infections, which pose a risk to CF patients, because it is highly transferrable between patients (Hodson et al., 2007).

To treat these chronic infections patients are prescribed with antibiotic treatments, which often form part of their daily treatment regime. However, when symptoms begin to deteriorate medication routines have to be adjusted. This will be reviewed in the following sub-section of this thesis.

As a result of periods of chronic infection, caused by bacteria, fungi and viruses (Bhatt, 2013) patients with CF are likely to experience periods of acute worsening of symptoms known as pulmonary exacerbations (Flume et al., 2010). Research findings have demonstrated an association between pulmonary exacerbations and declining lung function and it has been found that three exacerbations per year will usually lead to a long-term decline in lung function (Waters et al., 2012). However, the definition of an exacerbation is equivocal.

According to Fuchs et al. (1994) an exacerbation is the need for an additional intravenous antibiotic due to a recent change in at least two of 12 signs and symptoms which include: a change in sputum, new or increased haemoptysis (coughing up blood), increased cough, malaise, fatigue or lethargy, temperature of around 38°c and decrease in

pulmonary function by 10% or more from a previous recorded value. More recently the European Consensus Group validated a modified version (Bilton et al., 2011) of the Fuchs criteria which is categorised as a change in two of the following: change in sputum volume or colour, increased cough, increased malaise, fatigue and lethargy, anorexia or weight loss, decreased pulmonary function by 10% or more and increased dyspnoea (shortness of breath) (Flume et al., 2010). Although there is on-going debate relating to symptoms associated with exacerbation, it is consistently agreed upon in the literature that patients presenting with a change in symptoms should always receive urgent treatment (Bhatt, 2013).

Respiratory symptoms are a prevalent problem in people with CF (Goss et al., 2009). Tools that measure respiratory symptoms can aid the prediction of forthcoming pulmonary exacerbations (Quittner., 2005). It is incredibly important that symptoms, which may be linked with exacerbations, are closely monitored in CF patients. Exacerbation symptoms include cough, sputum volume and viscosity, breathlessness and fatigue as previously discussed.

Goss et al. (2009) identified six pulmonary symptoms from 25 qualitative interviews conducted in CF centres in the US. The symptoms reported included: cough, sputum production, wheeze, chest tightness, difficulty breathing/shortness of breath and fever. This has since been validated and developed into the Cystic Fibrosis Respiratory Symptom Diary (CFRSD) and Chronic Respiratory Infection Symptom Score (CRISS) (Goss et al., 2009).

Pain is one of the many non-respiratory symptoms of CF, and is widely reported (Lechtzin et al., 2016) although there remains to be little standardisation in the way in which it is measured (Harvermans, 2013). There is currently no measurement tool, which covers all aspects of pain in CF, however the Brief Pain Inventory (BPI) (Charles and Cleeland, 2009) is often modified to suit the needs of the population (Cleeland., 1991). The BPI has also been applied to conditions

including: depression (Rayner et al., 2016), fibromyalgia (Mease et al., 2011) and surgical pain in cancer patients (Tittle et al., 2003). The tool is one of the most widely used self-report measures of pain in clinical samples (Cleeland, 2009).

Lechtzin et al. (2016) studied pain experiences of adolescents (aged between 12-20 years) living with CF. Patients were asked to complete a 188 item questionnaire at baseline and again 6 months later, 73 patients completed the task at baseline and 53 completed at follow-up. Questions relating to pain in the survey were adapted from the Cystic Fibrosis Questionnaire Revised (CFQ-R) (Quittner et al, 2005), the Functional Disability Index (Walker and Greene, 1991) and also the BPI (Cleeland., 1991). It was found that high pain scores were correlated with a higher number of hospital admissions due to pulmonary exacerbations, however the correlation was not significant when age, gender and FEV1 (forced expiratory volume which is used as a measure of pulmonary function, the measure is taken using a spirometer) were adjusted for (Lechtzin et al., 2016). It could be argued that due to the small sample size perhaps the study is lacking sufficient power. Furthermore, there is also evidence of attrition within the study as only 53 out of 73 patients completed the follow-up. This could indicate some level of bias within the sample. However despite the small sample size within the group there was a varying level of predicted FEV1 (lung function) (22%-125%), a broad age range and a good representation of gender (56% female and 44% male). Therefore, whilst the results of Lechzin’s et al.'s (2016) study should be interpreted with some level of caution, the findings do provide a good insight into the significance of pain experienced by patients with CF.

Commonly patients with CF will experience symptoms relating to the digestive system. Due to the blockages in the system and limited function in the pancreas, patients are unable to absorb fat, protein and fat-soluble vitamins (Steinkamp & Wiedemann, 2002). According to Steinkamp and Wiedemann (2002) symptoms associated with the gastrointestinal tract include constipation, small bowel bacterial

overgrowth and gastroesophageal reflux. As a result of these digestive symptoms patients with CF are likely to have a low Body Mass Index (BMI). BMI is a measure of healthy weight which is calculated using the weight and height of a person, a healthy BMI ranges from 18.5-24.9 (NHS, 2023). However, there are drawbacks of the measure, BMI does not take into consideration body composition i.e fat-free mass and fat mass (Alvarez et al., 2016). Despite this the measure is used routinely in practice with patients in the UK (Cystic Fibrosis Trust, 2018) and is often used as an indication of a patient outcomes (Stallings et al., 2008).

Kerem and colleagues (2014) analysed data of the 14,732 patients recorded on the European Cystic Fibrosis Society patient registry and concluded that patients with low BMI were six times more likely to have severe lung disease than patients with a healthy BMI. Similarly digestive symptoms experienced by patients with CF have been found to be linked with life-expectancy and wellbeing of patients (Steinkamp and Wiedmann., 2002). The life expectancy and wellbeing of patients are factors which impact upon Quality of Life, this will be reviewed in the following section of this introduction.

In 1947 the World Health Organisation (WHO) defined health as ‘a state of complete physical, mental and social well-being not merely the absence of disease’ (WHO, 1947, p. 13). There is ongoing discussion within the literature which relates to the difference between health status, Quality of Life (QoL) and Health Related Quality of Life (HRQoL). According to Ferrans (1990) QoL is more than health status and has been defined by the WHO as individuals’ perceptions of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns’ (WHO, 2012, p.11). Wilson and Cleary’s (1995) model of health-related QoL, highlights how biological/clinical factors (for example living with a pulmonary condition or a cancer diagnosis), functional status, symptoms and general health perception all impact on the patient and their overall QoL.

According to Habib et al. (2015) it is of key importance to monitor QoL in patients with CF, as in recent years the life expectancy of patients has increased so dramatically, more information and insight into QoL is required. This information could enable clinicians to develop further understanding into what areas of QoL are commonly affected in people with CF and help guide interventions and resources designed to support the needs of individual patients and promote patients' QoL.

Abbott et al. (2015) recruited patients with CF into a longitudinal study and recorded clinical variables such as FEV1, BMI, diabetic status and whether or not patients had an intravenous device fitted. The relationship between such clinical variables and health-related quality of life in patients with CF was investigated every two years for a 12-year period. In total nine domains from the Cystic Fibrosis Quality of Life Questionnaire Gee et al. (2000) were used to assess QoL (physical functioning, social functioning, emotional responses, treatment issues, chest symptoms, body image, interpersonal relationships, career concerns and concerns for the future). It was found that having a lung transplant caused the largest changes to HRQoL. This event caused large increases in the following domains: treatment issues, chest symptoms, concerns for the future and emotional responses. However, it was found that receiving a transplant caused a decline in the following domains: career concerns, body image and social functioning. This longitudinal research undertaken by Abbott et al. (2015) offers insight into the disease trajectory and the impact it has on Quality of Life over several years.

In addition to the intense daily treatment regime, the clinical symptoms experienced by those living with CF are complex and as discussed, can impact on patients' Quality of Life (QoL) (Abbott et al., 2015). According to Havermans et al. (2008) lower FEV1 is associated with lower levels of physical functioning and lower general health perceptions. Additionally, a systematic review conducted by Habib et al. (2015) concluded that FEV1 and pulmonary exacerbations had the largest impact upon patients QoL. FEV1 predicted (%) was significantly

associated with all but one (digestion) of the domains of the CFQ-R. Which highlights the link between poor clinical outcomes and lower levels of QoL in this population. This demonstrates support for the work of Havermans et al. (2008) in highlighting the impact that poor lung function can have on both physical functioning and quality of life in patients with CF.

1.2 Assessment

A variety of patient reported outcome measures have been developed to assess the impacts of CF. Some focus on a specific type of impact (e.g. respiratory symptoms), whilst other measures assess the impacts of CF on QoL more generally. The Cystic Fibrosis Questionnaire Revised (CFQ-R) (Quitnner., 2005), is the main CF specific patient reported outcome measure. The measure consists of nine domains in total, the domains are as followed: physical, role/school, vitality, emotion, social, body image, eating, treatment burden and health perceptions. The measure is viewed as the 'gold standard' in the pharmaceutical industry, where it is often used to test the effectiveness of new therapies (McCarrier et al., 2020). As a result of this the CFQ-R has undergone an extensive amount of validity and reliability testing (Knudsen et al., 2016). The scale correlates with changes in lung function detected by spirometery (lung function) readings (Jarad and Sequeiros., 2012).

More recently, McCarrier et al. (2020) developed the Cystic Fibrosis Impact Questionnaire (CF-IQ) to assess the way in which CF impacts upon the lives of patients living with the condition. The measure was developed using qualitative interviews and cognitive interviews with 42 patients and caregivers of those with CF and assesses multiple domains, which may have been affected as a result of the condition. The measure is in the early stages of development and is currently undergoing psychometric testing in CF patients, findings of such have not yet been published.

There are various patient reported outcome measures which are specific to CF patients, for example the Cystic Fibrosis Quality of Life Questionnaire developed by Abbott et al. (2008) which includes nine domains and aims to provide an insight into how the condition is impacting upon all aspects of the patients life. In total there are six different CF Patient Reported Outcome Measures (PROMs) which have been developed are summarised in Table 1, the table includes detail relating to the focus of the PROM, the name and a brief description.

Table 1.
An overview of Cystic Fibrosis Specific Measures

Key symptoms/Focus	Measure	Description	Author
Consists of nine domains: Physical, role/school, vitality, emotion, social, body image, eating, treatment burden and health perceptions.	Cystic Fibrosis Questionnaire Revised	A disease specific measure of general health and wellbeing, symptoms and daily life. Recall period two weeks.	Quittner (2005)
Consists of nine domains: Physical, social, treatment, chest symptoms, emotional, body image, relationships, career and future	The Cystic Fibrosis Quality of Life Questionnaire	A disease specific measure of Quality of Life. Recall period of two weeks	Gee et al. (2000)
Domains include: Activity limitations, functional limitations, treatment burden and future outlook.	The Cystic Fibrosis Impact Questionnaire (CF-IQ)	A disease specific measure of the long-term impact of CF. Recall period of 7 days.	McCarrier et al. (2020)
Consists of five domains: Respiratory symptoms, chest symptoms, weight, digestive symptoms, emotional state.	Memorial Symptom Assessment Scale-CF	Adapted to measure burden, in psychological and respiratory symptoms. Recall period of one week	Sawicki et al. (2008)
Difficultly breathing, cough, coughing up mucus, chest tightness,	The CF Respiratory Symptom Diary	A disease specific symptom scale, which aims to	Goss, Edwards, Ramsey, Aitken and

wheeze, feeling feverish, tired and chills/sweats		measure the severity of the condition, with a recall period of 24 hours.	Patrick (2009)
There are four main symptoms: cough, sputum, breathlessness and fatigue which are scored from one to four.	Report Symptom Scale	A symptom score with a focus on Pulmonary Exacerbations. Administered on day 1 and day 14 of antibiotic treatment.	Jarad and Sequeiros (2012)

1.3 Treatment and Management of Cystic Fibrosis

It is evident from summarising the evidence relating to CF that the symptoms of the condition are widespread and affect many aspects of the body. Due to the multisystemic nature of the disease symptoms are not limited to the impact it has on the lungs and respiratory system.

Furthermore, living with CF is likely to impact upon the patients Quality of Life, in order to stay well for as long as possible patients with CF are often prescribed a complex treatment regime to target different aspects of the body (Altabee et al., 2022). For example, dietary management with replacement enzymes (Jones and Helm, 2009) and physiotherapy which tends to use airway clearance techniques (Arias Llorente et al., 2008).

In recent years, there has been major developments in the treatment of CF as new drugs named ‘modulator treatments’ are available and prescribed to patients with a particular genetic mutation named CFTR for patients with other mutations this treatment will not help (Fajac & De Boeck, 2017). In the UK treatments commonly prescribed include Orkami, Symkevi and Kaftrio (CF Trust, 2024), the drugs are taken orally in tablet form. The short terms effects of treatment include improvement in lung function, patients gaining weight and decreases in

the number of pulmonary exacerbations, all of these changes lead to better projected survival for patients (Taylor Cousar et al., 2023)

Respiratory symptoms and infections are treated with inhaled treatments such as nebulisers and in more recent years, modulator treatments. Nebulisers convert solutions of medications into a fine mist, which can be penetrated deep into the lungs, nebuliser treatments are associated with an increase in life expectancy for CF patients (Accurso, 2008). Patients may use a range of different nebuliser treatments dependent on their condition at the time. Dornase alpha (DNase) is a mucolytic used in patients with CF to help improve the clearance of sputum and also to aid pulmonary function (Burrows et al., 2002). Mucolytics such as DNase lower the elasticity of the mucus, therefore breaking it down so that the cilia (tiny hairs) in the lungs can remove it (Henke & Ratjen, 2007). hypertonic saline is another example of a mucolytic, a salt-water solution which has the same function as DNase (Elkins & Bye, 2011). Unlike DNase it also tends to increase coughing which can be helpful to clear mucus. The drug is used by 36.8% of patients with CF (CF Registry, 2019).

Nebulised antibiotic treatments such as Tobramycin and Colomycin are just two examples of treatments that are prescribed to treat specific bacterial infections such as *Pseudomonas Aeruginosa* (Webb & Dodd 1997). Developed in the 1980's there have been a number of studies that have shown that compared to a control group the drug reduces hospitalisation incidents and also the number of days experienced as an inpatient; MacLuksy et al. (1989) studied patients for 32 weeks, Ramsey et al (1993) studied patients for 28 days and Ramsey et al (1999) studied patients for 24 weeks.

1.4 Adherence

Horne and colleagues (2006) define treatment adherence as 'the extent to which the patient's behaviour matches agreed recommendations from the prescriber' (Horne, 2006, p. 66).

Previously adherence has been described using other terms such as concordance and compliance (Chakrabarti, 2014). Concordance is defined as ‘emphasising an agreement between the clinician and the patient, which takes into account each other’s perspective on medication-taking, to a broader process consisting of open discussions with the patient regarding medication-taking, imparting information and supporting patients on long-term medication’ (Chakrabarti, 2014, p. 30). Compliance is defined as ‘the extent to which the patients behaviour matches the prescriber’s recommendations’ (Chakrabarti, 2014, p. 30).

However now adherence is the most commonly used within the literature body (Chakrabarti, 2014), with the World Health Organisation (WHO, 2003) publishing their definition of adherence in 2003 as ‘the extent to which a person's behaviour – taking medication, following a diet, and/or executing lifestyle changes – corresponds with agreed recommendations from a health care provider (WHO, 2003, p. 18).

Adherence in the literature is often split into unintentional non-adherence and intentional non-adherence. Unintentional non-adherence is viewed as a more passive behaviour, which is not linked to cognitions (Wroe, 2002; Lowry et al., 2005) but to other factors such as forgetfulness. Intentional non-adherence is aligned much closer to personal beliefs, values and attitudes (Lehane & McCarty. 2007). Intentional non-adherence is when the patient actively chooses not to follow their prescribed treatment recommendations. Examples of intentional non-adherence include- changing or reducing a dose of medication as symptoms improve or believing that it is acceptable to have a holiday from treatment. According to Thorneloe et al. (2018) people with intentional non-adherence could believe they are demonstrating good disease control and awareness of their condition. This highlights the importance of understanding the reasons behind patient’s non-adherence and how this related to symptoms and exacerbations.

It is important that adherence is measured accurately. There are a number of techniques which have been used to measure adherence, however there are strengths and limitations associated which each approach and these will be discussed below.

Self-report measures of adherence can be more easily administered and can be less-time consuming than other methods of measurement (Lehmann et al., 2014). However, they are prone to inaccuracies: when reporting adherence patients tend to overestimate how much medication they take (Daniels et al., 2011). Social desirability bias is one of the drawbacks associated with self-report measures of adherence because patients have the opportunity to report higher levels of adherence when completing self-report measures, than are accurate (Wilson et al., 2009). Patients may feel healthcare professionals are likely to view them differently if they report poor levels of adherence, with potential impacts on the care that is available to them (e.g. eligibility for lung transplant) however, it could be unhelpful to provide inaccurate information about treatment behaviour to health professionals, in terms of them then being able to provide the most effective form of treatment and support for the patient.

There are multiple self-report measures which focus on adherence see table 2 below for a summary of three different self-report measures. One example is the Medication Adherence Report Scale (MARS-5) (©Professor Rob Horne) (Chan et al.,2020), the tool is used to measure participants willingness and ability to take treatments. This self-report measures intentional and unintentional non-adherence. The MARS-5 includes questions such as ‘I forget to take my medication,’ ‘I take less than instructed’ and ‘I try to avoid using it’, participants are asked to answer using one of the following options: (1) always, (2) often, (3) sometimes, (4) rarely, (5) never (Chan, Horne, Hankins and Chisari., 2020).

Chan et al., (2020) piloted the measure in over 400 patients with three different conditions: asthma, hypertension and diabetes. Cronbachs

alpha for the measure ranged from 0.67 (hypertension patients) to 0.89 (diabetic patients) demonstrating a good level of internal reliability within these patient populations, particularly the diabetic sample.

Goodfellow et al. (2015) utilised the measure in children with CF, adherence to three different types of therapies were monitored (MARS, pharmacy Patient Medication Records (PMR) and GP prescription data). PMR relates to the number of drugs dispensed and GP prescription data related to the GP issue records of prescriptions. It was concluded that there was a level of overestimation when using self-reports, however children's reports were closer to the pharmacy refill records and GP prescription data in comparison to parents.

Table 2.

Self-report measures of adherence

Author	Measure name	Example question	Disease specific measure?
Chan, Horne, Hankins and Chisari (2020)	Medication Adherence Report Scale (MARS-5) (©Professor Rob Horne)	'I forget to take my medication' and 'I take less than instructed'	No
Morisky, Green and Levine (1986)	The Morisky Medication Adherence Scale (MMAS)	'When you leave home or travel, do you sometimes forget to bring along your medications?'	No
Svarstad, Chewning, Sleath and Claesson (1999)	Brief Medication Questionnaire	'In the past week, how many times did you miss taking a pill?'	No

Although there a clear drawbacks associated with the use of self-report measures of adherence data, such as social desirability bias and recall bias (Daniels et al., 2011), self-report measures are often used in clinical trials and settings as a quick and cheap way to gauge adherence levels (Farmer, 1999; Lehmann et al., 2014).

Medicine Possession Ration (MPR)

Medicine Possession Ratio (MPR) is a measurement of adherence linked to pharmacy dispensing and the method is focused on whether the patient collects their prescriptions. MPR is calculated using a formula which uses the total number of days supply in a period, divided by the number of days in the period, multiplied by 100 to convert into a percentage (Steiner and Prochaza., 1997) as follows:

$$\text{MPR} = \frac{\text{Total number of days worth of supply in period}}{\text{Number of days in supply period}} \times 100$$

Eakin et al. (2011) used MPR to record the adherence of different treatments in 95 CF patients, aged six or over, for a 12 month period. The median MRP for hypertonic saline was 49%.

Quittner et al. (2014) used MPR and Composite Medicine Possession Ratio (CMPR) (an average of a 12 month MPR) it was found that the mean MRP for Dornase Alpha was the highest at 57%, inhaled tobramycin was 51% and hypertonic saline was 40%. However, unlike methods that capture adherence on a daily basis, CMPR is a calculation based over a longer period of time, such as a 12 month period. Therefore, it is not possible to understand patients daily habits based on this reading (Quittner et al., 2014).

The method is considered as an objective method of data collection as it is taken from pharmacy records and not from the patient directly, and therefore considered to be more rigorous in comparison to self-report

measures (Zobell at., 2017). However, it is difficult to determine with MPR if the medication is actually taken. Not all medications collected will be used (Wildman and Hoo, 2014), and it doesn't show if the prescription (dose, timing etc) is being followed accurately, as according to Zobell et al. (2017) patients could be stockpiling treatments.

Although there are limitations of using this method, Mitchell et al. (2021), who conducted a 5 year study observing the clinical outcomes of Ivacaftor, argued that MPR is the most commonly available source of adherence data that can be used to look at trends over months and years.

Electronic Monitoring

Electronic monitoring is an objective form of monitoring treatment taking (as opposed to medication collection) and collecting adherence data. Such systems enable data to be downloaded in clinic and viewed by the clinician and patient and used to facilitate discussion (Agent and Parrott, 2015). Electronic adherence monitoring has been viewed as the 'gold standard' approach within adherence literature (Chan, Horne, Hankins and Chisari, 2020). There are different types of electronic monitoring, the most common methods include Medication Event Monitoring Systems and the use of Integrative Nebuliser Systems.

Medication Event Monitoring System (MEMs)

Medication Event Monitoring Systems (MEMS) are similar in appearance to a pill bottle and also work in the same way, however the device tracks the time and date that bottle is opened (Siracusa et al., 2015). The data is saved and produces graphs, which can be downloaded; the graphs contain plots of the date and times the medication was taken. However similarly to MRP, there is a possibility that adherence data could be manipulated or reported to be higher if patients do not swallow the pill in which case, the data would be inaccurate (Siracusa et al., 2015).

Modi et al. (2006b) investigated adherence in children with CF using a range of methods including child self-report, parent self-report and pharmacy refill history and MEMs. For the self-report parents were asked to recall their activity through the use of a daily phone diary. Alongside the Disease Management Interview where both parents and children were asked to complete the 51-item self-report measure honestly. For enzyme capsule medication the rates of adherence varied from 89.5% for parent self-report, to 90% for child self-report to 42.5% for MEMs. Which demonstrates the large discrepancy between objective and subjective measurements of adherence, although there is no explanation offered in terms of why this may be, Modi et al. (2006b) attempted to limit social desirability as much as possible by agreeing that adherence data collected would not be shared with clinicians.

Integrative Nebuliser Systems

Integrative nebuliser systems such as the ETrack® (PARI)® (PARI) and the I-neb® (Philips Respironics) are examples of Adaptive Aerosol Delivery (AAD) which track treatment taking and can be used to objectively measure adherence.

The I-neb measures direct medication adherence (McCornmack, Southern and McNamara, 2012). The device contains a microchip which is downloaded and reviewed in clinic, providing information such as the date, time and the dosage inhaled. Landon and Fuchs (2017) conducted a pilot study using an electronic nebuliser called the eTrack® (PARI) to monitor and optimise patient's adherence to nebulised therapies whilst using Motivational Interviewing. According to Landon and Fuchs (2017) using devices such as the eTrack® (PARI) encourages the patient to be actively involved in their treatment. As the patient is more involved, this encourages co-care therefore caring for the condition is the responsibility of the care team and the patient (Landon and Fuchs, 2017). Objective methods of adherence monitoring are used with the CFHealthHub, using both eTrack and INeb across a total of 19 CF centres across the UK (Hoo et al., 2019a).

Daniels et al. (2011) compared objective adherence measures to self-reported and clinically reported adherence measures. Objective adherence data was collected via an Adaptive Aerosol Delivery (AAD) I-neb nebuliser for the three months prior to the study start. For the self-report, participants were asked to reflect on their adherence during an average week and over the three month period. Clinicians were asked to complete a questionnaire for each participant, which was also related to adherence for the three-month period.

Daniels et al. (2011) found adherence varied from 80% (self-report) to 36% (objective methods) and concluded that electric monitoring was the most accurate method of adherence monitoring, specifically over a long-term period. The questions were asked in relation to adherence habits over a three-month period, which questions the validity of using retrospective measures over this time period due to the likelihood of recall bias.

To summarise, the new objective measures of capturing nebuliser adherence allow relationships to be explored in more depth and detail than self-report measures could offer. There is currently an absence of data relating to how patients having access to objective data can be used to explore the relationship between adherence and symptoms experienced by patients with CF. This will be further explored within the studies of this thesis using data from the CF HealthHub.

Measuring Drug Metabolites

Drug metabolite is a measurement of adherence which involves taking biological samples from the patient such as blood, urine or saliva (Paterson et al., 2002). Costedoat-Chalumeau et al. (2016) investigated the use of metabolite blood levels in monitoring adherence to hydroxychloroquine in patients with lupus. It was concluded that blood tests revealed that 20% of patients had low levels of adherence. Clinically this was not noticed during appointments, therefore Costedoat-Chalumeau et al. (2016) suggest that utilising blood

metabolites can be an accurate objective measure of adherence to treatment.

Stocco et al. in (2010) analysed case study data of four different participants, all of which had been prescribed with azathioprine to treat either inflammatory bowel disease or autoimmune hepatitis. It was concluded that the findings from the study support the use of collecting drug metabolites in order to understand levels of adherence to prescribed treatments.

Although Stocco et al. (2010) and Costedoat-Chalumeau et al. (2016) view the use of measuring metabolites as a reliable objective measure of adherence, relevant training is required in order to utilise this method. For example, being trained to take blood from participants and also having relevant equipment to analyse the blood collected, and so has limited applications in real world settings.

As previously discussed, adherence can be measured using a number of different methods, which have been found to report varying outcomes. Table 3 below summarises levels of adherence in patients with CF using a range of different measurement tools.

Table 3.

Adherence to nebuliser treatments using different measures

Author of paper	Sample information	Measurement of adherence	Treatment	Reported level of adherence
Daniels et al. 2011)	78 adults with Cystic Fibrosis	Self-report	Nebuliser treatment (combinations of: colistin, tobramycin, dornase alpha, salbumtamol, ipratropium bromide, hypertonic saline)	80%
Pakhale et al. (2016)	42 participants with Cystic Fibrosis	Self-report measures	Hypertonic saline Nebuliser	42.4%
			Tobramycin Nebuliser	30.6%
Quittner et al. (2014)	3,287 patients with CF aged 6 year of over	Medicine Possession Ratio (MPR) and Composite Medicine Possession Ratio (CMPR)*	Dornase alpha	57%
			Tobramycin	51%
			Hypertonic saline	40%
Modi et al. (2006b)	37 children aged 6-13 with Cystic Fibrosis	Medication Event Monitoring System (MEMS)	Enzyme Capsules	42.5%
Daniels et al. (2011)	78 adults with Cystic Fibrosis	Objective methods (I-Neb AAD)	Nebuliser treatment (combinations of: colistin, tobramycin, dornase alpha, salbumtamol,	36%

ipratropium bromide, hypertonic saline)

1.5 Medication Adherence in Cystic Fibrosis

Patients are prescribed complex treatment regimens to manage the symptoms of their condition, which as discussed can be a burden to patients. However, ultimately the deterioration of symptoms and lung function is linked to poor outcomes for patients, such as increased hospital visits (Briesacher et al., 2011). As previously stated, the average life expectancy of a person born with CF is now around 50.6 years of age (CF Registry, 2020), which has increased drastically in the past 40 years (Abbott et al., 2019). Treating exacerbations with intravenous antibiotics is one of the several ways which medicine has advanced, and these treatments have impacted positively upon life expectancy in those with CF. Over half of intravenous (IV) antibiotics are delivered in hospitals, and can last for 21 days (Tappenden et al., 2017).

The side effects of receiving IV antibiotics treatments (specifically Aminoglycosides and Glycopeptides i.e. Tobramycin and/or Amikacin) in older patients can be serious and has been found to damage the auditory function in the inner ear, causing hearing loss (Garinis et al., 2017). Nebulisers deliver the drug directly to the source of the problem i.e. the lungs and are therefore less likely to produce side-effects compared to IV antibiotics which are delivered to the whole body (Cystic Fibrosis Trust, 2020b). Therefore, preventative medicine such as nebulisers is preferred in CF. However, this relies upon patients adhering to these treatments (Hind, 2019) which is a complex matter.

In 2013 patients with CF spent a combined 103,453 days receiving IV treatments (Hoo et al., 2018). These treatments are costly, it is estimated that £49.5 million could be saved in the UK over a 5-year period if children adhered to nebuliser treatments, this could be due to

less wasted medicines and better outcomes for these patients, thus less hospitalisations. It is estimated that these cost savings would be even higher in the adult population (Tappenden et al., 2017). Furthermore, there is a cost to the patient since patients with CF in England are not exempt from prescription costs which are around £108.10 per year in England. Prescriptions are free of charge for patients in Ireland, Wales and Scotland (CF Trust, 2020). In the US the mean cost for treating CF per year is $15,571, however for severe disease this can be up to $33,691. 29% of these calculated costs are associated with pharmaceuticals (van Gool et al., 2013).

Although different treatments react differently for different people (i.e. the length of time they take to work and possible side effects). It is clear from the work conducted in drug trials that adherence to treatment, specifically nebulisers will improve symptoms over time (Elkins et al., 2006).

Drug trials for different nebuliser treatments have demonstrated a range of different outcomes on symptoms. Wark et al. (2009) published a Cochrane review which reviewed 12 drugs trials with a total of 442 participants, all of the drug trials had investigated the effectiveness hypertonic saline. It was found that the treatment when used twice per day for a 48 week period was able to improve symptom related quality of life, attendance to work and school, however the evidence around improving lung function was limited.

Similarly, Ramsey et al. (2011) conducted a double blind, placebo-controlled evaluation of ivacaftor and also found improvement relating to quality of life and also improvements related to lung function. McCoy et al. (2008) investigated the use of AZLI to treat Pseudomonas in a double-blind placebo controlled study and also reported an improvement in respiratory symptoms.

However, the results of these drug trials should be interpreted with caution. Wark (2018) argued that only two of the studies (Rosenfield, 2012; Suri, 2002) reported using adherence to treatment as an

outcome measure. Ramsey et al. (2011) measured adherence in their study but this does not specify if it is related to patients adhering to the treatment as prescribed. Therefore, although the study or trial period is a specific time window it is not clear if participants have adhered to the treatment as instructed. As a result of this these findings there is some ambiguity relating to how much is needed to exert the benefits of treatment and how variable adherence can impact on health outcomes over time and for each individual. Despite this, evidence from such drug trials informs the treatment guideline such as the National Institute of Clinical Excellence.

Although the evidence from drug trials highlight the positive impact on clinical outcomes and respiratory symptoms, patients must adhere to nebulised treatments in order to see an improvement in their condition.

1.6 CFHealthHub

CFHealthHub (CFHH) is a digital platform and complex intervention designed for patients living with CF, which incorporates behaviour-change techniques and tools (Hind et al., 2019). The project was funded by the National Institute for Health Research (NIHR). In 2023 CFHH was implemented in over 70% of adult CF services across the UK (CFHealthHub.,2023), however in October 2024 the CFHealthHub was closed due to lack of funding.

When participants consented to being a part of the CFHH were provided with a chipped nebuliser system (eTrack, PARI Pharma GmBH; and Bi-neb, Philips Healthcare). Each nebuliser dose taken by the participant was stamped with the date and time by the nebuliser itself. The system was notified of how many doses patients should take according to their personal prescription and this was displayed with the actual doses taken above. The unadjusted adherence which was reported as a percentage is the is the actual doses taken compared to the prescribed amount (Hoo et al., 2021). The data collected through the CFHealthHub data observatory, provides data to the patient and to

the centre (with the patient's permission). For further detail relating to the data transfer in the CFHH please see subsection 3.5. This can enable the patient to monitor their adherence levels individually and also to work with HCP's to monitor treatments.

CFHH was developed using the COM-B model as a conceptual framework (Arden et al., 2021). There were seven stages of development adopted which included planning, designing, creating, refining, documenting and planning for future evaluation. Within these stages there was input from PPI groups, consultations with healthcare professionals and also a number of published studies which include qualitative studies (Drabble et al., 2019), pilot, feasibility studies (Hind et al., 2019) and more recently the trial itself (Wildman et al, 2021). The trial itself concluded that there was an increase in adherence in patients who had previously reported poor adherence (Wildman et al., 2021). However further work is required to explore why it was that increased adherence did not reduce levels of exacerbations.

The programme ran between August 2015 and October 2024 and presented users with real-time data relating to their nebuliser usage (Hind et al., 2019) and therefore collected objective real time adherence data.

The current thesis is not part of the CFHealthHub, however patients who have been part of the trial will be recruited and their adherence data will be used. Study 4 of this PhD involved exploring the perspectives of Health Care Professionals who work at sites that use the CF Health Hub.The doctoral researcher (RM) does not have any prior involvement with the CFHealthHub and was appointed by Sheffield Hallam University to conduct this funded PhD. RM has no prior clinical or personal experience of Cystic Fibrosis.

1.7 Self monitoring and feedback

Drug trials (Elkin et al.,2006; Wark et al., 2009; Ramsey et al., 2011) show that there is an improvement in clinical outcomes and symptoms overtime when nebulisers are used by patients with CF. However as

previously discussed, it is unclear how adherence may influence/limit the benefits of treatment and how long patients need to take treatments to notice an improvement in their symptoms. It has been suggested that patients must adhere for prolonged periods of time (e.g. up to 48 weeks) to notice benefits of treatment (Wark et al., 2009).

To date, it is not clear whether self-monitoring of symptoms, and the use of feedback data on the relationships between adherence and symptoms, could play a useful role in the management of Cystic Fibrosis. Lumley et al. (2022) investigated patients and Health Care Professional's (HCP's) perceptions of objective nebuliser adherence data used in the CFHealthHub. It was found that both HCP's and patients with CF welcomed the use of the data. The data was also described as being 'proof to the self' and 'proof to others' acting as motivation to adhere for some participants. However it is important to note that the study drew attention to the fact that data must be used responsibly and with caution as for some participants it can cause anxiety and added pressure. Tanenbaum et al. (2016) concluded in their work with adults living with type 2 diabetes that HCP's have a role to play in terms of guiding patients around the use of symptom monitoring apps and making recommendations for those which would be most beneficial. However a systematic review from 2020 Gandrup et al. (2020) reviewed symptom reporting systems in adults with long-term conditions and found that none of the final 12 studies included were of good enough quality to be shared with HCP's. This suggests that further work is required to bridge the gap between symptom tracking and this data being used in the clinical setting.

Gawande (2004) explained that often patients with Cystic Fibrosis will experiment with their treatments, making minor changes which could have large impacts upon their condition. Self monitoring and feedback could play an important role in helping the patient better understand their condition and the benefits of treatment. However, Gawande (2004) argues that patients often need support and guidance from healthcare professionals when interpreting changes in symptoms. It

may be that CF patients find it difficult to interpret feedback data relating to the relationship between their adherence to treatment and symptoms, especially if this relationship is quite complex. Feedback data therefore has to be presented in a way which the patient understands and research has shown the use of graphs can be invaluable in helping people interpret health data (Garcia-Retatamaro, 2016).

Therefore, it is of key importance that patients living with chronic conditions such as CF are able to understand data which contains information relating to their health. This is something which will be discussed in the next section of this chapter.

1.8 Graph literacy

To ensure participants understand graphical feedback data they are being presented with they must have some level of 'graph literacy'. Graph literacy has been described as the 'ability to understand graphically presented information' (Galesic and Garcia-Retamaro, 2011, p. 444). The ability to interpret such graphs can help patients to make decisions about their health and risk communications (Garcia-Retatamaro, 2016), which could include information relating to medication adherence.

According to Reading Turchioe and Mangal (2024) it is becomingly increasingly common that patients with long term health conditions are being asked to work with data, for example collecting data about their condition, interpreting it and then managing their condition accordingly. Furthermore, the presentation and discussion of graphical representations of patient's health data can improve communication between patients and physicians, enabling a more patient-centred approach in terms of treatment (Nayak et al., 2016). Patient data displayed in graphs can be sent to patients virtually via the use of online applications, which have played a large role in the recent expansion of digital healthcare. The use of digital healthcare has the potential to benefit both the patient and clinicians, with the potential to

empower patients to understand complex information about their health and play a more active role in decisions relating to their healthcare (Klasnja and Pratt, 2012).

Previous literature has concluded that patients with lower levels of graph literacy were less likely to utilise their online personal health records (Ruiz et al., 2016). According to Ruiz et al. (2016) it is important that healthcare professionals are aware of levels of graph literacy of patients when implementing systems such as personal health records.

One of the drawbacks of using graphs is if people do not understand graphs properly, communication through the use of graphs can cause errors in judgment and decision-making according to Okan et al. (2018). Higher levels of graph literacy have been linked to more accurate decision-making and interpretation of graphs (Okan et al., 2016, 2012).

Despite the potential usefulness of graphs in aiding people's understanding of complex health data there is evidence that there are common problems, which prevent people from being able to accurately interpret and extract information from health-related graphs. However, it is important to note that within the general population there are large differences in levels graph literacy (Okan et al., 2015). Galesic and Garcia-Reramero (2011) recruited samples from Germany (n=495) and America (n=492) to investigate cross-cultural differences in graph literacy. Around one third of both samples were found to have low numeracy skills, when measured objectively using scales such as the Berlin Numeracy Test (Cokely et al., 2012) and the Subjective Numeracy Scale (Fagerlin et al., 2007). Similarly one third of both samples were found to have low graph literacy, which was measured using the Subjective Graph Literacy Scale (Galesic and Garcia-Reramero, 2011).

Despite differences in graph literacy it is clear that information containing healthcare information is of key importance. Therefore there

is a need to investigate further how graphs can be made more simple and easier to understand, regardless of graph literacy. The findings of this literature body will be applied directly to study 1 of this thesis which will look at graphs which display healthcare data.

1.9 Theoretical explanations of adherence

There are key theoretical frameworks which provide support for the potential usefulness of using self-monitoring and feedback data in the management of CF. Two of these which will be discussed in depth are the Necessity Concerns Framework (Horne et al., 1999) and the COM-B model (Michie et al., 2011).

The Necessity Concerns Framework

The Necessity-Concerns Framework (NCF) (Horne & Weinman., 1999) is a conceptual model which addresses the beliefs and attitudes associated with adherence behaviour. It is theorised that when prescribed with a treatment patients will weigh the costs of taking the medication against the benefits and use this to make a decision about whether they want to take the treatment. According to this model it is proposed that those who chose to adhere to medication have stronger perceptions regarding the necessity of the treatment and fewer concerns related to their treatment (e.g. side effects).

Horne et al. (2005) discussed the concepts of intentional adherence and non-intentional adherence within their work. Unintentional non-adherence is defined as ‘capacity and resource limitations that prevent patients from implementing their decisions to follow treatment recommendations and involves individual constraints (e.g., memory, dexterity, etc) and aspects of their environment (e.g., problems of accessing prescriptions, cost of medicines, competing demands, etc)’ (Horne et al., 2005 p.14). Whereas intentional nonadherence is said to come from ‘the beliefs, attitudes and expectations that influence patients’ motivation to begin and persist with the treatment regimen (Horne et al., 2005 p.14). Horne and Weinman (1999) focus on the role of intentional non-adherence, suggesting patients will make their own

decisions relating to a treatment, based on an evaluation of their necessities (e.g. feeling better) and their concerns (e.g. possible side-effects of treatments). The NCF has been applied to explain adherence behaviour in long-term conditions, examples of such include; Asthma (Axelsson et al., 2013), Cystic Fibrosis (Bucks et al., 2009), HIV (Gonzalez et al., 2007), depression (Aikens et al., 2005) and cancer (Horne et al., 1999).

The NCF is one of very few models which was designed and created to specifically to explain medication adherence (Rich et al., 2015). However, it could be suggested that using necessities and concerns alone to explain the complex phenomenon of medication adherence is limited and requires support from other models of health and illness to explain other aspects of behaviour such as motivation.

If a patient's symptoms and adherence data clearly shows the positive impact adherence has on the patient's symptoms then it is possible that the use of this feedback data could enhance the patient's perceived necessity of taking the treatment.

Bucks et al. (2009) investigated the role of illness perceptions on treatment adherence in a sample of adolescents with CF and applied findings to the Necessity Concerns Framework. In the work of Bucks et al. (2009) adolescents with CF were asked to report their adherence to three different treatments; chest physiotherapy (CPT), enzyme supplements and antibiotics. Measures such as the Beliefs about Treatment Questionnaire, The Revised Treatment Questionnaire and the Beliefs about Medicines Questionnaire where also used. The study found necessity beliefs to be associated with higher adherence to antibiotics and CPT. Bucks et al. (2009) concluded that those who viewed treatments were not necessary were likely to have lower adherence across all treatments. In the study, adherence was measured using a series of different self-report, subjective measures such as the Medication Adherence Report Scale (Horne and Weinman., 2002).

Sawicki et al. (2015) conducted a qualitative study with adolescents with CF and aimed to further understand how barriers and facilitators to adherence are perceived. Sawicki et al. (2015) found individuals who cannot feel their treatment working are less likely to perceive it as necessity, which supports The Necessity Concerns Framework (Horne et al., 1999). Furthermore a meta-analysis completed by Horne et al. (2013) analysed the data of 94 adherence studies, although there were no CF studies used in the meta-analysis there were a number of studies which focused on other respiratory diseases such as asthma. The findings of the meta-analysis provided support for the association between perceived need for treatment and higher adherence to treatment. For each standard deviation increase in necessity beliefs odds of treatment adherence increased by 1.7%. There was also a significant relationship between treatment concerns, adherence and having few concerns in relation to treatment side-effects, which accounted for a moderate to substantial amount of variance within the data. These findings highlight and support the CF literature, which also highlights side-effects are a potential barrier to treatment (Horne et al., 2013).

In regards to the Necessity Concerns Framework (Horne et al., 1999) the application of the model is often measured using the Beliefs about Medicines Questionnaire (BMQ) (Horne et al., 1999), which has been criticised for being ambiguous and the general questionnaire is not always relevant for all conditions (Thorneloe et al., 2013). Thorneloe et al. (2013) suggested that specific questionnaires could be more useful. Since then, the scale has been translated into different languages and cultures (Gatt et al., 2017; Nguyen et al., 2019). However there is no evidence to suggest that specific questionnaires for different conditions have been validated.

Therefore, the perceived importance of medication clearly plays a key role in treatment adherence, if patients view their treatments to have a lower level of perceived importance to their condition, they may be less likely to adhere to treatments as prescribed and conversely those with

higher levels of perceived importance are more likely to be higher adherers.

The COM-B Model of Behaviour

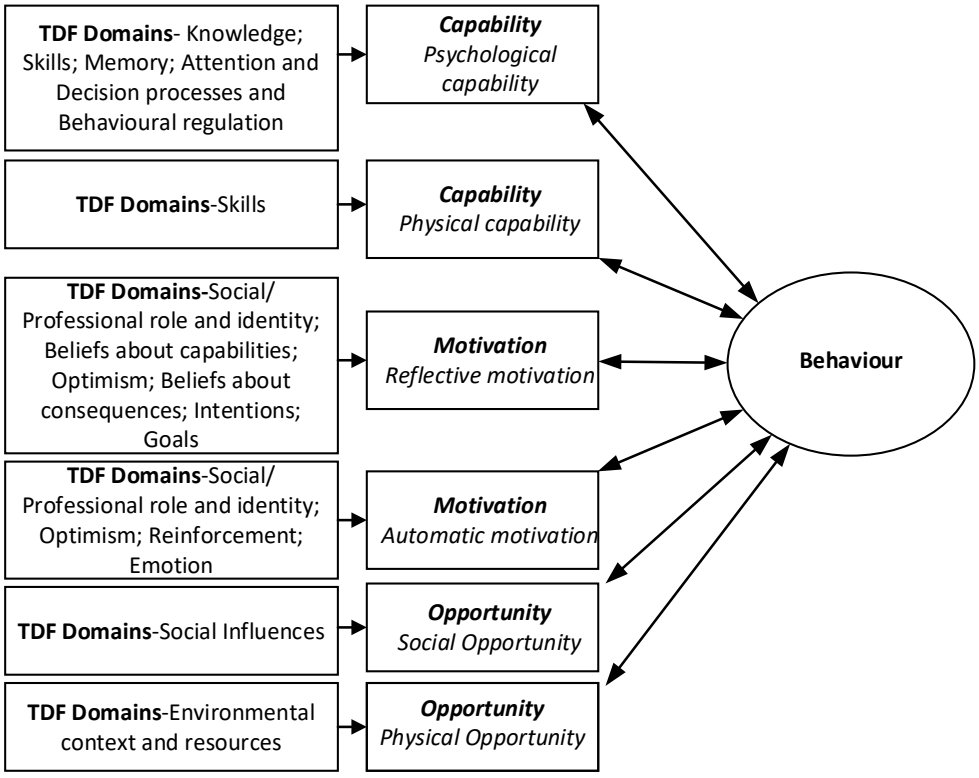
The COM-B model developed by Michie, van Stralen and West (2011) proposes a system of behaviour change which is based around three different components; capability, opportunity and motivation. The COM-B is at the centre of the Behaviour Change Wheel (Michie et al., 2011). Within each of the three components there are two constructs: capability (physical and psychological), opportunity (social and physical) and motivation (automatic and reflective). These constructs will be explained in further detail in the following section. For a visual representation please see figure 1 below for the full COM-B model. This figure is an adaption of the original diagram created by Michie et al. (2011).

The APEASE criteria (Michie et al., 2014) is a tool associated with the Behaviour Change Wheel which can be adopted to design and evaluate behaviour change interventions. The acronym refers to six different factors which will be considered here: Affordability- How cost-effective is the intervention? Can the intervention be created/designed within a specific budget? Practicality- How practical is it that an intervention can be implemented effectively? What can of training is required by staff to ensure that they can do this? Effectiveness and cost-effectiveness- In the applied setting could the intervention reach the outcomes which are desired? Acceptability-Is the intervention deemed acceptable by stakeholders? Side-effects/Safety- Are there any unwanted side-effects associated with the intervention which should be considered? Equity-Would the intervention reduce or contribution to health inequalities or disparities relating to health, wellbeing and standard of living? The APEASE criteria has previously been applied to interventions with patients living with Cystic Fibrosis such as the CFHealthHub (Arden et al., 2021)

The Theoretical Domains Framework (TDF) builds upon the COM-B and is designed to aid the implementation of behaviour change interventions. A synthesis of 33 theories of behaviour change and behaviour, which was originally split into 12 domains, however has been adapted to 14 (Michie et al., 2005; Cane et al., 2012) and 84 constructs (Phillips et al., 2014). The TDF acts as a framework not a theory, which aims to provide a theoretical lens (Atkins et al., 2017). The TDF can be used to understand what factors are influencing a health related behaviour such as adherence, and thus what factors could be the target of any behaviour change intervention aimed to improve adherence.

Figure 1.

TDF and COM-B Diagram



The model has been used previously to examine predictors of medication adherence (Jackson et al., 2014). Arden et al. (2019) applied the COM-B model and also the Theoretical Domains Framework (TDF) to the examination of nebuliser adherence in patients with CF. Within the work of Arden et al. (2019) who conducted qualitative research in this area, it was found that all three of the components (opportunity, motivation and capability) were related to medication adherence in people with Cystic Fibrosis. For example, capability related to patients having the skills to adhere but forgetting to plan their treatments in advance. Struggles with time-management and disruptions to routine over the weekend were related to opportunity and finally the beliefs around consequences (of poor adherence). Reinforcement was also identified with the motivation domain.

A person's reflective motivation (COM-B) and their beliefs about the consequences of taking their medication (TDF) could be influenced by feedback data which demonstrates impact adherences to their treatment has on their health/symptoms.

In reference to the COM-B (Michie et al., 2011), reflective motivation relates to the beliefs about the consequences of, or of not, conducting a specific behaviour. Evidence has suggested that patients beliefs about the importance of taking the nebuliser treatment and also the effectiveness of the nebuliser treatment can impact upon ones motivation to adhere.

A study conducted with people with CF in Australia (Hogan et al., 2015) identified perceived lack of importance of treatment as a theme in a qualitative study. In addition to this two published studies which were part of the CF Health Hub project (Arden et al., 2019 as previously discussed and Drabble et al., 2020) also found that the perceived importance of treatment taking motivated participants with CF to adhere to nebuliser treatments.

There are specific Behaviour Change Techniques which map on to the COM-B model and have been found to effectively increase motivation and health-related behaviours, such as adherence (Michie et al., 2011).

The Theory and Techniques Tool (Johnston et al., 2020) is an interactive database which triangulates evidence and represents links between different BCT's in a heatmap. Each relationship can be selected for further information relating to the strength of the relationship, this is informed by a literature synthesis study and an expert consensus study (Johnston et al., 2020).

The tool demonstrates that there is a link between *feedback on behaviour (BCT 2.2)* and motivation (p=0.08) and *feedback on outcome(s) (BCT 2.7) of behaviour* and feedback processes (p=0.02) which could suggest there is a potential benefit to using feedback data with CF patients. Therefore, if there is a relationship between objective

adherence data and subjective symptoms, then this feedback data could be potentially useful within the clinical management of CF.

Previous interventions which have been developed around the idea of feedback and self-monitoring have reported mixed findings. Wu et al. (2012) recruited participants with heart failure and created an intervention to improve medication adherence using data from Medication Event Monitoring System (MEMs). Participants were assigned to one of three conditions (theory based education intervention plus MEMS feedback, theory based education intervention with no feedback and a control group who received their care as usual). Using MEMs as feedback was shown to make a significant difference to medication adherence and cardiac event-free survival (meaning the patient survived without cardiac-related emergency department visit, cardiac-related hospitalisation, or cardiac death).

However, MEMs feedback is limited and as previously reviewed within this chapter it does not mean that the patient has taken the medicine they have simply opened it. Therefore it could be that patients were aware that levels of adherence presented to them was not accurate. Additionally there was a high level of adherence within this group, with only 36% of the sample not adhering to treatment, an issue which is common within adherence research (e.g. Clifford et al., 2008).

Furthermore often feedback studies are concerned with adherence only and presenting this to participants (Wu et al., 2012; Hill et al., 2020) rather than both adherence and symptoms together and the effect there variables can have on each other. This applies for studies which have recruited patients with Cystic Fibrosis for example McNamara et al. (2009) presented nebuliser data to children and Mikesell et al. (2017) collected airway clearance therapy data to monitor adherence in adults.

Wildman et al (2022) conducted the largest self-management intervention trial for adults with Cystic Fibrosis recorded, recruiting over 600 participants into the theory based intervention (CFHH). The

intervention was personalised for each participant and dependent on their needs different parts of the Necessity Concerns Framework (Horne et al., 1999) and the COM-B (Michie et al., 2011) were drawn upon. It was concluded that the intervention increased adherence without causing anxiety to participants, there was an increase in participants necessity to take medicine and a reduction in concerns about taking treatments. This study highlights the applications of presenting healthcare data to participants.

Medication adherence is complex and multi-faceted, there is not one psychological theory or factor which can be used to explain the behaviour. Whilst self-monitoring and feedback data may increase motivation, the perceived necessity of treatment and enables increased behavioural regulation. It is important to recognise that there are many other factors which influence treatment adherence.

A number of studies provide evidence for unintentional non adherence. For example ‘forgetting’ is a possible explanation of low medication adherence to nebuliser treatments in patients with CF. Dziuban et al. (2010) cited ‘forgetting’ to take treatment as one of the barriers to nebuliser adherence in CF. In total there were 60 adolescents recruited into the study and 67% of patients agreed with the statement ‘even though I want to follow my treatments, sometimes I just forget’. Similarly, Conway et al (1996) found that ‘forgetting’ to take treatment was the most cited reason for missing medication. Participants were asked to provide a reason when they missed their medication. In total 12 of the most prescribed treatments were included in the study, one of these was the nebuliser. However, it is important to acknowledge the age of this study, as it was published 25 years ago, during which time there has been large advances and changes in treatments and specifically the use of nebuliser treatments. Therefore these findings may need to be interpreted with caution.

However, according to Drabble et al. (2019), who investigated the concept of forgetting treatment in CF patients, those who had low

adherence described their intentional non-adherence as ‘forgetting’ to navigate expectations and norms. The work of Drabble et al. (2019) discussed how complex ‘forgetting’ behaviours are, and as the findings suggest, although forgetting may be used as a stated barrier to adherence, it is can disguised as other types of behaviour such as humour or avoidance.

Capability is another factor which is likely to influence adherence to treatment. Capability, which is one the constructs of the COM-B model, is the knowledge and skills one possesses about a specific behaviour. Faint et al. (2017) concluded that disease knowledge is associated with better levels of adherence, furthermore older adolescents were found to have higher levels of adherence than younger children which was a finding consistent with other work in the area (Bucks et al., 2009; Latchford et al., 2009). This could demonstrate that patient’s knowledge and understanding of their condition develops as they mature and therefore impacts upon their adherence to nebulised treatments. However, another possible explanation is that younger adolescents could feel that their choices relating to adherence will not impact them in the long-term.

Opportunity includes social and physical opportunities. According to Jackson et al. (2014) the opportunity component of the COM-B relates to influences which are outside of the individuals’ control, for example; the complexity of their treatment regime (Sawicki et al., 2009) and being able to afford the cost of medications are examples of physical opportunity (van Gool et al., 2013).

Social opportunity relates to the social norms and the impact of social support systems such as Healthcare Professionals (HCP) and specialist interventionists, has also been cited as an important facilitator to adherence behaviour (Colmbo, et al., 2018; Drabble et al., 2020). Furthermore, CF patients recruited into an intervention that recorded nebuliser adherence reported that providing HCP’s with the

permission to access their objective nebuliser adherence data acted as a prompt to encourage adherence (Drabble et al., 2020).

Conversely there are a numbers of barriers cited within the literature which relate to social opportunity. Such barriers include feeling embarrassed about using treatments in front of others (Jones et al., 2015). Demonstrating that for some patients adherence to nebuliser treatment can be a burden which impacts upon socialising and everyday life in some cases.

Physical opportunity can be used to explain some of the physical/environmental barriers to taking the nebuliser treatment, and feature in the Health Belief Model, for example time commitments, competing life demands, being too busy (Calthorpe et al., 2020; Dziuban et al., 2010; Hogan et al., 2015) and also having the required equipment and space to take the treatment effectively. These are barriers which participants feel are physically stopping them from adhering to their medication (Arden et al., 2021).

In terms of adherence to medication in CF, symptoms such as fatigue and tiredness have been cited as a barrier to patients effectively taking treatments (Arden et al., 2019; Calthorpe et al., 2020). This highlights the potentially complex and bi-directional relationship between symptoms and adherence. There is evidence to suggest that this can work the other way around for example, patients may take treatment in response to changes in symptoms (symptomatically). This was reported in the clinical guidelines and evidence review for medication adherence conducted on behalf of the Royal College of General Practitioners (Nunes et al., 2009), for specific conditions such as high blood pressure and rheumatoid arthritis.

However, there is limited evidence of this which is specifically related to the use of nebulisers in patients with CF. This could potentially be linked to the fact that nebulisers take time to work (Wark et al., 2005) and it is unlikely that patients will see an immediate change to symptoms as they may do when taking other medicines such as quick

relief asthma inhalers. For example salbutamol which can take action within 3-5 hours (National Institute for Health and Care Excellence, 2024). This could be explained through the cognitive approach of casual learning (Rottman et al., 2016), i.e. patients discovering how effective and necessary their treatments are and making decisions based on this.

Furthermore, for some taking medication could be a reminder of the seriousness and significance of the condition they live with, which could be a facilitator and a motivator to take treatment. As reported in the work of Arden et al. (2019) who cited reasons such as: feeling as if health depends on it, long term benefits and helping with symptoms as facilitators to adherence to nebuliser treatments in a qualitative study. However, participants with lower levels of adherence to CF treatments have reported avoidance as barrier to them taking treatment (Abbott et al; Arden et al., 2019)

It is clear that adherence to nebuliser treatments in patients living with CF is incredibly complex and theories such as the COM-B (Michie et al., 2011) can be helpful to organise the barriers and facilitators around the behaviour. However, Ogden (2016) highlights that there could be issues associated with creating standardised protocols when developing interventions tools using the BCW, suggesting that this can lack flexibility also takes the focus off how individuals respond, think or behave. Furthermore, Ogden (2016) also argues that generally by reducing the explanations of the behaviour to Capability, Opportunity and Motivation we are removing the variability in human behaviour (Ogden, 2016). This variability is something which Ogden (2016) argued should be celebrated rather than lost. This could suggest that the COM-B is oversimplifying complex behaviours such as medication adherence.

The barriers and facilitators to adherence in CF have been explored prior to the development of the COM-B (Lask, 1994; Conway et al., 1996; Kettler et al., 2002; Dalcin et al., 2007;). However, it is important

to note that more recently published papers have suggested that the COM-B can be a useful tool to explain/understand medication adherence in a number of different conditions, including CF and also help to develop interventions to improve the behaviour (King et al., 2023; Park et al., 2023; Arden et al., 2021 and Heneghan et al.,2020). On balance, this could suggest that despite Ogden's concerns (Ogden, 2016) the COM-B can usefully applied to work around medication adherence with positive applications, however it could be that such interventions lack in flexibility and the ability to take into account patient variability.

The NCF can also be criticised for being overly simplistic, It is likely that there are factors impacting medication adherence which go beyond the necessities and concerns, as identified above. Currie et al., (2023) explored the application of the framework to antenatal physical activity and concluded that although it is helpful a number of other factors influence complex behaviours and using the NCF in isolation is not enough to explain such behaviour. Furthermore, Clifford et al., (2008) suggest that there could be differences in the explanation dependent if the person is an unintentional non-adherer or an intentional non-adherer. For example having low levels of necessity of the medication and high levels of concerns could mean that patients are more likely to forget or feel less likely to have motivation to overcome barriers

The aim of this research is to investigate the feasibility and potential usefulness of symptom monitoring and using feedback data (illustrating links between adherence and health outcomes/symptoms) for patients

Chapter summary and next steps

Based on the rationale discussed within this chapter, this thesis will investigate the feasibility and potential usefulness of capturing symptom and adherence data for the management of CF. The next

chapter of this thesis will present the overarching aims and the aims and research questions of each individual study.

Chapter 2- Aims and Objectives of the research

2.1 Rationale/Overview

According to the CFHealthHub data observatory, which collected objective nebuliser adherence in 303 participants over a 49-week period, on average adherence was 34.9% (Wildman et al., 2022). Better adherence to nebulised treatments has been associated with fewer exacerbations (Eakin et al., 2011), whilst poor adherence has been linked to increased hospital visits (Briesacher et al, 2011). There is currently a lack of knowledge of the factors which influence adherence in adults living with Cystic Fibrosis. As reported within chapter 1 of this thesis, several papers cite the importance of the role of perceived treatment benefits/beliefs (Arden et al., 2019; Bucks et al., 2009 and Hogan et al., 2015) on treatment adherence. In order to increase treatment adherence it may be important that patients understand the impact treatment has on their CF symptoms over a specific period of time.

There is currently a paucity of research investigating the temporal relationship between CF symptoms and treatment, and how this relationship is understood by patients with CF, therefore this requires further investigation. The principal aim of this thesis is to explore the feasibility and usefulness of self-monitoring and using adherence and symptom feedback data with patients with Cystic Fibrosis.

This PhD research project comprises of four study chapters. The aim/s and research question/s addressed within each study are outlined below.

2.2 Study 1: Investigating the perception and comprehension of graphs displaying health-care data

Background

Previous evidence emphasises the importance of graph literacy and how this can impact on an individual's health and their health outcomes, in comparison to those who have good levels of graph literacy (Shah et al., 2019). Little is known about how best to present

important healthcare data to participants in a way which is clear and understandable, to ensure collecting the data is helpful in the management of their condition. Participants recruited into this study were from the general population. The findings of this study informed how the graphical health data could be simplified/presented to aid understanding and interpretation in in the subsequent studies.

Aim

To explore how well people can understand graphs which display healthcare data (symptoms and adherence) and investigate the ways that this data should be presented to people. The results of this study will inform how data will be fed back to participants in the N-of-1 study.

Research Questions

RQ1:Can participants understand graphs which display a relationship between symptoms and adherence?

RQ2: How should data on symptoms and adherence be displayed on graphs to aid understanding?

RQ3: Does including a text description aid the understanding of graphs?

2.3. Study 2: Examining the temporal relationship between treatment adherence and self-monitored symptoms in CF patients within an N-of-1 study and a series of observational studies

Background:

Nebulisers are commonly prescribed to patients with CF and can be effective in treating pulmonary symptoms (Burrows et al., 2002) and also to help manage chronic respiratory infections (Bell et al., 2020). However, there is less known about the changes nebulisers can make to symptoms in the short to mid-term, which is further explored within this study. This information could be valuable for CF patients in providing them with information about the importance of adhering and subsequently potential motivation to adhere.

This study presents a pilot mixed methods study (N-of-1 study and a qualitative study) and also a larger N-of-1 study which was four months long and recruited different participants.

Aim: Exploring the preliminary feasibility of self-monitoring within an N-of-1 study and examining the temporal relationship between treatment adherence and self-monitored symptoms in CF patients

Research Questions

RQ4: Is symptom monitoring in patients with CF acceptable and feasible?

RQ5: Do patients with CF understand feedback graphs, which display the relationship between their adherence and symptom data?

RQ6: Are there any barriers that prevent CF patients from undertaking symptom tracking?

RQ7: What is the relationship between self-monitored symptoms and adherence in CF patients

2.4. Study 3: A qualitative study to investigate the relationship between adherence and symptoms of Cystic Fibrosis

Background

Study 3 utilised the data collected and analysed within study 2. Individual's symptom and adherence data (taken from the N-of-1 analysis conducted using their four-month diary and adherence data) was presented to participants during data prompted interviews. This provided participants with an opportunity to discuss their data and their thoughts and feelings about any relationships between their adherence and symptoms. Participants were also asked about their experience of symptom tracking and if/how valuable it was in aiding the management of their condition

Aim

This study aimed to further develop an understanding of how people recognise the factors which influence their CF symptoms, how these

symptoms are influenced by treatment and the value of symptom tracking with patients with Cystic Fibrosis as a long-term tool.

Research Questions

RQ8: How valuable did participants find symptom tracking using daily diaries?

RQ9: How did participants understand the relationship between treatment adherence and symptoms of CF?

2.5. Study 4: Understanding Healthcare Professionals (HCP's) perceptions of the factors which influence adherence to nebuliser treatments in patients with CF

Background

Within the final study of the thesis a total of 8 Healthcare Professionals were recruited and took part in semi-structured interviews. During the study participants were asked questions relating to the perceived acceptability of symptom tracking in practice. Participants were also presented with a summary of findings from previous studies within the thesis to prompt discussion.

Aim

To further understand health professionals' perceptions of the relationship between treatment adherence and symptom experiences and explore the perceived feasibility and usefulness of using this data as part of clinical management of CF.

Research Questions

RQ10: To further understand HCP's perception of the factors which influence adherence to nebuliser treatment in CF patients and their understanding of how treatment influences symptom experience and management

RQ11: How feasible is it to use self-monitoring data alongside adherence data within the management CF?

RQ12: How useful is it to use self-monitoring data alongside adherence data within the management CF?

Chapter 3- Methodological Review

3.1 Aims of the chapter

This chapter aims to provide a comprehensive overview of the methods which will be used within this thesis to address the research questions and aims discussed in chapter 2.

3.2 Symptom and adherence assessment and monitoring

It is important that research is undertaken to explore whether symptom and treatment monitoring could help increase adherence in the CF population and thus improve clinical outcomes for this group of patients. One way which symptoms can be monitored is via daily diaries. The use of daily diaries is becoming increasingly popular, specifically within health psychology (Skaff et al., 2009). Daily diaries are an example of Ecological Momentary Assessment (EMA). The method was first developed by Health Psychologists Stone and Shiffman in 1994 (Stone and Shiffman, 1994). EMA utilises prospective methods of data collection, capturing participants experiences and thoughts in real-time. According to Shiffman et al. (2008) EMA studies have been used across a range of different populations to study different conditions/behaviours including: sexual behaviour, drug use, asthma, social support and depression.

The method enables the participant to capture data as they experience it, therefore retrospective memory bias is reduced (Lida et al., 2012) in comparison to asking participants to reflect upon a longer period of time. Hoeppner et al. (2010) recruited 323 students who were asked to record drinking habits retrospectively during a seven-day period and a 30-day period. Large discrepancies between the data were found and participants reported to drinking more over the 7-day period. This demonstrates that although EMA is still a form a self-report, long recall periods that reduce the accuracy of data, can be avoided by using EMA methods. Some studies have used daily dairies to monitor patients for long periods of time, such as a six-month period in patients with CF (Sarafaraz, Sund and Jarad., 2010) and others for a shorter period

such as a 12-week period in patients who experience migraines (Seng, Robbins and Nicholson., 2017).

Different methods can be adopted to help collect EMA data including using signal, time and event contingent prompts. A signal contingent method is when the prompt to collect data is sent at a random time each day. Burke et al. (2017) highlight the importance of taking precautions within the analysis to ensure the data collected is not biased as a result of the mood or level of energy at the time of the recording. Using an event contingent method the participant is asked to record data once a particular event has occurred each day (e.g. asking participants to record symptoms after breakfast) (Burke et al., 2017). Finally when adopting a time contingent prompt, the prompt is sent at the same time each day to remind the person to collect data at that time. Time contingent prompts will be adopted in the EMA studies in this thesis. This is the most common method with a recent review of 53 EMA studies finding that all studies used time contingent prompts (de Vires et al., 2021). Moskowitz and Young (2006) suggested time contingent prompts can help to reduce retrospective bias as participants are recording data in real time.

In the work of Cherenack et al. (2016) participants in the study were randomised to either the internet condition which was available on any web-enabled device or a voice reporting condition which was accessible via telephone, and asked to record for 33 days before swapping to the second condition for a further 33 days. Internet diaries were preferred (77.5%) compared to voice diaries (67.7%). The study also reported a good retention rate of 93.4%. This emphasises the acceptability of using internet diaries and demonstrates that although daily diaries can place time burdens on the patient/participant it is possible to achieve a good retention rate and avoid attrition when using the methodology.

A recent study looked at the use of electronic patient-reported outcomes (PROs) in patients who live with Rheumatoid Arthritis (RA)

(Bingham et al., 2019). The study was a trial, prior to a full RCT which attempted to use PROs to assess health-related quality of life in this group of participants. Participants were provided with a handheld device and asked to answer four questions during three windows within the day. It was found that there was a high compliance rate over the 12-week study period (on average over 90%). The minimal levels of attrition in the work of both Bingham et al. (2019) and Cherenack et al. (2016) demonstrate that collecting data in this way can be acceptable for patients living with long-term health conditions.

Furthermore, daily phone diaries used in the work of Modi et al. (2006a) were able to track experiences in patients with CF over a 24-hour period. Patients or their parents were contacted over the telephone each day and were asked about their mood, activities they participated in, the duration and whom it was with. Objective nebuliser adherence was also recorded and parents were asked about the barriers which prevented the use of their treatment. The use of daily interview diaries yielded around 20-30 minutes worth of data per day and allowed researchers to further investigate activity and barriers to adherence. In total 31 patients completed the daily telephone diary and attrition for the study was low with only two participants dropping-out of the study. This provides insight into the applications of EMA and the ability the method could have in detecting a relationship between activity and treatment adherence for individuals with CF.

Sarafaraz, Sund and Jarad (2010) also investigated the feasibility of electronic self-monitoring in patients with Cystic Fibrosis in which patients were asked to record symptoms and perform three spirometer reads once a day. However only 19 patients completed the study, which was 37.2% of the 53 participants who were recruited. The poor compliance rate is perhaps unsurprising as participants were asked to record their symptom score and spirometer reading through the use of an electronic diary using specific equipment each day for 6 months. A number of participants reported technical difficulties and therefore stopped using the device, however it is difficult to determine if

poor compliance is due to the extended time period or the use of technology, which was a hand-held computer. Perhaps using a hand-held computer was more burdensome to participants in comparison to an app on their mobile phones, however it is unlikely that apps were widely available at the time of this publication in 2009, since, for example, the Apple App Store was not launched until July 2008 (Apple.com, 2018). The study also failed to measure participants' thoughts and experiences of using the device each day to measure symptoms and adherence to medication was not monitoring during this study. Assessing the acceptability of the different methods available to monitor symptoms is of paramount importance if self-monitoring systems are to be developed for CF patients.

There are important requirements that must be carefully considered prior to choosing EMA as a method of data collection. A rapidly developing terminal disease would pick up large changes in disease progression or symptoms over a small period of time and a noticeable decline in functioning due to disease progression and therefore not suitable for EMA. Cystic Fibrosis is an example of a chronic disease that is caused by a genetic mutation, however, it is not clear currently how CF symptoms may fluctuate over time and therefore whether daily symptom tracking could be a useful tool for this group of patients.

It is evident upon reviewing the literature in this area that using EMA methods could have the potential to help patients to better understand their condition. Monitoring symptoms could be useful to patients and help them understand the factors associated with changes in their symptoms and the onset of infections. The relationship between these changes and medication adherence could be key to helping some patients understand the impact of adherence on their symptoms. However, the way in which this complex relationship is presented to participants must be in a format that is understandable and acceptable.

3.3 Analysis of prospective data (N-of-1)

When information relating to symptoms and treatment behaviours are collected using EMA methods a huge amount of complex data is obtained. N-of-1, single-subject or Single-Case Experimental Designs (SCED) adopt an individualised approach to data analysis and are reliant on prospective data collection of a specific outcome over a period of time (McDonald, Vieria and Johnston., 2020).

These methods were first adopted in medicine and pharmacology to test the success of drug treatments (Barr et al., 2015; Duan et al., 2013) and compare alternative treatments in groups of patients (Lillie et al., 2011). SCED's have been adopted to test how individual's respond to treatments and interventions for various conditions, rather than assessing the overall effectiveness of the intervention for a group/population, and this is considered to be 'individualised medicine' (Lillie et al.,2011). Treatments may appear to be effective across a group of patients on average, however certain patients may not respond well. Although RCT's are viewed as the gold standard they are often unable to shed light on the most effective treatments and optimal care pathways for individuals (Shaffer et al.,2015). N-of-1 trials can provide insight into the treatments which are best suited to individual patients (Shaffer et al., 2015).

Nikles et al. (2005) used an N-of-1 trial in patients with Osteoarthritis or Attention Deficit Hyperactivity Disorder (ADHD) to investigate the benefits of using of N-of-1 methods to help patients better understand their condition and treatment. It was concluded that 46 participants (65%) decided to change their medication to treat pain as a result of taking part in the study. Furthermore, participants were asked to complete pre and post trial questionnaires to collect open-ended responses to help further understand experiences of the trial and follow-up interviews were conducted on a sub-group of participants. Patients reported they viewed their participation in the trial favourably, have a better understanding of their condition and a sense of empowerment due to having a role in choosing their treatment as a

result of the study participation. It was concluded by the authors (Nikles et al., 2005) that N-of-1 trials were both acceptable and of benefit for participants within this sample.

Because of these advantages, N-of-1 methods have recently become increasingly popular in health psychology. Within N-of-1 methods there are two main types of design traditionally adopted within the literature, interventional and observational. Often the choice of such design is dependent on the research questions and aims of the research (McDonald et al, 2017b).

Interventional N-of-1 designs

There are varying types of interventional N-of-1 designs including: N-of-1 randomised control trials and AB designs. In AB designs participants monitor during a baseline period which is 'A' and then are provided with an intervention which is the 'B' period (McDonald et al, 2017b).

According to Shaffer et al. (2018) there are a number of requirements for an N-of-1 interventional study, which relate to different aspects of the study design. The requirements include the following: the disease itself must be chronic and slow progressing, the interventions should be rapid and with minimal crossover and there must be ability to have a washout period between interventions. A washout period is essentially a period of time which separates different treatment cycles (Kravitz & Duan., 2014), this enables the researcher to clearly understand which treatment is causing change to the patient. Furthermore, the data collected must be analysed using the appropriate statistical methods such as Bayesian meta-analysis or time-series analysis.

Previous psychological studies have used N-of-1 designs to investigate the effectiveness of interventions to promote 'healthy' lifestyle choices and behaviours for example treatment adherence (Piven and Duran., 2014) and physical activity (O'Brien et al., 2016).

Sniehotta et al. (2012) adopted an N-of-1 randomised controlled trial (RCT) as an intervention to increase walking in overweight adults. Two types of interventions were used in the study, the first was setting activity goals and the second was being blinded to daily step count compared to self-monitoring steps. Time-series analysis was adopted in this study to investigate the main effects of goal-setting and self-monitoring. This study was repeated with an older population who found that the self-monitoring intervention increased step count by an average of 900 steps per day, although it was just two participants out of ten recruited into the study which experienced statistically significant effects (Nyman et al.,2016). Sniehotta et al. (2012) and Nyman et al. (2016) concluded that the findings demonstrate that N-of- 1 trials are an effective means of testing interventions at an individual level in both adults and elderly adults.

As this thesis is not concerned with developing and testing an intervention it is not appropriate to use an interventional design, therefore an observational N-of-1 design will be adopted to help monitor temporal relationships over a period of time.

Observational N-of-1 designs

Generally observational N-of-1 studies are interested in monitoring a relationship between two variables over time. i.e. the measurement of the particular variables are taken repeatedly over a period of time (McDonald et al, 2017b). N-of-1 studies can be used observationally to test theory (McDonald et al., 2017b) and help researchers understand what is happening at an individual level without using an intervention. Observational methods have been used in various aspects of health psychology, those include; medication adherence (González-Pinto et al.,2010), physical activity (O'Brien et al., 2016) and weight loss (Nyman et al., 2016).

Kwasnicka et al. (2017) assessed adherence to a weight loss plan in participants aiming to lose weight. EMA questions were sent to participants twice per day (6.00am- 10.00am and 6.00pm-10.00pm).

The study aimed to assess theory-based predictors to physical activity, such as; self-regulation, habits, personal environment and personal resources. Questions were answered using a visual analogue scale, which ranged from 0-100. Questions were linked to relevant themes such as self-regulation and resources. Alongside this objective measurements were also adopted; such as Fitbit data and body weight, which were recorded for a six-month period. Due to the design of the study researchers were able to focus on the exact predictors and what this was impacting upon for example exercise, weight or adhering to the plan for each individual. The study concluded that adherence to weight loss maintenance was significantly associated with a number of variables including stable environment, habit and self-regulation.

McDonald et al. (2017c) used an N-of-1 observational study to investigate levels of physical activity in retirement. It was highlighted that levels of physical activity during the transition to retirement varied from person to person. Burg et al. (2017) assessed the bi-directional relationship between exercise and stress in participants using N-of-1 methods, once again it was concluded that there were significant levels of variability within the findings for example for several participants exercise was associated with lower levels of stress and for others higher levels of stress. These findings would not have been detected had a N-of-1 approach not been adopted. The recent work of Kwasnicka et al. (2017), Burg et al. (2017) and McDonald et al. (2017) emphasises the importance of using such methodology to understand the variances from person to person and create successful interventions to help implement behaviour change based on these findings.

Observational N-of-1 methods can be used to test how aspects of a psychological theory can be applied to understand health-related behaviour in a specific population. Hobbs et al. (2013) tested the ability of the Theory of Planned Behaviour (TPB) to explain physical activity in six individuals who had recently joined a fitness centre. Three types of physical activity were monitored and participants were asked to fill out

daily diaries twice per day either online or in paper format, exercise was logged objectively through membership card activity and step-count and through self-reports. Components of the TPB (e.g. perceived behavioural control, attitudes and norms) were measured individually in the daily diary, as specific questions aimed to address different aspects of the theory.

The work of Hobbs et al. (2013) and Kwasnicka et al. (2017) both emphasise that their findings focus on the individual, analysing data sets individually enables an in-depth understanding of each participant rather than making conclusions based on a whole group. Kwasnicka et al. (2017) concluded that there were considerable differences within each person recruited.

According to Cohen et al. (2014) one of the main advantages of single case design studies is that they provide evidence-based results applied to an individual. Furthermore, N-of-1 methodology is often used when the aim of a study is to examine daily and momentary events (Smith, 2012). However, a clear consideration is the amount of time participants must commit to participating in repeated measures N-of-1 studies, often participants will be asked to self-monitor on a daily basis. Therefore it is important that N-of-1 studies which use monitoring symptoms are deemed as feasible and acceptable to participants (Brookes et al., 2007).

Statistical power and sample size associated with N-of-1 design can be poorly understood. It is important to acknowledge that unlike traditional methods, in N-of-1 methodology the statistical power is related to the number of observations rather than the number of participants (Shaffer et al., 2018). With 50 observations being viewed generally as being ‘sufficiently powered’ (Tabachnick & Fidell., 2007). Small numbers of participants are recruited to N-of-1 studies across wider populations, however the level of focus on each individual recruited into such studies helps curate personalised interventions (Lillie et al.,2011). The adult CF population is quite small (approximately 11,000 patients

living in the UK) (Cystic Fibrosis Trust, 2024) and this means that recruiting sufficient participants to power a traditional study is very challenging. N-of-1 provides a design that is sufficiently powered by the number of observations rather than the number of participants and thus matched the constraints of the population well.

However, there are a number of limitations which should be acknowledged here. For example Single-Case Design Experiments (SCEDs) as a whole is that the findings are specific to that population and cannot be generalised (Ferreira et al., 2016). This is clearly a cause for concern if SCEDs are employed in a drug trial or to measure the effectiveness of a treatment. However, within the current thesis this is perhaps not so much a problem as the methods were used observed to investigate the relationship between symptoms and medication adherence over a period of time.

In addition to this the individualised aspect of the methodology creates a clear rationale for its use with the PhD thesis, as it allowed participants individual relationships between individuals symptoms and adherence to be analysed (Mc Donald et al., 2020), something which may not be able to investigate using other methods.

A further limitation of adopting observational N-of-1 design is that studies are not able to establish causality (Mc Donald et al., 2020) as there is no manipulation of the independent variable. Therefore establishing the cause and effect can be difficult when employing such methods. Finally, a large amount of data is required when utilising N-of-1 methods which means that the potential burden for participants should be monitored, participants are asked to provide data on a daily basis for a pro-longed period of time. This has been termed ‘high intensity measurement’ within the literature (Kwasnicka & Naughton, 2020) and as a result of this it can be difficult to recruit participants who perhaps need support (i.e. low adherers) as they are put off by the burden (Kwasnicka & Naughton, 2020). Alternative methods to analyse this prospective data are available and will be considered in below,

however it is likely that to understand this relationship further participants would need to record data on a daily basis regardless of the method.

Traditional methods such as Randomised Control Trials (RCT's) or clinical trials could be used to collect and analyse data, especially if the aim is to create a behavioural intervention e.g. improving medication adherence. However, generalising at average population level loses the nuances between participants, which for some patients could cause more harm than good. As previously state the CF population is small (around 11,000) (Cystic Fibrosis Trust, 2024) and therefore it is likely that there would be challenges in recruiting enough participants (Zhaori, 2024).

Therefore a mixed methods approach enables the relationship between nebuliser adherence and symptoms of CF to be investigated temporally using quantitative N-of-1 methods, and qualitative data-prompted interviews offers an opportunity to explore this data with patients living with CF and HCP's. These methods compliment one another well as seen in previous work (Kwasnicka et al., 2015) and also help to triangulate the data.

Selecting an entirely qualitative approach such as Ethnography, would mean that the relationship between variables could not be explored statistically but would also mean that the over-arching aim 'to explore the feasibility and usefulness of self-monitoring and using adherence and symptom feedback data with patients with Cystic Fibrosis', could not be explored appropriately. Importantly, the approach selected within this thesis addresses is able to address the aims set out appropriately. Using a mixed-methods approach enables to data to be captured and investigated but importantly discussed with both Healthcare Professionals and patients taking a pragmatic approach to exploring the use of symptom tracking in the real world.

Whilst N-of-1 studies are becoming increasing popular in the area of health psychology, this thesis will be the first study to use N-of-1

methods to examine the relationship between adherence to nebulised treatment in adults with CF and their symptoms. Both symptom and adherence data will be collected on a daily basis from participants to facilitate further understanding of the temporal link between the two variables and examine whether symptoms drive adherence or whether adherence impacts symptoms and how these relationships differ for different people.

To summarise EMA methodology is important and enables researchers to track daily fluctuations and reduce recall bias. Previous literature across chronic conditions highlights the potential benefits of using such methods for a range of time periods. N-of-1 analysis can enable insight and understanding into how relationships between symptoms and adherence may differ between people and change over time.

3.4 Developing the symptom questionnaire: Patient Participation Involvement work

Background

In order to develop the CF symptom monitoring questionnaire used in chapters 5 and 6 of the thesis, relevant literature was reviewed (see section 1.2-1.3) for a review of symptoms and associated measures), based on this relevant symptoms which are treated with nebulisers were selected. Furthermore, a Patient Participant Involvement (PPI) group was convened and consulted. According to Gray-Burrows et al. (2018) PPI groups can help form better research outputs by helping identify key priorities and relevant research designs. As CF patients were invited to take part in a number of studies within the PhD it was of paramount importance to ensure that patients were invited to provide their voice in terms of designing the study. The input from the group helped ensure that the studies were designed to limit any burden or stress associated with taking part in a research study whilst living with a life-limiting condition.

Aims

- To develop a short daily symptom questionnaire which is acceptable and feasible for adults with Cystic Fibrosis.
- To understand which symptoms are most relevant for patients with CF in relation to nebuliser adherence.
- To gain insight into the type of language and phrasing which should be used or avoided.

Scientific rationale

Within health and social care PPI work is viewed to be an important component of conducting research (Wilson et al., 2015). Using a PPI group to guide the creation of the survey meant that the questions were likely to be more relevant, clear and avoid jargon.

Method

A PPI group was convened and consulted, this PPI group was already arranged as part of the wider CFHH trial and the development of the survey was the topic of conversation on the specific dates in June 2017.

Questions asked were related to which symptoms they felt should be tracked, how many questions it would be acceptable to ask, the appropriate length of time and the appropriate device to use (mobile phone, computer, etc), the responses from discussions fed into the study design (see Appendix A for the PPI topic guides for both sessions).

Findings

Patients involved in the PPI group felt that questions would be more acceptable than an open-entry diary, that the symptoms recorded should not be exclusive to respiratory symptoms and they gave advice on which symptoms can be predictive of exacerbations (feeling generally unwell, tiredness and aching joints).

Specifically patients preferred to term mucus and sputum and felt this was one symptom which was a key predictor of a forthcoming exacerbation. Please see table 4 below for a summary of key findings.

Table 4.
Summary of key findings from PPI group

Question	Area of study	Examples of answers given
How do your symptoms change over time?	Selection of symptoms for daily diary	Achy joints and pain in joints, volume of sputum and colour of sputum, lack of energy, increased coughing, coughing up sputum.
What kind of symptoms do you experience before an exacerbation?	Selection of symptoms for daily diary	Feeling generally unwell, aching (two patients reported this), tiredness.
Can these symptoms be used to predict exacerbations?	Selection of symptoms for daily diary	Can be hard to recognise symptoms as they become the norm.
Do you change anything during this time? Do you feel there is anything you could change to prevent or delay the exacerbation?	Selection of symptoms for daily diary	One patient reported that they often ignore symptoms; other patients were in agreement and said they would wait until they next see their CF doctor.
How would you feel about tracking symptoms in the form of a diary?	The acceptability of a symptom diary	Patients thought a 'diary' may mean a lengthy entry but they were more accepting of answering questions on a scale on their phone.

Advantages and disadvantages

Within the survey development no formal measures of reliability or validity were measured, which is an important limitation to be noted.

Although the PPI group were able to provide valuable insight into how they feel the survey should be sent and the types of symptoms which should be monitored.

In addition to this, the literature was also consulted to strengthen this which demonstrates the symptoms are linked to respiratory symptoms which is the reason nebuliser treatments are prescribed. For example other self-report symptom measures were reviewed e.g. The CF Respiratory Symptom Diary (Aitken and Patrick, 2009), The Cystic Fibrosis Questionnaire Revised (Quittner, 2005) please refer to the introduction for further information.

Furthermore, relevant iterations made to the survey during the course of the thesis are discussed in appropriate chapters, demonstrating the iterative approach taken. The approach supports the pragmatic underpinnings of the thesis is that this option was available and within the time constraints of the PhD thesis

3.5 Objective nebuliser adherence and the CFHealthHub

Objective nebuliser adherence was measured in real time from patients chipped nebuliser systems and transferred to the CF Health Hub (CFHH). See figure 2 which explains how data from the CFHH is transferred in three different stages. The three stages of data transfer are:

Step 1. Participants are provided with a plug-in hub device and when the I-neb nebuliser is used a Bluetooth data transfer will occur.

Step 2. The data is transferred to the secure CFHH server.

Step 3. The CFHH data is available in real-time on tablets, mobile phones and computers. Data can be accessed by the patient alone or with the consent of the patient clinicians are also able to view data.

Unadjusted nebuliser adherence (a percentage for each day was provided, based on how many of the individuals prescribed doses were taken) is recorded within the CFHH digital platform. Following appropriate ethical approval and with the correct participant consent, a

member of the research team was provided with access to the data of the participants who were recruited into the studies. .

Figure 2.
CF HealthHub diagram

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Adherence data from CFHH was used in N-of-1 quantitative studies and also used for DPI qualitative studies. DPI's are discussed below.

3.5 Qualitative methodology

Data Prompted Interviews

Data-prompted interviews (DPI) are a qualitative method of data collection which use individualised prompts to help collect data, these prompts may include; graphs, text extracts, videos and photographs (Kwasnicka et al., 2015). According to Kwasnicka et al. (2015) there are three main aims of DPI's which include: encouraging discussion through the use of data-driven prompts, to explore contrasts between the participant's experience and the data and to discuss participants opinion of their personal data. Using prompts such as graphs and charts displaying N-of-1 data in DPI's can act as aids to prompt discussion, particularly relating to patterns and trends in the data presented (Kwasnicka,White, Dombrowski & Sniehotta, 2015).

Previous N-of-1 designs in psychological literature demonstrate how N-of-1 methods and DPI can be used in partnership in mixed-methods designs (et al., 2013; Sniehotta et al., 2012). This can aid discussion of data generated from a participant over a monitored time period. Kwasnicka et al. (2019) used DPI and N-of-1 observational methods to gain further understanding into weight loss maintenance from participants who had successfully lost weight. DPI's have been associated with positive applications, for example providing participants with the option add clarification or further meaning to something

Previous work which has adopted the use of DPIs in patients with CF, Arden et al. (2019) presented patients with their objective adherence data from the previous six months. This demonstrates the value of

presenting CF patients with adherence data during data-prompted interviews, something that was used within this thesis; to explore feasibility and acceptability, and to understand the relationship between symptoms of CF and adherence.

However, there is a risk when using data prompted interview that the interview will be based around explaining/discussing the materials, therefore interview schedules were carefully planned to ensure that there is appropriate time for the participant to discuss experiences of symptom tracking and not just the data.

Focus groups could be used as an alternative method, however due to the individuality associated with the relationship between symptom and adherence and also ethical issues associated with sharing data, interviews were the most appropriate method (Kwasnicka et al., 2015).

3.6 Summary of methods

To answer the overarching aims of this thesis a number of novel and traditional methods were adopted. Please see table 5 for a summary of the methods used in the thesis.

Table 5.
Summary of methods for each study of the PhD

Study number	Methodology	Summary of research design	Recruitment strategy
Study 1	Quantitative	An online survey to investigate the comprehension and preferences of graphs which communicate symptom and adherence data.	Participants recruited from the general population and asked to complete an online survey
Study 2	Mixed method (pilot study and study)	A series of N-of-1 observations to explore the relationship	Patients with Cystic Fibrosis recruited from three UK sites.

		between symptoms and objective nebuliser adherence. This study includes a pilot study with N-of-1 and qualitative data. Followed by a large 4 month N-of-1 study.	
Study 3	Qualitative	A series of interviews with participants who took part in study 3. To further investigate the relationship between symptoms and adherence in CF.	Patients with Cystic Fibrosis recruited from three UK sites (sample from study 3 invited to participate)
Study 4	Qualitative	A series of interviews with Healthcare Professionals to explore symptoms and nebuliser adherence.	NHS Healthcare Professionals recruited from 3 sites in the UK.

3.7 Research paradigm

This thesis adopted a mixed method approach, which included; a series of N-of-1 observations, semi-structured interviews (with both patients and staff members) and quantitative data collected in the form of an online survey.

According to Frey (2018) the pragmatic paradigm is not focused on what is true or real but what works in the 'real world'. This paradigm lends itself to the current thesis in terms of the mixed methodological approach which has been adopted (Frey, 2018) and also the fact that data from a number of studies was collected over time (Holtrop and Glasgow, 2020). Pragmatism was the selected methodology for this thesis as it is able to answer and address the research questions. The

paradigm also offer flexibility in its approach to address real world issues Feilzer (2009).

However, the pragmatic paradigm has been subject to critique, specifically for the lack of guidance the approach offers in relation to what is useful (Hesse-Biber, 2015). More recently pragmatic research has been applied to clinical research, according to Holtrop and Glasgow (2020) although the approach serves a different purpose it is 'equally rigorous' to traditional efficacy research. In order to reflect upon this appropriately parts of the sub-sections below will be written in first person.

Reflexivity

According to Omos-Vega et al. (2023) 'reflexivity is a set of continuous, collaborative, and multifaceted practices through which researchers self-consciously critique, appraise, and evaluate how their subjectivity and context influence the research processes' (p.242).

Below is my personal reflexivity statement:

> *Prior to the PhD I had no experience of working with patients with CF. Neither I or anybody within my close group of family and friends have CF. Therefore I would consider myself as an 'outsider' to the CF community. I have experience of living with a chronic condition of which the onset was when I was 18, therefore I have an understanding of what it can be like to be a young person living with and managing a health condition. However because I had limited knowledge of CF despite spending time reading a range of books which spoke about lived experience there was particular terms and acronyms which I was unfamiliar with, I was honest with participants about this which meant they explained this and I had a better understanding.*
>
> *The programme itself sat outside of the CF Health Hub, however I did work with members of the team to aid with recruitment, data transfer and conference attendance. Furthermore, two of my supervisors (Prof Maddy Arden and Dr Martin Wildman) were part of the CFHH trial. I have no medical or clinical training so working with patients gave me a real insight into what living with CF can be like.*

The patients I met/worked with did not know me before this and I was there simply to work with them as a researcher. Therefore I felt I could maintain a distance from participants, something I felt was helpful both myself and the participants. I could make it clear to participants that I was not there to judge their adherence levels and how they chose to manage their condition.

However, during the data collection period the COVID-19 pandemic began and we were sent into lockdown. This meant that the final interviews with participants were conducted online, and meant that life changed quickly for everyone, especially with patients with CF due to their condition.

Later in the PhD programme when working on my corrections I recruited and interviewed Health Care Professionals, once again I felt being an outsider and being honest with them that I have limited experience and how things work in practice in CF care helped encourage open conversation.

(Please see additional reflexivity statements in studies 3 and of the thesis).

According to Braun and Clarke (2013) Ontology relates to reality and whether or not one believes this sits separately from experiences and human interactions. Therefore considering the question to what extent is knowledge reflective of our own perspectives? It has been argued that due to the mixed-methods aspect of this approach it is important to see objective and subjective view of reality, whilst avoiding any biases (Johnson and Christensen, 2012).

Pragmatism is underpinned by the idea that knowledge is based upon ones social experiences, in turn this will impact upon how we perceive the world around us (Kaushik and Walsh, 2019), what we know and how we know it.

As discussed within the reflexivity sub-section, as an ‘outsider’ I do not have experiences of living with CF and therefore I am able to distance myself from the lived experience of participants and was able to remain relatively objective when undertaking data analysis.

However it could be said that there is an influence of objectivist epistemology within the N-of-1 studies of the thesis and a subjectivist epistemology within the qualitative studies, to ensure that both the relationship between variables and also the experience of participants can be understood. This has been defined as epistemological pluralism within the literature body (Ghirara, 2019).

3.8 Next steps

The next chapter of this thesis is the first of four study chapters and will present a survey study which investigated how best to present graphs which display healthcare information.

Chapter 4- Investigating the perception and comprehension of graphs displaying health-care data

4.1 Chapter Overview

In order to address the over-arching aims of this thesis it is important to understand how to present data to participants in a way that is clear and understandable. If participants or patients are able to understand the data it is likely to be more helpful in the management of their condition.

Within this first study of the thesis participants were asked to complete a survey which provided insight into how best to present graphs, levels of graph literacy. The study also investigated the use of text description to support the interpretation of graphs.

4.2 Introduction

Graph literacy has been described as the 'ability to understand graphically presented information' (Galesic and Garcia-Retamaro, 2011, p. 444). Graphs have a multiplicity of functions for the general population and can be used to present information and to help inform decisions (Okan et al., 2015). One of the more specific types of data presented using graphs is medical information (Schrodt et al., 2020) The ability to interpret such graphs can help patients to make decisions about their health and risk communications (Garcia-Retatamaro, 2016).

The interpretation of graphs is an integral part of health literacy. Health literacy is defined as 'the degree to which individuals have the capacity to obtain, process, and use basic information and services needed to make healthcare decisions' (Ratzan and Parker, 2000 p.6). According to Shah et al. (2019) health literacy is in a constantly changing state, which is dependent on our emotional and mental wellbeing at that time. Skills such as understanding quantitative data and graphs are a key component of health literacy (Peters, 2012).

For those living with long-term health conditions the ability to understand graphs and healthcare data is of particular importance. However, there is a paucity of research in this area. One of the many

reasons that graph literacy is important for patients with chronic conditions is so that they are able to correctly interpret their own health related data and thus better understand aspects of their condition.

The presentation and discussion of graphical representations of patient's health data can improve communication between patients and physicians, enabling a more patient-centred approach in terms of treatment (Nayak et al., 2016). Patient data displayed in graphs can be sent to patients virtually via the use of online applications, which have played a large role in the recent expansion of digital healthcare. The use of digital healthcare has the potential to benefit both the patient and clinicians, with the potential to empower patients to understand complex information about their health and play a more active role in decisions relating to their healthcare (Klasnja and Pratt, 2012).

Previous literature has concluded that patients with lower levels of graph literacy are less likely to utilise their online personal health records (Ruiz et al., 2016). According to Ruiz et al. (2016) it is important that healthcare professionals are aware of levels of graph literacy of patients when implementing systems such as personal health records.

One of the drawbacks of using graphs is if people do not understand graphs properly, communication through the use of graphs can cause errors in judgment and decision-making according to Okan et al. (2018). Higher levels of graph literacy have been linked to more accurate interpretation of graphs (Okan et al., 2016, 2012).

Shah et al. (2019) investigated the link between frailty, health literacy, graph literacy and numeracy in older adults. In total 470 American, male adults with a mean age of 56.8 year were recruited into the study and asked to complete measures relating to graph literacy, numeracy and health literacy. It was concluded that there is an association between higher levels of graph literacy and a lower risk of frailty in the sample recruited, therefore as suggested by the authors graph literacy may be a modifiable risk factor for frailty in older adults. There was no

relationship between levels of numeracy, health literacy and frailty, which emphasises the importance of graph literacy on health outcomes. According to Shah et al. (2019) having the ability to understand and interpret graphs is a modifiable factor, which has the potential to change high mortality and morbidity rates in the older adults recruited.

Despite the potential usefulness of graphs in aiding people's understanding of complex health data there is evidence that there are common problems which prevent people from being able to accurately interpret and extract information from health-related graphs. However, it is important to note that within the general population there are large differences in levels graph literacy (Okan et al., 2015). Galesic and Garcia-Reramero (2011) recruited samples from Germany (n=495) and America (n=492) to investigate cross-cultural differences in graph literacy. Around one third of both samples were found to have low numeracy skills, when measured objectively using scales such as the Berlin Numeracy Test (Cokely et al., 2012) and the Subjective Numeracy Scale (Fagerlin et al., 2007). Similarly, one third of both samples were found to have low graph literacy, which was measured using the Subjective Graph Literacy Scale (Galesic and Garcia-Reramero, 2011).

There are different ways to present data graphically, and understanding which way is better understood is also important. Okan et al. (2018) found that participants who are more graph literate are more prone to 'within-the-bar' bias when presented with bar charts. Within-the-bar bias is the idea that when presented with a bar graph one is more likely to be drawn to the whole bar or the area within the bar, rather than the area outside of the bar (Newman and Scholl, 2012), which can lead to bias. This suggests that bias is not limited to those with lower levels of graph literacy. The type of graph patients are presented with is important for example bar charts potentially bias healthcare data when presented to patients. However, bar charts can be useful for making comparisons and they are also a type of graph that members of the

general public are likely to be familiar with (Lipkus, 2007). According to Brewer et al. (2012) test results in tabular format can be more burdensome for patients to understand and therefore graphs are the preferred option.

It is argued that graphs which contain accompanying text to aid understanding may help people accurately interpret health data. Rowlands et al. (2015) reviewed 64 different healthcare materials used in the UK and found that none of these materials were exclusively numeracy based but 50 sources (the vast majority) contained a mixture of literacy and numeracy information. Supporting the argument that text description is seen as an aid to support people when interpreting graphs, and recommending that summaries of graphs and their meaning should be included in text format (Lipkus, 2007).

Conversely, more recent findings have presented an opposing argument to Lipkus (2007), suggesting that the use of words can introduce a level of ambiguity in the way they are interpreted amongst individuals (Douglas, 2021). Furthermore, Visser et al. (2021) suggest that when working with patients who are experiencing cognitive impairment when living with conditions such as dementia it can be hard to communicate risk effectively and clearly. Therefore visual displays are the recommended option within this population.

There are many different types of graphs which can be used to display health-related data and therefore it is important to understand people's preferences for how graphical information is presented. Kuijpers et al. (2016) investigated the preferences of cancer patients and healthcare professionals for different types of graphs. They found almost half of the patients had no preference when it came to the format of the graph (line chart or bar chart). Consultant specialists, however, preferred line charts and contrastingly nurses preferred bar charts suggesting that it is likely that preferences may differ between clinicians and patients and that different options of graphs should be made available. Although participants have different preferences, according to Slutsky (2014) it is

important that the most appropriate style of graph is selected to present the data.

Previous evidence emphasises the importance of graph literacy and the outcomes this can have on an individual's health. According to Rowlands et al. (2015) trying to increase literacy and numeracy skills in schools and adult education is likely to have health benefits. Furthermore, according to Rowlands et al. (2015) GP's have an important role when delivering care and commissioning care to ensure health materials are written in such formats which are accessible for all.

There is a paucity of research which focuses on how people can interpret graphs which present symptom and adherence data. Understanding this is important because later studies within this thesis involve graphs of data that are presented to participants and which they need to be able to understand (studies 2 and 3). It is key that participants are able to use and understand the graphs and data presented to them if this is designed to help them better understand their condition, and any relationship between treatment adherence and symptoms. Therefore the findings from this study will be used to inform the development of the graphs which will display participants symptom and adherence data, to ensure they are as clear and useful as possible.

The current study aims to explore how well people can understand graphs which display healthcare data (symptoms and adherence) and investigate the ways that this data should be presented to people. The results of this study will inform how data will be fed back to participants in future studies within this thesis. The following study has three research questions: Can participants understand graphs which display a relationship between symptoms and adherence? (RQ1) How should data on symptoms and adherence be displayed on graphs to aid understanding? (RQ 2) Finally, does including a text description aid the understanding of graphs? (RQ 3)

4.3 Methods

Design

This study used a survey design which was completed online, using Qualtrics © an online survey development tool. There were two independent variables (IV 1: type of graph and IV 2: text description). IV 1 had three levels and was a within participant variable (bar chart, mixed chart or line chart). IV 2 had two levels (description or no description) and was a between participant variable. Therefore the study 3x (2) design. The dependant variable was the score participants received on the Cystic Fibrosis Graph Survey questionnaire. Participants were given 1 point per correct answer and 0 for an incorrect answer (please see analysis section below for more information). A mixed factorial ANOVA was used to analyse the data collected within this study.

Participants

In total 132 people gave consent to take part in the online survey. However, only 106 participants completed the study in full and therefore in line with BPS guidelines for internet mediated research (BPS, 2021) only data collected from these participants was analysed. A post-hoc power analysis revealed that the study was powered to .99 which is considered to be sufficient as it is over the .8 threshold (Cohen, 1988).

All other studies within this thesis have recruited participants from the CF population or clinicians who work with people with CF. While this would have been preferable for the this study, the timing of data collection and the need to complete the PhD within a practical timeframe meant that we could not seek NHS ethical approval and therefore needed to avoid recruitment via the NHS. Therefore the current study participants were recruited from the general population. The limitations of this approach are considered in the discussion.

The inclusion criteria for the study were as followed:

I. Participants must speak English
II. Participant must live in the UK
III. Participants must be 18 or older
IV. Participants must have access to a tablet, phone or computer to complete the survey.

Recruitment

Participants were recruited via social media, the survey was advertised on both Facebook and X (Twitter). The post shared used the Qualtrics © link to the study and explained that the survey was investigating how best to display healthcare information on graphs. Participants were invited to share the survey with their own friends and followers. The survey was accessed using an anonymous link to an online survey. Participants were given the option of providing an email address at the end of the survey to be entered into a prize draw (£20 voucher).

Ethics

The study received ethical approval from Sheffield Hallam University Research Ethics Committee (Ethic Review ID: ER12789084). Participants were presented with an online participant information sheet (PIS) and consent form at the beginning of the online questionnaire and also debrief information at the end of the study to ensure ethical guidelines were fulfilled (see Appendix B for participant facing documents). Participants who wished to be entered into the prize draw were asked to provide an email address if they wished to enter the prize draw which was voluntary. Email addresses were stored separately from the survey data, in line with GDPR requirements and the information provided in the PIS. If participants did not wish to enter the draw their response was anonymous.

Materials

Demographic Questionnaire

Participants were asked to complete a demographic questionnaire that consisted of items about gender, age and educational level.

Graph Literacy Scale (GLS)

The Graph Literacy Scale (GLS) (Galesic and Garcia-Retamero, 2011), scale has 13 items and measures whether participants can accurately interpret data presented in graphical format. When the scale was tested using both a German and American sample the Cronbach's Alpha of the scale was 0.86 (Okan, 2019), which indicates an acceptable level of internal validity (Cortina, 1993). The GLS consists of presenting participants with a graph displaying information about fictional or non-fictional diseases and the participant is presented with questions relating to the figure. Some of the questions are multiple choice and others provide a space for the participant to note their answer.

In the current study participants were asked to complete the GLS to assess their ability relating to reading and interpreting graphs relating to healthcare data generally. Average scores of participants recruited into this study were compared to other populations/samples.

Cystic Fibrosis Graph Survey

All graphs presented data for at least two variables (e.g. adherence and symptom data). Options included: a bar chart (Graph A) a line chart (Graph B) and finally a mixed graph than contained a line and bar chart (Graph C). Participants were presented with one graph at a time followed by four questions relating specifically to that graph. Participants were given no specific instructions other than being presented with the graph and answer choices.

Example questions include 'On the graph above, what percentage of prescribed treatment does the patient take on day 7?', 'On the graph

above what is happening to the relationship between the cough symptom score and adherence?'. The questions aimed to measure participants ability to read different graphs, understand the relationship the graph presents and also correct identify different variables on graphs. Participants were provided with a range of multiple choice answers, only one answer was correct. Therefore the highest score participants could receive was nine.

The final question for each graph asked the participant how easy the graph was to interpret, participants were asked to chose one answer from a five point Likert Scale (ranging from very easy- very difficult).

Furthermore, the different types of graphs were shown to participants to examine preferences of type and format of graphs, in order to address RQ 2 (how should data on symptoms and adherence be displayed on graphs to aid understanding?). Participants were asked to place three different graphs (which displayed identical information) in rank order of preference (see figures 3,4 and 5). Participants were then shown a graph, followed by a series of four questions, three of which assessed understanding.

Figure 3.
Graph A as displayed to participants

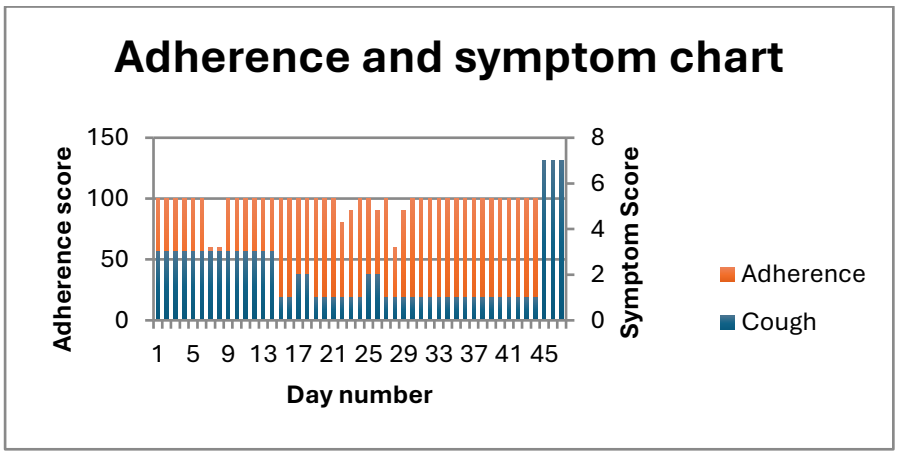


Figure 4.
Graph B as displayed to participants

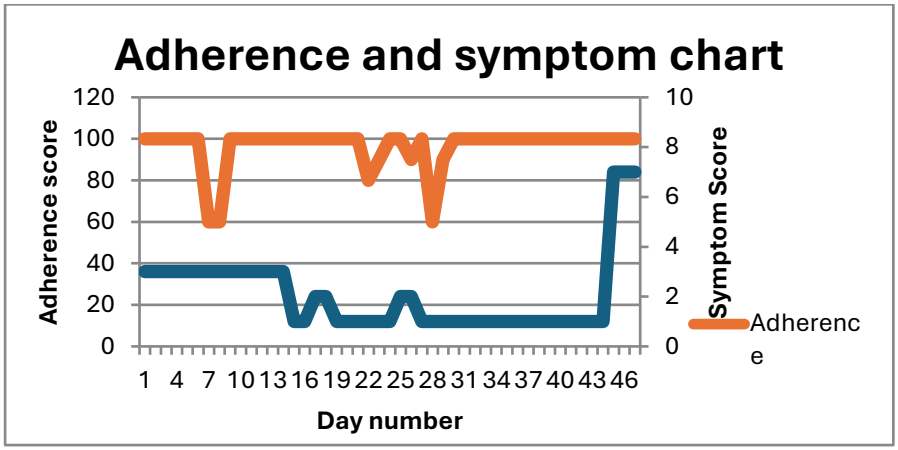
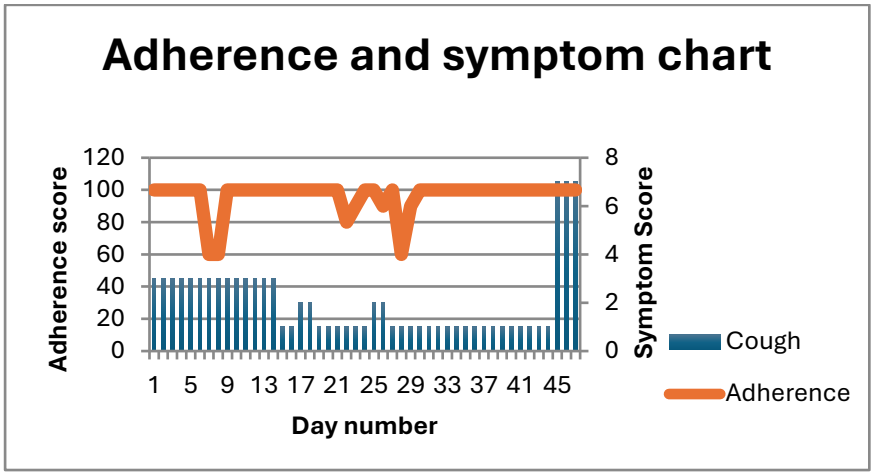


Figure 5.
Graph C as displayed to participants



In order to investigate the impact of text description when interpreting graphs (RQ3. Does including a text description aid the understanding of graphs?), half of the participants were randomly allocated into a condition, which were presented with a description to individually support and explain each of the graphs presented. See figure 6 for an example of the text description. The other half of the sample were randomised to the 'no description' condition and were not presented with an accompanying description. This survey was designed by the researcher and supervisory team specifically for use within this study.

Figure 6.
An example of the text used to support graphs in the 'text description' condition

> This graph shows one person's cough score as a blue line (shown on the axis on the right hand side of the graph) and also the percentage of prescribed medication that they take as a red line (shown on the axis on the left hand side of the graph). The graph shows these scores and percentages each day over a 47 day period.

The graphs presented were based around a fictional patient with Cystic Fibrosis and therefore contained both adherence data, which ranged from zero to over 100% (as some patients will take more than their prescribed dose at particular times) and a symptom score which was rated from zero to ten.

Scoring

To prepare the data for the inferential analysis correct answers were coded with a '1' and incorrect scores coded with a '0'. Scores were totalled for each graph variance: line graph with description, line graph with no description, mixed graph with description, mixed graph with no description, bar chart with description and finally bar chart with no description. A second variable was set up entitled 'description' or 'no description' participants 1-53 were in the description group and participants 54-106 were in the no description group.

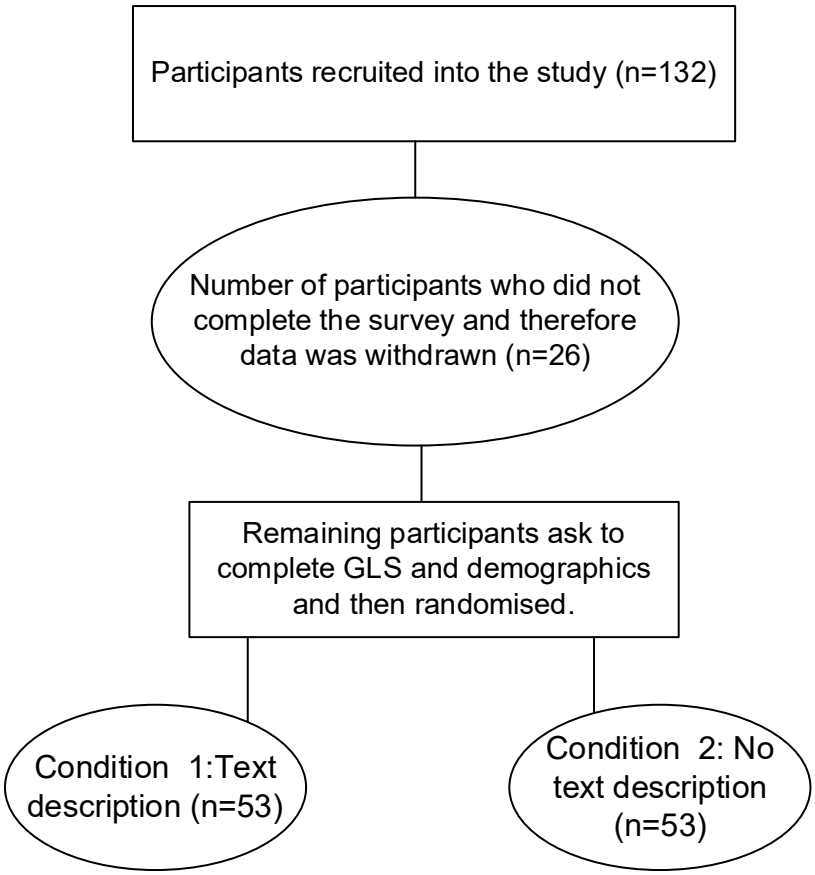
Procedure

Participants were invited to complete an online survey, the survey was created using an survey software, Qualtrics© (https://www.qualtrics.com). The study procedure is explained within figure 7.

Participants were randomly assigned through Qualtrics© to one of two conditions; text description or no text description (see figure 7). Group one received the text description, which provided detail about the graph presented, such as what the axis were displaying (see figure 6 for an

example of this), group two were presented with the same graphs with no text explanation. All participants were asked the same questions relating to the graphs and asked to answer using the multiple choice options presented to them. Only one of the options were correct. This was to determine whether participants could accurately interpret/understand the symptom and adherence data. All participants were asked three questions which related to the specific graph (bar chart, line chart or mixed) and then one question related to their preference. The answers to the preference question was not included in the analysis and was analysed descriptively.

Figure 7.
Study procedures



Analysis

Data collected was analysed using IMB's SPSS Version 24 (Armnok, NY: IBM Corp) and also Jamovi Version 2.5 (The jamovi project, 2024).

Frequencies from the preferences questions were calculated to determine which graphs participants preferred. In terms of the Graph Literacy Scale the number of correct responses from each question was calculated and a participant total was also calculated. The data from the Graph Literacy scale was not included in the inferential analysis but was used almost as a baseline to compare participants

scores to other samples. For the Cystic Fibrosis Graph Survey, questions relating to preferences were totalled and answers from participants were scored against the correct answers (1 point per correct answer and 0 for incorrect answers). Descriptive statistics were also calculated which consisted of age, gender and educational level.

In terms of inferential analysis the study had two independent variables: IV 1 had three levels and was a within design (bar chart, mixed chart or line chart) and IV 2 had two levels (description or no description) and was a between design. The dependant variable was the score participants received on the questionnaire. A mixed factorial ANOVA was used to analyse the data collected within this study 3x (2) design. Post-hoc tests were used where appropriate.

4.4 Results

Demographic information

The average age of participants was 37 years (SD=13.3) with a range from 19 years to 64 years old. In total there were 26 males (24%) and 80 females (75%). Most people recruited into the study had either a bachelors degree (31.1%) or a masters degree (28.35).

In comparison to the CF population, according to the CF Registry (2023) 1049 (15.9%) of the population who are over 16 are in full time education, however it does not state at which level e.g. college, undergraduate or post-graduate.

For further information relating to demographic information, please see table 6 below.

Table 6.
Participant demographic information

	Gender		Highest Educational Achievement					
Age	Female	Male	GCSE's or equivalent	AS/A Levels or equivalent	Bachelors degree	Masters degree	Doctoral degree	Other
36.94 (13.33)	75.5%	24.5%	12.3%	17%	31.1%	28.3%	5.7%	5.7%

Graph Literacy Scale

The Graph Literacy Scale is scored out of a total of 13. The average score for participants in the current study was 11.34 (SD=1.45). The mean scores reported in previous general population samples in Germany is 9.4 (.17) and in the United States is 9.3 (.18) (Galesic and Garcia-Retamero, 2011) and 10.25% in a group of American prostate cancer patients (Nayak et al., 2016). This suggests the graph literacy of the current sample is slightly higher than samples from previous studies (Galesic and Garcia-Retamero, 2011).

In the current study all participants answered question 1 correctly, this was the only question in which all respondents answered correctly. Participants were presented with the graph in figure 8 and asked the question 'what percentage of patients recovered after chemotherapy?'

Figure 8.
Additional material from question 1 of the GLS

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Participants preference

Participants were asked to place three different graphs (which displayed identical information) in rank order of preference (see figures 4, 5, and 6). In total 65 (61.3%) participants rated graph 2, a double line chart (figure 4) as their preferred graph, in comparison to 34 (32.1%) participants who preferred graph 3, a mix of line and bar chart (can be seen in figure 5) and only 6 participants (6%) who rated graph 1 (see figure 6), a double bar chart as their preferred option. Demonstrating that approximately two thirds of participants recruited into this study preferred adherence and symptom information to be presented in the form of a line graph.

Descriptive and Inferential analysis

In order to address research question 1 (Can participants understand graphs which display a relationship between symptoms and adherence?).The highest score participants could receive on the questionnaire was 9. The mean for total questionnaire score for participant in the description group was 5.36 (SD=1.29). The mean total for participants in the non description group was 5.02 (SD=1.18). Highlighting only a small difference between the two groups.

In relation to specific questions the questions which were most likely to be answered incorrectly across both groups were questions 4, 8 and 9. This related to question such as ‘On this graph what is the patients cough score on day 34?’, ‘On the graph above what percentage of prescribed treatment does the patient take on day 7?’ and ‘On the graph above what is happening to the relationship between the cough symptom score and adherence?’. Please see table 7 for the percentage of participants who answered each question correctly below.

Table 7.
Questions from the CF Graph Literacy questionnaire and percentage of participants who answered correctly for each condition

Condition	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9
Description	83%	95%	83%	52%	96%	94%	89%	35%	57%
No description	74%	85%	74%	33%	93%	93%	83%	33%	56%

In relation to RQ 2, the type of graph (e.g. line chart, mixed chart and bar chart) and how this impacted the questionnaire score. The descriptive statistics for the

scores of each chart were: line chart (M=1.58 SD=0.06) mixed chart (M=2.32 SD=0.06) and bar chart M=1.25 SD=0.00). Suggesting that on average participants answered more questions related to the mixed chart correctly. The analysis revealed a significant main effect of type of graph on questionnaire score ($F(2,208) = 88.79$, p =<.001, n^2_p<.461), with a small to medium effect size.

Post-hoc tests were conducted to further investigate the significant main effect of type of graph on questionnaire conducted score. This revealed that the difference between the mean scores of the line chart and the mixed chart was significant (M=-0.734 SE=-0.74 P=<.001), meaning scores for the mixed chart are statistically significantly higher than the line chart. The difference between the mean scores for the line chart and the bar chart significant (M=0.33 SE=0.09 P=0.001), meaning scores for the line chart are statistically significantly higher than bar chart.

Finally the difference between the mean scores for the mixed chart and the bar chart was also statistically significant (M=1.06 SE=0.08 P=<.001), meaning scores for the mixed chart are statistically significantly higher than the bar chart. Suggesting that participants were able to accurately answer questions presented on the mixed and the line chart better than the bar chart.

In relation to research question 3, the highest score participants could receive on the questionnaire was nine. The mean for total questionnaire score for participant in the description group was 5.36 (SD=1.29). The mean total for participants in the non description group was 5.02 (SD=1.18). Therefore on average participants in the description group scored slightly higher, however the analysis revealed that the main effect of description or no description on questionnaire score was not significant ($F(1,104) = 2.60$, p =<.110, n^2_p<.024). Therefore text description did not make a significant difference to participants score on the questionnaire. Furthermore, the interaction effect of type of graph and the description condition was not significant ($F(2,208)$ =.345, p =.709, n^2_p<.003). This data addresses research question three (Does including a text description aid the understanding of graphs?).

4.5 Discussion

The current study aimed to investigate the way in which healthcare data relating to symptoms and adherence could be presented to maximise understanding and interpretation. The study specifically investigated three research questions: RQ1: Can participants understand graphs which display a relationship between symptoms and adherence? RQ2: How should data on symptoms and adherence be displayed on graphs to aid understanding? RQ3: Does including a text description aid the understanding of graphs?

Overall, in relation to research question one, the mean scores of the Cystic Fibrosis Graph Survey demonstrate that participants did find some of the questions difficult to answer. Specifically those which related to identifying levels of adherence or symptoms on a particular day and also understanding the relationship between variables being displayed on the graph. This could suggest that participants are able to understand some of the information presented on the graph but for more specific or complex details discussion with a Health Care Professional could be required. A systematic review conducted by Schrodt et al. (2020) concluded that presenting patients with graphs can be a useful in supporting decision making around diagnosis and medication for patients.

In relation to research question 2, the descriptive statistics collected in this study suggest that the double line graph was the preferred option. Furthermore the factorial ANOVA revealed that the type of graph made a significant difference to participants score on the questionnaire with the mixed and line chart resulting in higher levels of accuracy. In terms of preference the descriptive statistics suggests that participants preferred data to be presented on the line chart. Previous research in this area presents a mixed argument, Lipkus (2007) suggests that bar charts are more familiar to the general public which could mean they are more likely to be interpreted correctly. This was also replicated in more recent research van Weert et al. (2021) which reported bar charts are often preferred and also understood.

Finally, in terms of addressing research question 3, the findings of the ANOVA suggest that the text description made no difference to participants ability to interpret graphs in this sample. The clear preference for the double line graph will be reflected in future studies within the thesis, however as over half of the

participants preferred other types of graphs this highlights the importance of providing patients with an option as suggested in the work of Kuijpers et al. (2016). Although the personal preference of the individual who is reading the graph is important, previous research has highlighted the significance of selecting the most of appropriate graphs when presenting different types of information (Slutsky, 2014). Choosing a graph that does not display the data in an appropriate format could be detrimental to those interpreting it correctly.

Limitations

It is important to note that a possible limitation of the current study was those recruited in the current sample had a slightly higher average score on the GLS in comparison to those recruited in previous samples. The sample were also more educated (31.1% of participants had a bachelor's degree). This could suggest that the participants recruited were in fact more able to correctly interpret graphs than suggested in previous literature in the American population (Lipkus et al., 2001) and also in some health care professionals (Dowding et al., 2018). However Nayak et al. (2016) suggested that even amongst highly educated samples there can be discrepancies.

Despite the efforts made to recruit as widely as possible there is the potential of sample bias in the current study. The survey was ran exclusively online which excludes members of the population who may not own computers, phones or laptops or may not be literate in such technology. Literature has suggested that digital exclusion is complex but associated with older adults, lower educational achievement and particular geographical locations (Wilson-Menzfeld et al., 2024). This highlights potential health-inequalities and suggests we may not be aware of the graph literacy levels of a large group of people who may in fact have the most difficulties with literacy, leading to a further decline in health outcomes. Furthermore, it is possible that participants who felt uncomfortable or were unable to understand the graphs presented dropped out of the study and did not submit their response. Incomplete responses (participants who did not submit their answers) were not recorded in concordance with ethical procedures. Previous literature has noted the fact that objectively testing numeracy can be anxiety provoking for participants (Peter and Bjalkebring, 2012).

It is possible that participants in the text condition did not read the text or at least in a suitable amount of detail to add to their understanding of the graph. However, there is no evidence to support this and without using more laboratory based research methods such as eye-tracking it is impossible to say either way. Previous studies have used eye tracking techniques to investigate the interpretation of graphs (Harsh et al., 2019; Okan et al., 2015; Thomaneck et al., 2015). Harsh et al. (2019) suggested that those less experienced with graphs are more likely to look sporadically at the information whereas those with more experience are more likely to look for patterns in the data.

For the purpose of this thesis the findings will be used to help inform how graphs with 'real-life' data should be presented to patients with Cystic Fibrosis in a format they are most likely to understand, however it is important to highlight that the patients recruited into this study were not patients with CF. This could mean that they are less likely to have experiences of receiving health data and therefore less likely to have good graph literacy. However, previous literature (Ferri-Guerra et al., 2020) reported that there was no association between hospital admission and graph literacy which could suggest that when patients are being treated more often or seeing Healthcare Professionals their graph literacy is not improved. It is impossible to say which of these, if any, have impacted upon the findings of the study. There is some evidence that different groups of participants have different preferences. For example, Kuijpers et al. (2016) found that patients living with cancer did not have preferences about how graphs should be presented, whereas healthcare professionals did. However, the findings of the study do provide some valuable insight into how graphs could be designed and displayed in the first instance, and this can then be followed up with exploring how participants with CF interpret and understand these graphs. Therefore the results of the study are still informative and offer contribution to this PhD thesis.

Applications

This study has clear applications within the healthcare setting and highlights the importance of ensuring patients understand healthcare data presented to them. The current study helps us to understand how symptom and adherence data could be provided to patients in a way which maximises understanding. The use of digital healthcare has the potential to benefit both the patient and clinicians,

with the potential to empower patients to understand complex information about their health and play a more active role in decisions relating to their healthcare (Klasnja and Pratt, 2012). However, if patients are able to access their healthcare data at home, without the assistance of a healthcare professional available to help explain the data to them, then it is extremely important that patients are able to accurately interpret this data. This work begins to build up knowledge of how researchers and clinicians can maximise people's understanding and interpretation of graphical data.

Chapter Summary

To summarise, in the current study participants were asked to complete an online survey in order to address three research questions which related to the preference and ability to interpret healthcare data. Participants were found to have a clear preference for a double line chart when being presented with two types of healthcare data (adherence and symptom). There was no significant difference found between those in the text description group and those in the no description group. This would suggest the accompaniment of a text description did not improve the participants interpretation of healthcare graphs. Finally, in terms of the interpretation of the graphs the results were mixed. It was found that out of nine questions asked there were three where less than 70% of participants answered correctly.

The data demonstrated that the graph literacy of the participants recruited was higher than the general population and therefore results should be interpreted with caution. However, the findings from this study such as graph preference will be applied to future work in this thesis, which will present participants with CF with complex adherence and symptom charts.

Next steps

The findings from this study will be used to inform the type of graphs which are presented to participants in future studies within this thesis. The next study will be a series of N-of-1 observations to further investigate the relationship between symptoms and adherence. There will be a qualitative component to this study in which graphs with symptom and adherence data will be presented to participants with CF to further develop the understanding generated from this initial study.

Chapter 5: A series of N-of-1 observations to investigate the relationship between adherence to treatment and symptoms in patients with Cystic Fibrosis

5.1 Chapter overview

As highlighted in chapters 1 and 3 adherence to treatments in patients with Cystic Fibrosis is a complex and multifaceted issue. However, several psychological theories propose that adherence is to some extent dependant on people understanding the benefits and importance of treatments. Previous literature in the area has suggested that some patients perceive that their treatment makes little or no difference to their condition (Arden et al., 2019), which could therefore have a negative impact on their motivation and thus their adherence to treatment. The aim of this chapter, is to use mixed methodologies consisting of N-of-1 methods and qualitative interviews to explore the relationship between symptoms and adherence in patients with Cystic Fibrosis. This chapter consists of a pilot study and a larger study.

5.2 Introduction

In 1994 and 2001 guidelines were published in relation to how nebulisers should be prescribed and used by patients with Cystic Fibrosis by the British Thoracic Society (1991) and the European Respiratory Society (Boe et al., 2001). In England there are a number of different nebulised treatments, including antibiotics and mucolytics, which are prescribed to patients to improve lung function and treat infection (see section 1.3 for further detail on nebuliser treatments). Surprisingly, there is a paucity of research investigating the relationship between adherence and symptoms in patients with CF. Drug trials have demonstrated that varying periods of time are required for nebulisers to aid the improvement symptoms in this patient group (Ballmann and von der Hardt., 2002; Hodson and Shah.,1995; Quan et al., 2001; Wark,

2018). Quan et al. (2001) concluded that treating young CF patients with dornase alpha takes a total of 96 weeks to reduce the risk of exacerbations. However, in comparison, drug trials which have tested different treatments such as hypertonic saline and rhDNase (dornase alpha) have reported a much shorter time window before effects are noticeable (Ballmann and von der Hardt., 2002). Ballmann and von der Hardt (2002) conducted a small scale trial in which participants were asked to take hypertonic saline and rhDNase. It was found that after a period of only three weeks 30% of participants showed a 'clinically relevant' increase in FEV1,although these findings should be interpreted with caution as a total of only 14 participants were recruited into the study.

Within drug trials adherence to treatments is not always reported, for example within the review conducted by Wark (2018) only two of the studies reported (Rosenfield, 2012; Suri, 2002) adherence to treatment as an outcome measure. Although measuring adherence in drug trials can be useful, it cannot be assumed that adherence would be of the same levels outside of the trial, when patients are not being monitored. In addition to this there are further considerations if subjective methods of adherence measurement are adopted (as discussed in section 1.12). When adherence has been included in drug trials it has been treated as the predictor variable with symptoms as an outcome, however what remains unclear is whether symptoms could act as a predictor or driver of adherence behaviour.

In terms of theory, the Necessity–Concerns Framework (Horne and Weinman, 2002) has been applied to long-term conditions to explain why patients do not adhere to their treatment plan. It is theorised that people who adhere to medication have stronger perceptions regarding the necessity of the medication (e.g., health benefits) and fewer concerns relating to the adverse side effects associated with taking their prescribed treatments. This was highlighted by Sawicki et al.(2015), who interviewed 20 pairs of CF youth patients (aged 16–21 years old) with their parents and found that patients thought their

treatment “makes no difference” to how they felt, which affected their intentions to adhere.

These findings have been supported by the work of Arden et al., (2019), who found that some patients with CF have “dysfunctional beliefs” in terms of believing that adhering to their nebuliser treatment/s has no impact upon their health. It was also found that some patients reported adhering to treatment when they experienced more symptoms (Arden et al., 2019), which could suggest that for some individuals, symptom experience predicts adherence to nebuliser treatments.

If patients with CF could be provided with feedback about how their adherence to treatment improves their CF related symptoms, this could influence their perceptions regarding the importance (i.e., necessities) of the treatment and potentially improve their subsequent adherence behaviours. However, in order to investigate whether interventions that utilise the *feedback and monitoring* behaviour change techniques/strategies (BCTs) (Michie et al., 2013) could be beneficial or feasible, it is first important to examine the relationship between these variables for CF patients. It is also important that when investigating the relationship between symptoms and adherence, causality is examined.

There are a number of different elements, which fall within the definition of the term self-monitoring, including; drug management, management of psychological impact and symptom monitoring (Barlow et al., 2002). This study will utilise daily symptom monitoring and adherence tracking to investigate the relationship between these variables.

Pilot studies can provide important information on the feasibility and acceptability of methods of the study design. According to Arain et al. (2010) pilot studies should be used to test how individual mechanisms of a study design work together, furthermore Hassan et al. (2006) concluded that although pilot studies can be time consuming they are necessary in providing important information for research projects.

According to Gillian et al. (2004) pilot studies in health are important as they can ensure that studies have scientific rigour and also that appropriate methods of analysis are selected. The feasibility and acceptability of symptom monitoring has been assessed for a number of different chronic health conditions. Heijmans et al. (2019) undertook research with individuals with Parkinsons and concluded that monitoring for a short period of time (2 weeks) was acceptable for these patients. However, for a longer period the system would require some adaptions, such as ensuring the wearable technology is more comfortable and adapting the experience to reduce the intensity for participants. For patients living with Bipolar disorder Schwartz et al. (2016) demonstrated that EMA on a Smartphone device was feasible for this population.

It has been reported that when trialled in patients with COPD, symptom tracking was viewed by researchers as an important tool because it can be used to help detect an oncoming exacerbation and can motivate patients to take their prescribed medication (Turnock et al., 2005). Although, in Turnock's study this was dependent on the type of symptom and also the individual (20% of participants did not monitor any of the five key symptoms). Warwick et al. (2010) concluded in their study, which looked at the self-monitoring and symptom-tracking in this population, that tracking symptoms was not 'ideal' as more than 20% of participants did not monitor any of the five key symptoms. Warwick et al. (2010) suggest that those who experienced worse symptoms were more likely to self-monitor and therefore it could be that experiencing symptoms is itself a cue to self monitoring. Furthermore those with the support of a spouse were also more engaged with the self-monitoring. Therefore, although symptom tracking can be a useful tool, it is apparent that it is not feasible for all patients living with long-term conditions.

There is a limited body of research which investigates how people experience symptoms of CF over time. Sarfaraz et al. (2010) asked patients to monitor symptoms using a handheld computer device and

spirometer readings using a second device (to test how much one breathe in and out within one second and also the total amount one can exhale), three times per day for six months. The symptoms participants were asked to rate were: cough, sputum, breathlessness and fatigue. However, only 37.2% of participants completed the study (19/53) and some of the patients reported technical difficulties and stopped using the spirometer.

These findings raise questions relating to both the length of time participants are able to monitor symptoms for and the type of technology most suitable for use in these studies. Perhaps the 'out-dated' hand-held computer system which participants were asked to use to track symptoms on is one of the reasons which could explain the poor completion rate for this study or the additional equipment required to record the spirometer reading. Additionally the study required patients to take a spirometer reading each day, which is more complex and time-consuming than rating symptoms. It is important that participants track symptoms for a sufficient period of time to collect enough data which enables clear conclusions to be drawn. However, it is equally important that the burden for participants is minimised and risk of attrition reduced, especially in the context of CF where treatment burden is already high (Altabee et al., 2024).

Roehrer et al. (2013) conducted a pilot study which looked at the use of at home symptom monitoring and spirometry in CF patients. In order to collate feedback on the perceived usefulness and usability of the diary semi-structured interviews were conducted pre and post trial. Roehrer et al. (2013) concluded that using symptom monitoring enabled the CF health care professionals to detect and predict exacerbations in patients. Participants in the intervention arm were asked to record their respiratory symptoms using the Cystic Fibrosis Respiratory Symptom Diary (CFRSD) and also their spirometry twice per week for 52 weeks. In total only 33 participants (24%) withdrew from the intervention arm, a huge difference from the earlier work of Sarafaraz et al. (2010) who reported that only 37.2% of participants completed the study. It was

concluded that this type of self-monitoring was feasible for patients in this population. Trials such as those completed by Roehrer et al. (2013) and Sarafaraz et al. (2010) were able to generate large amounts of data, however if it is to be used as part of an intervention, it is important that patients are able to understand and utilise the data they have spent a significant amount of time collecting.

The nature of the relationship between symptom perception and adherence is currently unclear. It could be that participants who do not adhere to treatments are not aware of the consequences of this. Conversely, other patients maybe prompted to adhere if they notice a change or decline in symptoms (Bucks et al., 2009). The NCF (Horne and Weinman., 1999) and associated evidence can be used to develop understanding of the relationship between adherence and symptom experience, however existing research and theory does not provide evidence about how exactly adherence and symptoms are related and the direction of this relationship for people with CF.

Specifically, understanding the relationships and causality between variables such as adherence and symptoms is important. Data collected can be used to promote discussion during appointments and to help patients and clinicians keep track of condition in-between appointments. However there are limited ways in which this data can be analysed, the current study will adopt observational N-of-1 methods. Observational N-of-1 studies are often interested in monitoring a relationship between two variables over time (such as symptoms and adherence) (McDonald et al, 2017). According to McDonald et al. 2017 such methods can aid the understanding of relationships at individual levels without the need for an intervention. For more discussion related to N-of-1 methods please refer to chapter 3 of this thesis.

The current study is separated into two phases- phase 1 a pilot study and phase 2 a main study and aims to address four research questions:

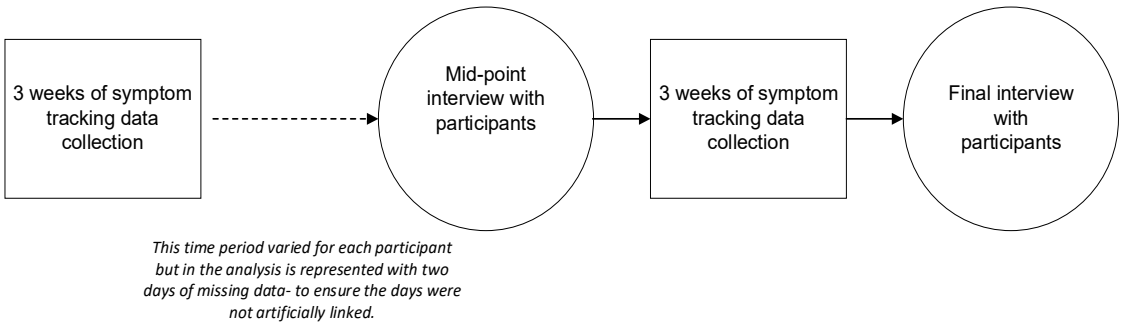
- Research question four of the PhD: Is symptom monitoring in patients with CF acceptable and feasible?
- Research question five of the PhD: Do CF patients understand feedback graphs, which display the relationship between their adherence and symptom data?
- Research question six of the PhD: Are there any barriers that prevent CF patients from understanding symptom tracking?
- Research question seven of the PhD: What is the relationship between self-monitored symptoms and adherence in CF patients?

Therefore this chapter will report the findings of two studies. Firstly a pilot study which adopted a mixed methods design and secondly the main study which adopted a quantitative design.

5.3 Pilot Study Method

The methodology and design of the pilot study will be discussed in detail below. For the full study protocol of the pilot and main study please see Appendix C. Please see figure 9 below for a summary of the pilot study timeline which provides detail about how long participants were symptom tracking for.

Figure 9.
Study timelines



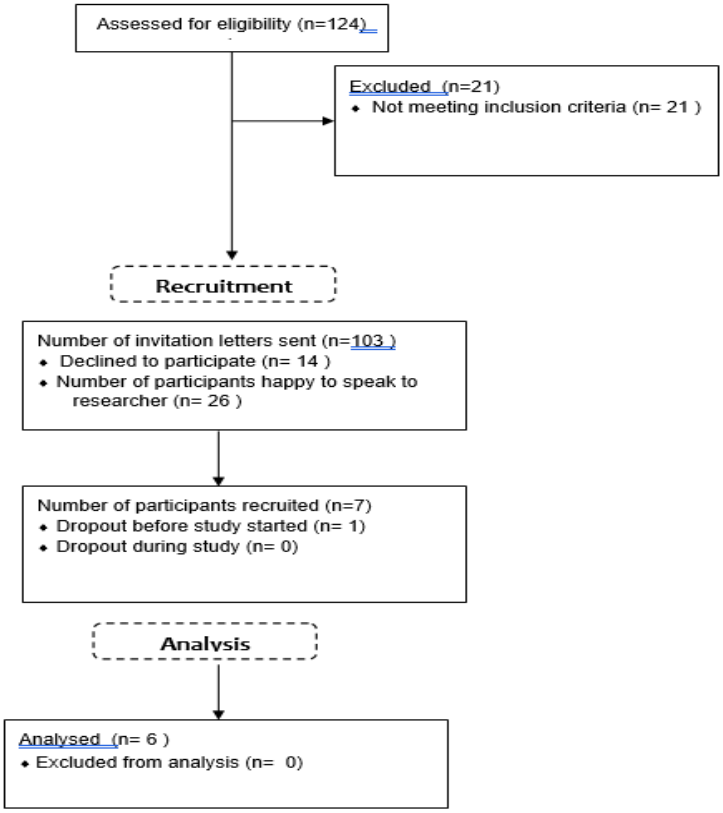
5.3.1 Design

An observational N-of-1 design was adopted in this study, which meant data from each participant was analysed separately. The predictor variable was the participants' adherence to nebuliser treatments, which was measured objectively via an eTrack® (Pari GmbH, Stanberg, Germany) nebuliser. The outcome variables were the symptoms of Cystic Fibrosis which were self-reported via a web-based Qualtrics © (https://www.qualtrics.com) questionnaire on a daily basis. The variables were decided on prior to the data analysis. This study was designed as a pilot study.

5.3.2 Participant Recruitment

In total seven participants(n=1 male and n=5 females) were recruited into this phase. Participants were identified by selected staff members and interventionists on the CF ward, all participants who met the inclusion criteria and agreed to be contacted about further research (when they consented to the CFHealthHub research) were contacted about the study. Please see figure 10 below for further information relating to recruitment and drop out. An invitation letter and information sheet was sent to participants in the post by the clinical team, the invitation letter explained that a member of the clinical team would contact them directly or discuss the study with them during their next appointment. Either the interventionist or researcher (RM) took consent from participants. Once participants consented RM enrolled them onto the study programme. Please note all participants who were willing to take part were recruited into the study, a number of patients shown interest but did not consent, reasons for this were not recorded. One participant gave consent but then withdrew before the study started, due to family commitments.

Figure 10
CONSORT Diagram for the pilot study recruitment



Further details on the demographics of participants can be seen in table 8. The table highlights that the average objective adherence for the participants from the month before the study began ranged from 15%-100%, all participants were taking more than one nebulised treatment and Predicted FEV ^{1} ranged from 45%-96%.

Table 8
Participants demographic information, nebuliser treatments and average step-count

Participant Number	Sex	Predicted FEV [1](%)	Baseline Adherence (%)	Prescribed Nebuliser Treatment/s	Total doses of treatment prescribed per day
1	F	89%	73%	2 mucolytics	3
2	F	89%	99%	2 mucolytics	3
3	F	73%	15%	1 mucolytic and 1 antibiotic	5
4	M	80%	68%	2 mucolytic and 1 antibiotic	9
5	F	96%	100%	1 mucolytic and 1 antibiotic	6
6	F	45%	41%	1 mucolytic and 1 antibiotic	6

Inclusion and Exclusion Criteria (For both the quantitative and qualitative component)

The inclusion criteria for the recruitment of participants were as followed:

I. Patients were 16 years or older and being treated by adult services within the NHS (a CF clinic in the North of England).
II. Participants were part of the CFHealthHub Data observatory (see section 3.5) and had agreed they were happy to be contacted about future research.
III. Participants were receiving treatment, using an eTrack® (Pari GmbH, Stanberg, Germany) nebuliser system.

IV. Translation was not available so participants must speak English to ensure consent could be obtained accordingly and the study could be completed.
V. Finally, participants were required to own a smartphone to complete the online survey each day.

The exclusion criteria for the recruitment of participants were as followed:

I. CF patients who were under the age of 16 (the change of transition into adult services in the NHS).
II. Patients who were not using nebuliser as a part of their daily treatment and not receiving treatment through Sheffield Teaching Hospitals.
III. Patients who were in the late palliative phase of treatment (i.e., people in the end stage of their illness for whom the emphasis of care was comfort).
IV. Finally patients who were pregnant or on the transplant list at the start of the study were also excluded from taking part in the study due to the stress likely to be experienced in such experiences.

5.3.3 Ethics

The study received ethical approval from London Bromley Research Ethics Committee (17/LO/1769) on the 16th November 2017 and the Health Research Authority (12th December 2017). Prior to this the study was given approval from Sheffield Hallam University. All participants in the study gave informed consent. See Appendix D for the study consent form and information sheet.

5.3.4 Daily Symptom Diary

A Patient Participant Involvement group (PPI group) were consulted and contributed to the design of the daily diary study. For further information about this see section 3.4.

The symptoms, which were chosen to be tracked for the six-week period were: cough, wheeze, difficulty breathing, pain, tiredness and mucus amount. Participants were asked to rate the severity of each symptom using a visual analogue scale which ranged from 1 to 10 (a total length of 10cm) where 0 is not at all and 10 is a great deal.

The questionnaire was sent to participants each day via email. Messages were time-contingent as participants were asked to respond to a timed prompt each day. Previous work has suggested that the time-contingent approach is likely to encourage the participant to complete the data collection when prompted and reduce the chance of retrospective bias (Moskowitz and Young., 2006). Although participants were sent the survey at the same time each day they did not have to complete the survey at that specific time as the link did not expire it would simply time and date stamp the submitted responses. The survey was developed and hosted using an online survey software Qualtrics© **(**https://www.qualtrics.com).

In order to address concerns relating to the acceptability of the study (particularly the symptom tracking aspect), the symptom tracking period was split into two three-week blocks. This ensured that participants were given a break and also enabled the researcher to explore the acceptability and feasibility of symptom tracking in the form of a qualitative interview during the midpoint of the study before recommencing data collection (and provide a stop point if participation had been too burdensome or had negative consequences, however participants did have the right to withdraw at any point). The findings of the qualitative aspect of the study are also reported within this chapter of the thesis.

Figure 11 provides an indication of how the symptom tracking questionnaire was presented to participants on their smartphone. The questionnaire was sent using electronic methods due to evidence (Cherenack et al., 2016) and findings from the PPI group which both demonstrate how electronic methods are preferred. Therefore, the

questionnaire could be completed on a Smartphone, tablet or computer. Prior to entering data, participants were asked to enter a unique code which they were provided with so it was clear which participant had submitted which responses and data could be analysed accordingly.

Figure 11.
Preview of Qualtrics© daily symptom questionnaire

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5.3.5 Physical Activity Monitoring

Participants were given the option of wearing a Fitbit for the duration of the study period so that step-count could be monitoring over the six week period. A Fitbit is an activity tracker watch which monitor step-count. Participants were provided with the device for the duration of the study, both the participant and the researcher had access to the account username and password which meant they could log on and access the data.

All participants were happy to wear a Fitbit which was provided, however one participant chose to stop wearing the device at the mid-way point as they preferred to wear their own.

The step count data collected was analysed descriptively (see table 9), however the data was used as an additional prompt in the interviews to encourage the participants to reflect upon their activity levels, the data was not analysed using N-of-1 methods. Step count ranged from 3141-10,776 and the number of days participants wore their loaned device ranged from 14 days- 46 days.

Table 9.
Step count data for participants in the pilot study

Participant Number	Average step-count
1	10,776.38 (worn for 29 days)
2	10,269.77 (worn for 14 days)
3	3,400. 41 (worn for 46 days)
4	7337.47 (worn for 45 days)
5	6395.44 (worn for 45 days)
6	3141.09 (worn for 46 days)

5.3.6 Objective adherence data

Objective adherence was measured using the eTrack Neubliser and displayed in the CFHHhub. Adherence data was recorded along with the patient's prescription data (number of doses prescribed per day). This data was used to calculate a total number of doses taken per day and the proportion of prescribed doses taken per day (%) was calculated. Therefore it is possible for data to be over 100% if patients take more than their prescribed dose. This often happens if patients take doses late at night (after midnight) as the system will record it as a treatment for the next day, or if they take some medications pro re nata (PRN) (as required in the circumstances).

To ensure data was transferred securely- a secure, encrypted and password protected data transfer request document which included participants CFHH code and appropriate dates (the duration of their study period) was sent to the Clinical Trials Research Unit at The

University of Sheffield (the CFHH data observatory). Appropriate data was sent back once again using a secure, encrypted and password protected document and anonymous codes.

5.3.7 Analysis

Data was analysed using IMB's SPSS version 24 (Armonk, NY: IBM Corp). Each participant's data was analysed separately using an N-of-1 approach (Hobbs et al., 2013) where statistical analyses are powered by the number of observations rather than the number of participants.

It is challenging to accurately estimate the required number of observations for a given power level as there have not been any previous N-of-1 studies undertaken in this patient group which explore the correlates of adherence. However, it is suggested that 50 observations should provide sufficient power (Tabachnick and Fidell, 2007).In this pilot study there was over 1,000 data observation points.

The following stages of analysis were adopted for analysis of the pilot study data:

1.Addressing missing data: A missing value analysis was conducted on all symptom questions for all participants. Little's Missing Completely at Random test (Little, 1988) revealed all data was missing completely at random and therefore no cause for concern. A stimulation-based statistical technique, multiple imputation was adopted to handle cases of missing data (Jakobsen et al., 2017), as advised by (McDonald et al., 2020). There was no missing data for the objective measurement of adherence. As there was a break for all participants after a three-week period, two additional data points of missing data were added to the data files for all participants; this was to ensure adjacent data points before and after the break were not linked artificially. Adherence was measured during this period, but symptom scores were missing as no data was inputted on these days.

2.Descriptives statistics: Descriptive statistics were calculated for each symptom and adherence. Sequence charts were produced for each symptom (cough, wheeze, difficulty breathing, pain, tiredness and

mucus amount) and also for objective adherence scores for the six-week symptom-tracking period to show the temporal relationship between variables.

3.Plotting the data: Following the first two stages, the pre-whitening method was used with the data, using the stages outlined in the paper entitled 'A starter kit for undertaking N-of-1 trials' written by Felix Naughton (Naughton, 2014). All variables were plotted using sequence charts to provide the opportunity of visual inspection across all variables individually.

4.Checking for autocorrelation: Autocorrelation charts must be created for the variables as it is critical to address autocorrelation within the data. Charts are created by selecting analyse, forecasting and autocorrelations.

The days which pass the confidence intervals on the partial autocorrelation plot provides a good indication of the days which must be lagged due to a chance of autocorrelation. This step was taken for all symptoms included within the analysis.

5.Pre-whitening the data: A "prewhitening" procedure was applied to each symptom; this was to ensure that autocorrelation was removed between data points. Autocorrelation is 'the association between sequential data points within the same variable' (Naughton and Johnson, 2014. P.203). Naughton and Johnson (2014) provide a clear and comprehensive definition of autocorrelation within their N-of-1 Starter Kit paper. According to their definition autocorrelation examines the relationship between variables at individual time points for example between T0 and -T24 (hours) which would be lag one, T0 and -T48 (hours) would be lag two and so forth. Taking a cautious approach to address autocorrelation, each symptom was pre-whitened by at least one lag (the equivalent of 24 hours), if there was further evidence of autocorrelation symptoms were lagged accordingly.

6.Producing cross-correlation charts: To investigate relationships between symptoms and adherence, cross-correlations were examined in line with the recommendations of Naughton and Johnson (2014).

If the cross-correlation charts were indicative of a relationship (this was measured by any points passing through the confidence interval, as indicated by the bold black line on the chart above). Cross correlation charts for each relationship can be seen in the analysis below. This was further investigated using a linear regression which will be outlined in step 7.

7.Inferential analysis using Linear Regression: If there was initial evidence of a relationship on cross-correlation charts (above the 95% confidence interval), a linear regression analysis was conducted to determine statistical significance of this association. The analysis was exploratory in nature to explore the cross-correlations identified rather than testing specific associations (e.g adherence will predict cough in 1 day).

Pilot Study- Qualitative

5.3.8 Qualitative Design

Participants who were recruited into the pilot study were invited to take part in two interviews during the course of their participation, the interviews covered slightly different topics, please see table 10 for further detail. The interviews provided participants with the opportunity to provide some feedback about their experience. All participants agreed to take part in the first interview which was at the 3 week point, however one person was not able to take part in the second interview (at the 6 week point) due to family commitments. Patients were

presented with their symptom and adherence data which was presented using a double line chart based on the findings from chapter 4.

Table 10.
Additional information relating to pilot study interviews

Interview	Number of participants	Study time point	Topics covered
Interview 1	6	3 week (mid-point)	Daily diary related questions e.g. how long did it take? Was it acceptable? Questions relating to graphs e.g. patterns and ability to understand the graphs. Qualtrics usability e.g. how was this and would this be a preference over pen and paper.
Interview 2	5	6 week (end-point)	Experience of symptom tracking, graphical preferences, more detailed questions relating to symptoms and adherence, including discussing data.

5.3.9 Qualitative Analysis

Interviews were audio-recorded and transcribed verbatim by the researcher. The interviews were focused on understanding the feasibility and acceptability of symptom tracking in participants with CF. A qualitative content analysis was adopted to analyse the data sets. To undertake a qualitative content analysis data is coded and categorised into primary patterns (Krippendorf, 1980; Patton, 1990).

Stages of Content Analysis (method adapted from Akhavan and Lungdgren, 2012)

1. Understanding the rationale for the study- this relates to the research questions of this study which are: RQ4: Is symptom monitoring in patients with CF acceptable and feasible? RQ5: Do patients with CF understand feedback graphs, which display the relationship between their adherence and symptom data? RQ6: Are there any barriers that prevent CF patients from undertaking symptom tracking?
2. The transcripts are then read individually and repeatedly with the aims/rationale of the study in mind.
3. Data which was relevant in terms of answering the research questions was coded as appropriate.
4. Codes were then grouped into sub-categories
5. Finally, the report is written in full.

5.4 Pilot Study Results

Observation points

Five out of the six participants had recorded data on over 70% of the study days and the number of observation points per participants

ranged from 275-826. In total there was over 1500 data points. Two participants completed the self-monitoring diary every day; the largest amount of missing data for a participant was 38%. The mean daily completion rate for all participants was M = 87.6% (SD = 15.52). Daily completion rates for all participants can be seen in table 11 below.

Descriptive statistics

Across all participants the symptom with the highest mean was tiredness (M=2.90), followed by cough (M=2.45). Difficulty breathing had a mean of 1.05 and mucus amount 1.96. The mean score for wheeze and pain were both below 1 (wheeze M=.57 and pain M=.85). Therefore all of the mean symptom scores were below 3, this demonstrates the scores for all symptoms across all participants were relatively low. However, there was more variation with objective nebuliser adherence which ranged from 97.55%-16.67% between participants. Descriptive statistics for each symptom variable and adherence for all participants are presented below in table 12.

Table 11.
Participants daily completion rate

Daily completion rate	Participant 1	Participant 2	Participant 3	Participant 4	Participant 5	Participant 6
	71%	*62%*	*88%*	*100%*	*88%*	*100%*

Table 12.
Descriptive statistics

Participant Number	*Cough	*Wheeze	*Difficulty breathing	*Pain	*Tiredness	*Mucus amount	Objective adherence (%)	*Range of Weekly Adherence*
P1	*3.85 (0.99)*	*0.10 (0.34)*	*1.22 (0.93)*	*0.04 (0.15)*	*3.47 (0.96)*	*2.93 (0.94)*	*82.5 (52.19)*	*71.5–100%*
P2	*0.26 (0.40)*	*0.19 (0.30)*	*0.48 (0.54)*	*1.52 (1.03)*	*4.26 (1.57)*	*0.15 (0.28)*	*97.55 (10.26)*	*94.3–100%*
P3	*5.49 (2.42)*	*2.80 (1.88)*	*4.02 (1.64)*	*2.93 (1.07)*	*6.28 (1.86)*	*4.23 (2.22)*	*16.67 (35.66)*	*0-47.6%*
P4	*1.47 (0.83)*	*0.09 (0.30)*	*0.00 (0.00)*	*0.53 (0.70)*	*1.41 (1.11)*	*1.44 (0.80)*	*75.30 (29.85)*	*52.3–100%*
P5	*2.55 (0.53)*	*0.25 (0.48)*	*0.22 (0.47)*	*0.08 (0.32)*	*1.94 (1.31)*	*2.28 (0.57)*	*87.78 (27.80)*	*71.4–100%*
P6	*1.11 (1.22)*	*0.00 (0.00)*	*0.39 (1.13)*	*0.00 (0.00)*	*0.32 (0.86)*	*0.73 (0.66)*	*45.64 (36.04)*	*0–78.6%*

*Symptom rating score ranged from 1(not at all)- 10 (a great deal) Adherence score (%) could be over 100% if patients took more than the prescribed daily dose.

The relationship between nebulised treatments and symptoms of Cystic Fibrosis

Cough

Cross-correlation charts for participants 1, 3, 4 and 6 did not reveal any relationships between cough and adherence; therefore, no further analysis was undertaken.

For participant 2, cross-correlation charts were indicative of a relationship between adherence and cough on day zero (rlag0 = −.338). To investigate this further, a linear regression was conducted which revealed a statistically significant negative relationship between coughing and objective nebuliser adherence on the same day (F = 5.30; B = −8.95; 95% CI –16.80– –1.10; R^2 = 0.115; P = 0.026). This suggests that lower adherence is related to more severe cough occurring on the same day for this person. For participant 5, cross-correlation charts were indicative of a positive correlation at lag -2 (rlag-2 = 0.336). However, when the relationship was tested using a linear regression, it was not statistically significant (F = 0.407; B = 5.70; 95% CI –12.33–23.74; R^2 = −0.014; P = 0.527)

Wheeze

Cross-correlation charts for participants 1, 2, 3 and 4 were not suggestive of a relationship; therefore, no further analysis was undertaken. Participant 6 reported wheeze as zero for the duration of the study; therefore, no further analysis was undertaken.

For participant 5, there was indication of a negative relationship between the variables on the cross-correlation chart, rlag-5 = −0.392. As there was a lag at -5, this means that wheeze precedes adherence by 5 days. A linear regression was conducted to determine the relationship between wheezing and adherence for participant 5, which was found to be non-significant (F = 0.997; B = −9.80, 95% CI −29.65–10.05; R^2 = 0.025; P = 0.324.

Difficulty breathing

Cross-correlation charts for participant 2,3,5 and 6 were not indicative of any relationship between the variables difficulty breathing and adherence; therefore, no further analysis was undertaken. Participant 4 reported difficulty breathing as

being at zero for the duration of the study; therefore, no further analysis was undertaken.

Therefore, there was only one participant (participant 1) who presented evidence of a relationship between difficulty breathing and nebuliser adherence. For participant 1, cross-correlation charts revealed evidence of a positive relationship between difficulty breathing and adherence at lag 6 (RLag6 = 0.446). As this was a lag at day 6, this would mean that adherence precedes difficulty breathing by six days. A linear regression revealed that this relationship was not statistically significant (F = 0.059; B = 2.70; 95% CI −19.95–25.36; R^2 = 0.002; P = 0.810). These findings would suggest that for all participants in the study, there was no significant relationship between experiencing difficulty breathing as a symptom and adherence to nebuliser treatments.

Pain

Participant 6 reported pain as being a zero for the duration of the study; therefore, no further analysis was undertaken.

Cross-correlation charts revealed no evidence of a relationship for participant 1 and 3; therefore, no further analysis was undertaken. Cross-correlation charts for participant 2 revealed a moderate negative correlation between adherence and pain (RLag0 = −0.311). This relationship was found to be statistically significant when analysed using a linear regression (F= 4.40; B = -4.46; 95% CI −8.76– –0.164; R^2 = 0.97; P = 0.042). This suggests that for participant 2, lower nebuliser treatment adherence is associated with higher pain on the same day.

Participant 4's cross-correlation charts revealed evidence of a positive relationship between pain and adherence, Rlag-2 = 0.36 and Rlag0 = 0.34. The cross-correlation suggested that it was possible pain proceeded adherence by two days or that there is a possible same day relationship. The variables (lag = 0) were analysed using a linear regression which revealed a significant relationship (F = 4.40; B = 15.11; 95% CI 0.553–29.69; R^2 = 0.102; P = 0.042). However, when the lag at −2 was investigated further, the regression revealed a nonsignificant relationship (F = 2.13; B = 13.70; 95% CI –5.33–32.73; R^2 = 0.056; P = 0.153). This suggests only the relationship on the same day was significant; i.e. higher pain was associated with lower adherence.

For participant 5, cross-correlation charts revealed evidence of a relationship between pain and adherence (RLag0 = −0.467; RLag-5 = −0.438. A linear regression revealed that this relationship (lag = 0) was statistically significant (F = 12.00; B = −43.81; 95% CI –69.32– –18.30; R^2 = 0.218; P = <.001). However, when the lag at –5 was investigated further, this relationship was not significant (F = 0.044; B = 3.12; 95% CI –26.90–33.15.1; R^2 = –0.024; P = 0.834). These findings suggest there is a significant moderate relationship between pain and adherence on the same day for this participant.

Tiredness

Cross-correlation charts revealed no evidence of a relationship between tiredness and adherence for participants 1, 3, 2, 4 and 6; therefore, no further analysis was undertaken.

Participant 5 cross-correlation charts for tiredness and adherence were indicative of a possible negative relationship at Lag 0 (rlag0 = −0.319). A linear regression revealed a significant relationship between tiredness and adherence (F = 4.87; B = −7.87; 95% CI –15.00– -0.682; R^2 = 0.102; P = 0.033). This suggests that for participant 5, there is an association between higher levels of tiredness and lower adherence to nebuliser treatment on the same day.

Mucus

Cross-correlation charts for participants 1, 4, 5 and 6 revealed no evidence of a relationship between mucus amount and adherence; therefore, no further analysis was undertaken.

Cross-correlation charts for participant 2 were suggestive of a moderate negative correlation at 2-day lag (rlag-2 = –0.470), which would suggest higher mucus is related to lower adherence 2 days' later for this participant. However, when this was investigated further using a linear regression, this relationship was not statistically significant (F = 0.735; B = 5.71; 95% CI –7.76–19.18; R^2 = 0.018; P = 0.396).

Cross-correlation charts for participant 3 were suggestive of a correlation at –1 and 5-day lag (rlag-1 = –0.350; rlag5 = −0.343). However, when this was investigated further using a linear regression, these relationships were not

statistically significant for lag −1 (F = 1.14; B = −2.87; 95% CI –8.28–2.54; R^2 = 0.027; P = 0.291) or lag 5 (F= 0.778; B = −2.84; 95% CI –9.37–3.69; R^2 = 0.022; P = 0.384).

5.4.1 Summary of significant relationships

To summarise these findings in one page please see table 13 below. As demonstrated on the table out of 36 possible relationships only six were significant (significant findings are highlighted using an asterisk (*). For four out of six participants there was a significant relationship between pain and adherence. Wheeze, difficulty breathing and mucus however revealed no significant relationships across all the participants. In terms of findings per participant, the data of three participants demonstrated evidence of a relationship with at a least one symptom. However for the remaining three there was no evidence of a significant relationship between any of the symptoms and adherence.

Table 13.
Inferential statistics for all participants

Participant	Cough and adherence	Wheeze and adherence	Difficulty breathing and adherence	Pain and adherence	Tiredness and adherence	Mucus and adherence
1	No relationship	No relationship	*Lag 6 r= 0.446 p = 0.810*	No relationship	No relationship	No relationship
2	**Lag 0 r= −0.338 p = 0.026*	No relationship	No relationship	**Lag 0 r= −0.311 p = 0.042*	No relationship	*Lag -2r = −470 p = 0.396*
3	No relationship	No relationship	No relationship	No relationship	No relationship	*Lag 5 r= −0.350 p = 0.384 Lag -1r = −0.343 p = 0.291*
4	No relationship	No relationship	-	**Lag 0 r = 0.339 p = 0.025 Lag -2 r = 0.362 p = 0.153*	No relationship	No relationship
5	*Lag -2 r= 0.336 p = 0.527*	*Lag -5 = −0.392 p = 0.325*	No relationship	**Lag 0 r = −0.467 p = 0.001 Lag -5 = −0.438 p = r0.834*	**Lag 0 r= −0.319 p = 0.033*	No relationship
6	No relationship	-	No relationship	-	No relationship	No relationship

*= significant at p<0.05

5.4.2 Pilot Study- Qualitative Findings

Qualitative data collected in this study was analysed using content analysis. See table 14 below which outlines key categories from the data, the number of times the categories were identified and a short summary. The 'participation is easy' category was identified by all participants with the study, however 'happy to use the wearable device' was only reported by two participants. The table also links the relevant categories to the APEASE criteria (Michie et al., 2014) and provides an explanation of whether such categories are linked to the Affordability, Practicality, Effectiveness/ Cost Effectiveness, Acceptability, Side-Effects or Safety or finally the Equity of the pilot study. The APEASE criteria is explained in detail in section 1.9 of the introduction.

Table 14.
Qualitative findings summary

Category	N	Summary	APEASE (where relevant)
Preferences for a specific type of graph	3	Some of the participants had a preference of the line or bar graph.	Acceptability- preferences in terms of what graph is acceptable.
Being able to interpret graphs	2	Two participants discussed the ability to understand the graphs.	Practicality-the ability to understand the data.
Difficulty understanding graphs	1	One participant discussed difficulties associated with understanding the graphs.	Practicality- a potential barrier relating to understanding data.
Struggling to remember to participate	3	For some participants it was a challenge to remember to complete the study.	Practicality- a potential barrier to the use of symptom tracking.

Using technology over paper format was preferred	5	The majority of participants referred using technology over the option of paper format.	Acceptability- Preferences around format of the data.
Happy to use the wearable device	2	Some participants were happy to wear the Fitbit device.	Acceptability- Willingness to wear a Fitbit device.
More awareness about condition- positive impact	3	Some participants felt study participation	Effectiveness- a possible benefit of the study.
More awareness about condition- negative impact	2	Some participants felt study participation	Side-effects- consequences of participation, being more aware of their condition.
Participation is easy	6	All participants confirmed that participation was easy.	Practicality- participants understood what they were being ask to do.
Participation is quick	5	The majority of participants felt participation was quick.	Practicality- participants felt participation was not time consuming.
Barriers to adherence	3	Participants spoke of barriers which made medication adherence difficult.	Not specifically related to the use of symptom tracking.
External influences on symptoms	3	Participants discussed external influences which cause changes to their symptoms.	Not specifically related to the use of symptom tracking.
Heart rate monitoring	3	Some participants suggested that monitoring heart rate would be a worthwhile	Effectiveness and cost-effectiveness- Suggestions for improvement.

addition to the symptom-monitoring.

Understanding information presented on graphs

During the interviews participants were presented with their individualised symptom and adherence charts. Participants were asked about the graphs presented and their interpretation of them.

One of the participants spoke of the usability of graphs which are currently used within the CFHH app and suggested that it would be useful if the graphs could be formatted in the same (see Appendix E for example of CFHH graphs).

> ‘Ermm I think I don’t know it’s not quite as easy to read. I don’t know why. Have you seen the CF Health Hub charts?’ Participant 4 Line 112-113

The participant then refers explicitly to the colour coding which is used on the app.

> ‘Yeah I think the colour coding helps because then you can see its sort of like because originally I hadn’t done anything and its not showing it but when I have it shows green, orange if you haven’t quite hit as many nebs as you should of done and then red if you haven’t hit any. So…’ Participant 4 Line 144-148

Some of the participants were able to read and interpret the graphs more easily than others. The participant below suggested that they could read the graph but would need some explanation of the relationship or correlation of the variables.

> ‘Yeah they are easy to read. Its good when you put these two together but I couldn’t work out if there ‘s a correlation.’ Participant 2 Line 191-192

The graphs presented to the participants were in the form of line charts, however one of the participants referred to a preference for bar charts, as this would help give an instant overview of the data presented.

> ‘Ermm… maybe for me and its because probably because I'm a little bit old school but for me bar charts would probably bit a little bit easier because you know you can see if there’s nothing there you know there’s a gap. Do you know what I mean? Whereas that’s probably for a first glance

your having to study it for it to get the information. That's the only thing I would say.' Participant 6 Line 95-101

If participants are to use the data presented to them in graphical format and make use of this data, it is of key importance that the graphs are understandable and clear. However it is not clear how best to present graphs given that there may be different preferences.

Experiences of the pilot

Participants were invited to share their experience of the symptom tracking study during both interviews.

Acceptability of the technology

Technology played an important role within the study as the survey link was sent via email each day and participants were asked to complete the survey online and also wear a Fitbit device. All of the participants agreed that overall using technology (mobile phone/ tablet or computer) was preferred over using paper format. Participants preferred using their phone for different reasons such as the ease of having their phone with them.

'Its quite an easy one this because all you have to do is wear that (Fitbit) and fill it in, so it doesn't take that long' Participant 1 Line 231-23

'On my phone because I've always got it with me, like glued to me' Participant 6 Line 56

Others preferred symptom tracking online as paper copies require storage and would be an additional thing to take out of the house, whereas most people will carry a mobile phone automatically.

'Er mobile I think, otherwise you'd have to remember to take the sheets with you and you'd have to store them at the end of it whereas you've always got your phone haven't so um hm..' Participant 5 Lines 78-80

Participants had mixed opinions in responses to wearing the Fitbit devices. One participant in particular preferred to wear an Apple Watch and decided after the first three week period to continue the study without using the Apple Watch.

I: Yeah yeah, how did you find wearing the Fitbit?

P: I didn’t like it because I wear my apple watch. Participant 2 Lines 126-127

One participant found the watch slipped off the wrist easily and had concerns about losing the Fitbit, however in terms of the data collected and presented on the app she preferred this over another brand she had experienced previously.

‘Yeah yeah, I think the only problem I’ve had with it is when it slipped off, this is why it comes off because the go in but it slips off (the clasp) really easily so that’s why it fell off. Whereas this one is quite tight but the only thing is I do prefer the Fitibts data. I prefer the way it collects data’ Participant 4 Lines 217-221

Awareness of condition

For some participants the daily symptom diary acted as a reminder of their condition when perhaps previously they had tried forget about CF where possible. Although monitoring symptoms had given the participant an indication that their symptoms were deteriorating prior to an appointment.

‘Yeah cos I tend to sort of like 'la la la I'm fine I'm fine I'm fine' erm but like towards the end of the study was when I had a clinic admission as well errr a clinic appointment… And you know, I was already aware that things had been getting abit worse, probably because the having to monitor it’ Participant 4 Lines 41-45

However, this participant then goes on to suggest that being more aware of her condition is perhaps a positive thing and has encouraged her to act rather than ignore the signs of feeling unwell.

‘a good thing really. Just because I don’t know if sort of like if I could get my head around the physio and nebulisers then if I am thinking about it more then I can go right okay I need to up my treatment. Rather than doing my whole blank thing of 'Im probably feeling worse, I don’t care'. Participant 4 Line 69-73

Although for another participant recording their symptoms when they are higher can be an unwelcome reminder of their illness which could cause them to feel unhappy.

> ‘Erm (pause) a little bit I mean it makes me feel a little more conscious because if I’m ill that day then I have to write it down, I might be actually more conscious of the fact that I’m feeling a bit down. Or if I’m coughing more at the minute its easier to remember when I’ve written it down.’ Participant 1 Line 48- 52

These findings suggest that symptom monitoring can be useful in heightening awareness of the condition, especially in preparation for appointments or even seeking help from the medical team. However, it is important to be aware that for some participants feeling more aware of their condition is not always perceived as a positive experience by the patient.

Remembering to participate

One of the participants had referred to the difficultly experienced in terms of remembering to complete the questionnaire.

> ‘Just me not remembering, I need an hourly text. That’s what I was thinking it would be really good if erm somehow you could get that, if you hadn’t done the survey like a text to say have you remembered’ – Participant 2 Lines 35-37

On the contrary other participants referred how using their treatment as a prompt to complete the survey helped serve as a reminder:

> ‘Like when I’m doing my treatments I’ll think ‘oh I need to do my questionnaire as well’- Participant 1 Lines 76-77

Although some participants were able to remember to complete the survey there was occasions when they were unable to remember if they had already completed it for that day. At the moment there is no option for the participant to look at their data for previous day.

> ‘I think the only problem I had was remembering whether I had done it or not. A couple of days I went 'have I actually filled in that?' then I thought 'well I best not do it again'. Erm but yeah’ Participant 4 Lines 58-61

These findings suggest that for some participants remembering to complete the survey can be a barrier, further the ability to see if the survey has been completed for that day is something that could be useful going forward.

Understanding symptoms and adherence

Participants spoke about their experiences of symptoms, including how they change over time, factors which can impact upon symptoms and their experience of specific symptoms.

External influences on symptoms

Participants spoke of external factors, which influence the symptoms they experience on a daily basis as part of their condition. Examples which will be discussed include: the side effects of medication, seasonal changes and being on holiday.

Although medicines are prescribed to help relieve symptoms, obviously there is always the risk of associated side-effects. The participant below explained that the medication she was prescribed with actually made her feel worse than the original symptom of a dry cough did.

> ‘the medication you are on causing side effects or whatever, because like I say I were fine then I were having that like dry cough so to me I were in a worse position symptoms wise (as a result of taking medication)’ Participant 6 Lines 26-28

A number of participants were tracking symptoms over the summer period and therefore some were on holiday during that time. One participant became aware that she was coughing less due to increased physical activity on holiday.

> ‘I noticed that when I was on holiday and I was walking around a bit more and everyday, I noticed that I wasn’t erm coughing up as much stuff’ Participant 8 Lines 82-84

When asked about changes to symptoms over the six week symptom tracking period, some participants referred to seasonal changes such as high pollen

count which can cause hay fever and therefore impact upon respiratory symptoms such as wheeze.

> ‘Some days it is just worse. Erm I think there are some days when I’ve been cutting the grass and that had sent me so wheezy and because of my hay fever erm it had been a bit ‘worse.’ Participant 4 Lines 124-127

Barriers to adherence

One of the participants discussed the fact that they were unable to see the benefits of adhering to nebuliser treatments which acted as a barrier to adherence.

> ‘Yeah my adherence has been crap. Basically what happened is I was actually doing really well with it when I first got out of hospital and then I caught a cold and it just went… I physically didn’t have the energy to get up and do it ermm then its not sort of picked up since’ Participant 4 Line 72-75

The same participant also cited that cleaning and charging the nebuliser was a barrier to adherence.

> ‘well I struggle to see the benefits of them and because of the treatments actually doing them. Its not so much the.. I mean they don’t take long they take like one to three minutes each neb and there’s only two nebs. It’s the cleaning of them and making sure the Inebs charged because its got chargers like its all that side of it that’s sort of like just remembering really hmm..’ Participant 4 Line 287-293

Another barrier cited by the participants was the time associated with taking treatments.

> ‘Erm if I have an infection then I might take antibiotics, depends on how tired it makes me because sometimes I just think treatment can be too time-consuming’ Participant 2 Line 77-79

Individual experiences

Participants recruited into the study had varying levels of adherence, FEV1 (lung function) and therefore symptoms. As a result of this participants spoke

about different experiences of symptoms generally and also symptom tracking. Which highlights the importance of looking at this data on an individual level.

One of the participants who had experienced minor symptoms felt the symptom tracking tool may not be useful for them going forward. However they did note that this could be more useful for others.

> ‘I don’t get like any symptoms so its not really useful for me personally but for other people it might be useful to see’ Participant 6 Lines 115-116

For participants with more severe symptoms some spoke the way in which symptoms present themselves. Specific symptoms or even clusters of symptoms can be linked to an oncoming exacerbation or respiratory infection.

Experiences of specific symptoms

Pain was a symptom which several participants explicitly referred to in their interview. On occasion there was confusion about the recording of this symptom and if/how the pain was CF related or not, for some participants understanding if the pain was CF related was easier than it was for others.

> ‘Erm I’m not sure I mean I know when I started my CF treatment, I got diagnosed at 25 and I use to get headaches but then the headaches went down so I think some of it is infection related which will be due to CF and some of them.. I don’t really know.’ Participant 1 Lines 179-183

One of the participants suggested it should be split into two separate questions.

> ‘Maybe have two questions for that so lung pain and other pain’ Participant 4 Line 46-47

However for others severe pain was something they experienced often and the cause of this was unknown.

> ‘I mean the pain is generally most days I am in some sort of pain. Yeah at the minute actually these last few days I would say my pain is actually up there somewhere (points above the chart). Yesterday was and I don’t know why.’ Participant 4 Lines 214-217

Participants were asked about their experience of tiredness and in particularly if they felt this was related to the number of steps recorded by the Fitibit.

For one participant they felt the link was clear, they felt more tired on the days that they were more active.

> ‘I think maybe it your more activity, your probably more tired. I know I am tireder when I’ve done more activity, erm yeah’ Participant 4 Lines 360-361

Contrastingly, the participant below felt that during a period of high levels of tiredness step-count was low.

> ‘I mean when I was really tired when my tiredness was high I was doing less steps but it could also be that the medicine was working or it could be that I was getting use to the hospital bed because I really don’t like the hospital beds either I have I don’t sleep well on them’ Participant 5 Lines 180-183

As previously discussed a number of external factors have been cited by participants which impact upon the severity of symptoms, this was found specifically for tiredness. One participant spoke of how the heat, especially when wearing her work uniform can impact upon energy levels.

> ‘yeah I think with the tiredness anyway the heat has obviously made a difference. Definitely it just takes it out of your doesn’t it and you know we have got to wear certain clothing and everything you know its just draining isnt it’ Participant 5 Line 252-255

Suggestions and recommendations for improving the design of the symptom tracking study

In order to develop and improve the design of the symptom tracking to be as feasible and acceptable as possible for participants, participants were asked about what kind of things they would like to be changed or improved going forward.

During both interviews participants were asked if there was anything else they would like to see included in the questionnaire in the future. A total of 2 participants suggested that heart rate monitoring could be helpful and felt this

could help predict exacerbation. This would be something they would be interested in recording for a period of time.

> ‘Erm it’s a really short study, which was the only thing that came to me, I mean I don’t know what your funding is like but I think having heart rate data would be really interesting. Hmm and maybe sleep data because I know some patients are on like oxygen. I mean I would just find it interesting to see the differences between them and the people that aren’t on oxygen’. Participant 1 Lines 201-206

> ‘For your larger study like I think it would be good to add a heart rate monitor’ Participant 1 Lines 113-115

> ‘I think a heart rate thing might give a feedback as well because surely I'm no doctor or anything but I would of thought it your tired your feeling weak I would have thought..’ Participant 6 Line 256-258

5.5 Pilot Study Discussion

Although it is useful to investigate the temporal relationship between variables it is important that the monitoring period is acceptable and feasible to the participants. The findings from this study suggest that participants are comfortable with the use of technology and prefer to track symptoms on their electronic device rather than through the use of pen and paper. Issues with technology is a barrier cited within the work of Sarafaraz et al. (2010), which could suggest why participants have engaged well with the current study.

Within the interviews some of the participants reported that symptom tracking was a daily reminder of the condition they are living with, which is something to be mindful of when using symptom tracking. McDonald et al. (2017a) found one person out of ten in a study which tested the acceptability and feasibility of self-monitoring symptoms in Glaucoma using a web-based diary, reported that taking part led to negative feelings due to constantly focusing on symptoms.

All six of the participants recruited into this part of the study reported that participation in the study was easy and five reported it was quick. All of the participants chose to continue symptom tracking after three weeks for a further three weeks which could suggest participants were comfortable completing the

symptom questionnaire on a daily basis. Furthermore within the six week symptom tracking study response rates were between 62%-100%.

Originally one of the aims of the PhD was to develop an intervention which involved utilising the *feedback and monitoring* behaviour change techniques/strategies (BCTs) (Michie et al., 2013) by presenting the adherence and symptoms to participants in an attempt to increase adherence. However based on the findings from the quantitative aspect of the pilot study and the lack of clear relationships between adherence and symptoms a decision was made to extend the observation period. Therefore the amount of time adherence and symptoms were monitored for was extended rather than developing a feedback intervention because of the lack of evidence that this type of intervention would be effective for participants.

However, it is important to acknowledge that the lack of significant findings identified in this study could be due to the fact that the relationship between symptoms and adherence in patients with CF is limited or indeed non-existent. Therefore, there is the potential that a longer symptom tracking period will not find any significant relationships between symptoms and adherence

The pilot study assessed the preliminary feasibility and acceptability of the study design, which according to Sekhon et al. (2017) is useful in terms of assessing the acceptability of any future potential use of these types of activities. The findings from this study suggested that a longer period of time was required to observe the relationship between the two variables. The qualitative findings from the current study did reveal, however, that participants were happy to track symptoms over a longer period of time and the tracking method was acceptable and feasible.

The iterations are outlined within the next sub-section of this chapter, however to summarise the main changes were: an increased symptom tracking period, the opportunity to nominated a symptom to monitor and the removal of the Fitbits.

Physical activity was monitored within the pilot study and discussed with participants in qualitative interviews, however due to infection control one of the sites involved in phase 2 did not allow participants to be provided with Fitbits

therefore to ensure participants were all experiencing the same study design, Fitibits were removed from the main N-of-1 study.

Based upon this there were a series of iterations which were informed by the findings of the pilot study when planning the main study which will be reviewed in the next part of this chapter.

5.6 Main N-of-1 study

5.6.1 Summary of changes from pilot study to main study

The main study consisted of a four-month long symptom tracking period, with no break planned within the design (unlike phase 1 which had a break after three weeks). Based on the positive feedback received relating to symptom tracking in the pilot study the decision was made to extend the study, in the hope that this may detect more changes in symptoms and adherence.

Based on different experiences of different symptoms participants in main study were invited to ‘nominate’ a symptom. Also to encourage higher rates of recruitment two additional sites were included (a total of three sites). Iterations were made or at least considered based on the qualitative findings from phase 1. See table 15 for a summary of feedback from participants.

Table 15.
Feedback on study design from phase 1 participants

Comment	Was this adapted?	Explanation of the iteration or why the iteration was not undertaken
The addition of heart rate monitors was suggested by participants.	No	The decision was made not to include this adaption in study seven due to limited time and funding associated with the study.
The extension of the symptom monitoring period was viewed as feasible and acceptable within patients with CF	Yes	The symptom monitoring period was extended from six weeks to four months
Participants experienced different symptoms- some of which were not monitored.	Yes	The option of the nominated symptom was added to provide participants with an additional opportunity to individualise the study to suit them.
Timings of email containing the Qualtrics link	Yes	Participants were still able to request a time which suited them best, however it was suggested that the time was after 12 noon to give the participant the ability to assess their daily symptoms as accurately as possible

5.6.2 Design

An observational N-of-1 design was adopted in this phase of the study, which meant data collected from each participant was analysed separately.

As the relationship between adherence and nebuliser treatment is potentially bi-directional, the outcome variable changed depending on which variable predicted which using a data driven approach, this was identified through the use of exploratory cross-correlation charts. Participants' adherence to nebuliser treatments was measured objectively via an eTrack® (Pari GmbH, Stanberg, Germany) and the nebuliser recorded the date and time of treatments taken. The symptom variables were the six (seven if participants chose to nominate a

symptom) symptoms of cystic fibrosis which were self-reported via a web-based questionnaire (Qualtrics © https://www.qualtrics.com) on a daily basis. The symptoms were: cough, wheeze, difficulty breathing, pain, tiredness and mucus.

5.6.3 Inclusion/Exclusion Criteria

The inclusion and exclusion criteria did not differ from the pilot study with the exception that participants who had taken part in the pilot study were not permitted to take part.

5.6.4 Participants

In total 19 participants were recruited from 3 different CF centres in the UK, the participants recruited into the pilot study were not involved in the main study. Please see Appendix F for the relevant participant facing documents.

Participants were recruited from three adult Cystic Fibrosis centres in the UK. Participants who had given consent previously to be contacted about further research (when consenting to the CFHealthHub) and those who were in the inclusion criteria were contacted regarding the study. Unfortunately due to the complexity of the study across the three different sites, no data is available relating to how many participants were invited to the study and how many declined.

Recruitment was slightly different at different sites depending on the requirements of the site. As this was prior to the outbreak of COVID-19 where possible visits were made to patients who fit the criteria and who were interested in the study, to discuss the study and to take consent (participants at site 1 and some participants at site 2). However staff who were trained in research ethics and taking consent were able to help should a participant wish to sign up to the study on a day the researcher could not make it into the hospital.

However, the researcher was not able to attend site 3 due to the distance, therefore members of the clinical team and interventionists who had received training in research ethics were able to take consent.

Where possible participants were recruited purposively to ensure a range of participants in terms of rates of adherence and lung function. Participants were categorised into the following groups: good adherence (>80%), moderate adherence (50-79.9%), low adherence (<50%), good lung function (>70%) and not so good lung function (>70%) which was measured by $FEV^{1.}$ The clinical teams and site interventionists were responsible for this recruitment and FEV^{1} was not recorded for the study. Mean adherence for participants during the study period ranged from 45%-96%.

The recruitment sites all used a digital platform called CFHealthHub (CFHH) through which prescribed treatments were recorded and participants objective adherence data was collected and displayed from (see section 1.13 for more information on the CFHH).

The number of observations relates to how many data points were collected for each participant. With 50 observations being viewed generally as being 'sufficiently powered' (Tabachnick & Fidell., 2007). The number of observations recorded for each participant in this study ranged from 275-832 and a total of 11,572.

See table 16 below for further information relating to participants gender, average adherence and number prescribed nebuliser doses per day, nominated symptom if applicable and finally number of captured observations.

Table 16.
Summary of demographics for participants recruited into the main study

*Participant Number	Sex	Mean (standard deviation) of adherence over the study period	Inter-quartile range of adherence over the study period	Total doses of prescribed nebuliser treatment per day	Nominated symptom	Number of observations
7	F	*37.42% (36.48%)*	50%	*4 or 5	Breathlessness	443
8	F	*29.33% (27.13%)*	50%	4	Fatigue	725
9	M	*74.90% (9.84%)*	0%	4	None	677
10	M	*49.59% (4.51%)*	0%	2	Throat pain	621
11	M	41.99% (60.95%)	100%	*1 or 3	None	630
12	F	14.75% (35.61%)	0%	1	Motivation	743
13	M	*96.14% (11.10%)*	0%	*1 or 4	None	832

14	M	*47.33% (30.39%)*	20%	*3 or 5	Headache	678
15	M	*95.16% (25.04%)*	0%	1	None	385
16	M	*90% (30.13%)*	0%	1	Motivation	586
17	F	*69.35% (42.15%)*	50%	*2 or 1	None	694
18	F	*96.77% (13.40%)*	0%	4	None	720
19	F	*94.64% (51.80%)*	*83%*	*3,5,6 or 8*	Fatigue	826
20	M	*95.86% (50.27%)*	*83%*	*1*	None	367
21	F	*94.78% (19.40%)*	*0%*	*3*	Fatigue	719
22	M	*70.16% (51.20%)*	*67%*	*3*	None	676
23	F	*43.47% (28.94%)*	*57%*	*3*	None	275
24	F	*43.27% (28.98%)*	*57%*	*4 or 3*	None	476
25	F	*24.66% (31.49%)*	*67%*	*3*	None	499

5.6.5 Daily Symptom Diary

The symptom diary used in main study was the same as the one used in pilot study with the addition of the nominated symptom question. Qualtrics ©

(https://www.qualtrics.com) was used once again to record and store the survey responses. Participants were all provided with a unique number and asked to input this each day so their responses were associated with them.

5.6.6 Physical Activity Monitoring

Participants were not given the opportunity to monitor step count in this part of the study. Due to infection control, permissions to distribute Fitbits to patients from all the Trusts involved in the study was not received. However, participants were encouraged to write qualitative comments in the additional comments box which could include things like exercising, doing something they would not usually do or being busy which could be used as memory cues and/or discussion points in the interviews.

Duplicates

Participants were not asked to submit the date of their entry, instead the Qualtrics © **(**https://www.qualtrics.com) time-stamp was used to understand the time and dates of data. However, a number of participants submitted more than one entry on the same day. There were three possible ways in which this data was managed, which are detailed below:

i. If data was submitted within the early hours it was changed to the entry for the day before (assuming that there was not an existing entry, if there was see point iii).
ii. If the participant entered a comment which suggested the data provided should be used on a specific day it was used for the specified day.
iii. If the submissions were both during the day time a mean of the data points was calculated and used in the analysis.

5.6.7 Analysis

Between the pilot study and the main study a new paper was published by McDonald et al. (2020) entitled ‘Analysing N-of-1 observational data in health psychology and behavioural medicine: a 10-step SPSS tutorial for beginners’ which highlighted clear stages of analysis. This method allowed correlations

with variables (e.g. adherence predicting adherence in 2 days) to the observed as well as the relationship between variables.

For an example of how each participant's data set was analysed using this method please see Appendix G.

Note: Steps 1 and 2 are conducted for each participant's data set as a whole (includes all symptoms).

Step 1. Formatting the data set

Each of the participant's data was collated into an individual data set, this included symptom data, adherence data and date and time. Each variable was represented by a separate column in the data set as suggested in the work of McDonald et al. (2020). Any missing dates were added at this point and these gaps were addressed (see step 2).

Step 2. Addressing missing data

A missing value analysis was conducted on all symptom questions for all participants. The amount of missing data for each variable was calculated and following this Little's Missing Completely at Random (Little, 1988) was conducted to check the patterns of missing data. For any missing data a missing value analysis was undertaken and missing data was completed using the Estimated Means option. If the data for a specific variable was missing by 40% or more the variable was excluded from the analysis.

Note: The remainder of the steps were conducted to investigate the relationship between each symptom (as recorded individually by each participant) and adherence to nebulised treatment. With the exception of any symptoms which had missing data of 40% or more, or had been rated as a constant zero.

Step 3. Plotting the data

Sequence charts were produced for all of the symptom variables individually and also adherence to allow for the visual inspection of the data across the study period. The sequence charts are not used for any form of the inferential analysis. The charts provided insight into variability over time (McDonald et al.,

2020) and a visual way to explore relationships between variables (i.e. symptoms and adherence).

Step 4. Pre-analysis exploration of temporal relationships between adherence and symptom variable

It is important to note here that this step of the analysis is not one outlined in the work of McDonald et al (2020) and was added with the aim of clearly identifying which variable is the predictor and which is the outcome (i.e. symptom or adherence to nebulised treatment). As within this study the development of the hypothesis is data-driven and informed by the cross-correlation charts. The predictor variable and outcome variable will be identified when investigating the relationship on the cross-correlation charts between adherence and each symptom recorded by each participant.

The symptom variable and objective nebuliser adherence are inserted into the cross-correlation, which provides information about the relationship between the variables. The outcome variable will be determined based on the results of the cross-correlation chart, how this decision is made is explained below.

All cross -correlation charts which indicate a possible relationship between variables (i.e any of the symptoms with adherence for relevant participants) can be seen in Appendix H and will be referred to in the analysis below.

If the cross-correlation chart shows no evidence of a relationship (i.e. no data on the chart clearly passes the confidence interval) no further analysis is undertaken.

Step 4a. Assess the stationarity within the outcome variable

This step is followed as suggested in the work of McDonald et al. (2020) and aims to check the variance of the data over the specific time period within the outcome variable (which has been previously identified within step 3 of this analysis).

Within the current study two new variables were created for each participant/data set. One variable was split into two halves and the other was split into three thirds, the partitions were split as equally as they could be.

For example if there was 120 days of data the partition in two would be split equally, the first 60 days would be coded ‘1’ and the second would be coded ‘2’. For the second variable which splits the data in three the first 40 days would be coded ‘1’, the second 40 days coded ‘2’ and the third coded ‘3’.

Following on from this the file was split which enabled descriptive statistics to be calculated for each section. It was anticipated that there would be a difference between the means of the different sections.

This step is observational is not relevant to the final regression, it is simply to identify the variance of data.

Step 4b. Assessing time trends within the outcome variable

In order to assess whether there are any trends or patterns within the outcome variable (as previously identified in step 3 of this analysis) over the time period (for example an increase or decrease in the behaviour) a regression was calculated to look at the curve estimation. Both linear and non-linear (quadratic, cubic, logarithmic, logistic and exponential) time trends are assessed.

The variable used here was ‘day number’ or ‘study day’ this simply relates to the day of the study starting from one and finishing at the number which was the final day of participation for each participant.

If a significant linear or non-linear relationship is identified the ‘day number’ variable will be included within the final regression. If there is no evidence of a significant relationship it is concluded that there is no evidence of a trend overtime and no further analysis relating to this is undertaken. Further information relating to how this was included in the relevant regressions is discussed within the results section of this chapter.

Step 4c. Assessing periodic patterns within the outcome variable

It is possible that there may have been periodicity within the outcome variable , i.e. cycles in the data which repeat overtime, this could be a weekly, daily or monthly cycle. Within the current study this could be something like not taking medication at the weekend.

Within the current study the differences between weekdays and the weekend were investigated. To do this one new variable was set up (e.g. Periodicity) and

the data was coded accordingly (e.g. 1 for weekdays and 2 for days at the weekend). A regression was calculated and the periodicity variable was added as an independent variable and the outcome variable (either symptom or adherence) was used as the dependent variable.

According to McDonald et al. (2020) if the 95% confidence interval from this regression output includes 0 there is no evidence of periodicity and therefore the variable (e.g. weekday) was not included in the final model or further investigated. Further information relating to how this was included in the relevant regressions is discussed within the results section of this chapter.

Step 5. Check for autocorrelation in the outcome variable

Autocorrelation charts were first created for the outcome variable. Charts were created by selecting analyse, forecasting and autocorrelations in the programme.

The days which pass the confidence intervals on the partial autocorrelation plot provides a good indication of autocorrelation (the association between data points i.e. data on different days). For example if there is evidence of autocorrelation between T0-T-24 hours (lag 1) the data will be lagged by 1 day in an attempt to investigate further this lagged variable will then be included within the final regression model. If the chart shows evidence of autocorrelation on more than one day which passes through the confidence interval the most is selected.

Within the current study either adherence or the symptom could be the outcome variable depending on which variable preceded which (see step 3). However, autocorrelation was also investigated within the predictor variable as an additional exploratory step. If there is evidence of autocorrelation within the predictor the results of the regression should be interpreted with caution.

If there is theoretical evidence to suggest that relationships will have particular lags then they can be lagged as appropriate (McDonald, 2020), however this was not the case in the current study (all lags created were data driven).

Step 6. Created lags with the outcome variable

Data was lagged using the create time series option in SPSS. According to McDonald et al. (2020, p43) ‘the lag number represents the interval between data points, e.g. lag1 refers to the immediately preceding data point, lag2 to two data points before, and so on.’

Step 7a. Confirm autocorrelation has been adequately specified

To ensure there is no remaining autocorrelation and the variables have been lagged sufficiently lagged variables must be added to a linear regression with the original variable so an unstandardized residual variable can be created.

Once the unstandardized residual has been created the autocorrelation plots for this variable are created and visually inspected to ensure none of the autocorrelations for the days pass through the confidence interval. If none of the days pass through the confidence interval this would suggest that autocorrelation had been sufficiently addressed. However if they still pass through, this could suggest there is autocorrelation within the variable and the results should be interpreted with caution.

Step 9. Conduct a dynamic regression

A final regression was conducted to investigate whether the relationship between the predictor and outcome variable was significant whilst controlling for autocorrelation. Due to the nature of the analysis and the previous steps, different variables were used within each regression. See appendix I for detail relating which variables were included in the regressions based on the work of McDonald et al. (2020).

5.7 Main study findings

5.7.1 Descriptive statistics

Across all participants tiredness was the symptom with the highest mean (M=4.62) and a range of 2.82-8.72. Followed by cough (M=3.01, range= .26-7.65). Difficulty breathing, pain and mucus had the same or very similar mean scores (difficulty breathing M= 2.82; pain M= 2.82 and mucus M= 2.80) with ranges of 0.00-7.63, 0.04-7.67 and .22-7.49. The mean for nominated symptom was a little lower at M=2.50 and the range was .33-8.15. Wheeze was

collectively the lowest rated symptom (M=2.35) with a range of 0.00-5.46. This demonstrates that across the symptoms and participants other than for tiredness and cough, on the mean scores are less than 3.Descriptive statistics (means and standard deviations) for each symptom variable and adherence for all participants are presented in table 17 below

Table 17.
Means and standard deviation for all symptoms and participants

Symptom	P8	P9	P10	P11	P12	P13	P14	P15	P16	P17	P18	P19	P20	P21	P22	P23	P24	P25
Cough	2.72 (1.10)	2.88 (1.11)	3.72 (1.08)	4.07 (1.11)	3.28 (1.90)	6.76 (.98)	2.03 (.81)	1.459 (.66)	1.25 (.51)	4.00 (1.22)	5.15 (1.40)	7.65 (1.18)	1.92(1.00)	1.48 (.91)	.26(.61)	1.94(1.10)	4.47 (1.41)	3.03 (1.36)
Wheeze	2.19 (1.31)	4.27 (1.20)	1.77 (1.14)	3.16 (1.24)	2.51(1.60)	5.21 (1.27)	1.54 (.69)	.66 (.58)	.47 (.51)	1.90 (.84)	5.46 (1.26)	2.66 (1.65)	2.26 (.85)	.93 (.26)	.00 (.00)	1.80 (1.31)	3.68 (1.48)	1.93 (1.12)
Difficulty Breathing	2.07 (1.18)	4.31 (1.07)	3.82 (1.34)	4.16 (1.17)	2.14 (1.21)	5.95 (1.13)	3.45 (1.28)	1.37 (.49)	*	1.66 (.91)	4.34 (1.47)	7.63 (.99)	2.62 (1.08)	.00 (.00)	.00 (.00)	1.09 (1.29)	3.19 (1.28)	2.88 (1.80)
Pain	1.51 (1.37)	3.67 (1.16)	1.85 (1.50)	3.64 (1.32)	5.66 (2.38)	4.66 (1.34)	3.00 (1.41)	1.50 (1.74)	*	1.16(.985)	4.31 (1.16)	3.41 (2.52)	7.67(1.01)	1.28 (.54)	.04 (.33)	1.71 (1.05)	2.18 (1.35)	3.53 (2.04)
Tiredness	3.54 (1.48)	2.82 (1.17)	4.98 (1.44)	4.87 (1.21)	5.67 (2.29)	7.97 (1.05)	3.34(1.49)	2.25 (1.15)	4.06 (2.30)	4.03 (1.22)	4.68 (1.31)	8.72 (.96)	7.73 (1.71)	3.41 (.62)	3.16 (1.76)	4.20 (2.11)	4.02 (1.25)	3.77 (1.56)
Mucus	3.06 (1.30)	5.16 (.58)	3.33 (1.00)	2.53 (1.51)	2.32 (1.50)	7.49 (1.13)	1.53 (.63)	1.15 (.59)	1.24 (.51)	2.02 (.65)	4.00 (1.25)	6.27 (1.55)	.75 (.96)	1.28 (.70)	.22 (.62)	1.78 (.97)	3.17 (1.03)	3.00 (1.59)
Nominated Symptom	2.76 (.68)	3.33 (5.77)	3.00 (3.28)	*	3.23 (1.62)	*	3.67 (1.68)	*	7.66 (1.38)	4.269 (1.09)	4.06 (1.03)	8.15 (.90)	.33 (.58)	3.39 (.55)	.11(.55)	*	1.00 (2.00)	*
Adherence (%)	29.33 (27.13)	98.78 (9.84)	49.59 (4.51)	41.99 (60.947)	14.75 (35.61)	96.14 (11.10)	47.33 (30.39)	95.16 (25.04)	90 (30.13)	69.35 (42.15)	96.77 (13.41)	94.64 (51.80)	95.8 (50.27)	94.3 (19.40)	70.16(51.20)	43.47 (28.94)	43.27 (28.98)	24.49 (31.49)

Note-All symptoms were rated on a scale of 0-10 (0 being not at all and 10 being a great deal. Note-Descriptive statistics calculated before any missing data is inputted

*- One or less data points recorded.

5.7.2 Missing data

Within the table 18 participants have been grouped into categories dependent on how much missing data they had, 8/19 participants were placed into the green category meaning they missed between 1-14 days of data collection. As depicted in table 19 a total of 3 participants were excluded from the analysis, participant 7 missed a total of 30 days. Participant 23, missed a total of 39 days of data collection and participant 24 missed a total of 59 days of data collection. Participants 7, 23 and 24 therefore had >40% missing data. Therefore this data was excluded from the analysis.

It is important to highlight that some participants would miss symptoms that perhaps were not relevant to their condition. If missing data was over 40% for a particular symptom this symptom was excluded from the analysis (as shown in red on table 18).

Further information on the total number of days of missing data for each participant can be seen in table 18 below and missing data for each symptom can be seen in table 19 below.

There was no missing nebuliser adherence data. However, for participant 13 there was a technical fault with the synchronisation of the data for this participant. Therefore, adherence data was only available for two months. This period of data which was analysed with reported symptoms for the same time period.

Table 18.

Daily completion rate of the symptom survey for participants in the main study

Symptom	P7	P8	P9	P10	P11	P12	P13	P14	P15	P16	P17	P18	P19	P20	P21	P22	P23	P24	P25
Daily completion rate	30 days	34 days	5 days	30 days	30 days	32 days	5 days	15 days	12 days	6 days	11 days	3 days	1 day	44 days	4 days	27 days	39 days	59 days	22 days

	1-14 days of missing data (1.2%-4.8%)
	15-28 days of missing data (18%-33%)
	29-42 days of missing data (34.8%-50.4%)
	43 or more days of missing data (51.6% or over)

Table 19

Percentage of missing data for each participant's symptoms (%)

Symptom	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
Cough		28.01	9.78	24.39	26.83	27.05	4.88	19.35		5	8.87	3.23	1.68		9.60	29.01			33.7
Wheeze		29.75	9.78		26.83	27.87	4.88	27.42			35.48	4.30	0.84			31.30			
Difficulty breathing		28.01	5.43	24.3	26.02	26.23	4.88	12.01				3.23	0.84			31.03			
Pain		28.01			30.08	26.23	4.88					3.23	0.84	38.94	7.20	31.03			
Tiredness		29.75	7.61	24.3	26.03	29.51	4.88	12.1	17.7	10	9.68	3.23	0.84	38.94	5.60	27.48			30.43
Mucus		28.93	11.96	24.3		27.05	4.88	20.1		5	23.39	3.23	0.84		8.87	29.01			
Nominated		28.01				27.05	N/A			5	8.87	5.38	1.68		4.84	29.01			

	>40% of missing data

5.7.3 Observations relating to stationarity of the outcome data

The stationarity of the data was assessed for each outcome variable, which was analysed as outlined in step 4a of the method section, again this step is to observe changes in the data over the study period. All data was split into 2 and 3 partitions to assess differences between partitions, however this data was not used in the inferential analysis in accordance with McDonald et al.'s guidance (2020). Instead descriptive statistics from each were compared to investigate any differences over time.

5.7.4 Time trends and periodic patterns in the outcome variable

As discussed with section 4b and 4c of the steps of analysis, time trends and periodic patterns within the outcome were assessed prior to the final regression to look at the curve estimate on and also cyclic differences (e.g. weekday vs weekend).

5.7.5 Regressions and associated relationships

See table 20 for a summary of all the relationships between variables. The table splits the types of relationships into four: relationship A (adherence predictor and positive relationship), relationship B (adherence predictor and negative relationship), relationship C (symptom predictor and negative relationship) and relationship D (symptom predictor and positive relationship). Relationship C and D occurred most common (a total of 13 times) and relationship B least commonly (3 times), relationship A occurred 11 times.

For some participants all or the majority of the significant relationships were the same relationship type, for example participant 21 and relationship C and for participant 19 all but one symptom was in the relationship A category.

Full statistical evidence will be reported on the following pages. The four types of relationships will be discussed in detail in the discussion section of this chapter.

Table 20.

Explanation of all regressions and associated relationship

Symptom	P8	P9	P10	P11	P12	P13	P14	P15	P16	P17	P18	P19	P20	P21	P22	P25
Nominated Symptom	NA	NA	NA	NA	Adherence Predictor-Adherence (lag 7), nominated symptom (lag 10), day number	NA	NA	NA	NA	NA	NA	Adherence Predictors-Nominated symptom (lag 1), adherence (lag 3), day number.	NA	Nominated Symptom Predictor-Adherence (lag 1), nominated symptom (lag 1), day number.	NA	NA
Cough	Adherence Predictors-Cough (lag 1), adherence, day number	NA	NA	NA	Symptom Predictor-Adherence (lag 1), cough (lag 6), day number	NA	Symptom Predictor-Cough (lag 7), adherence (lag 1).	NA	NA	Adherence Predictor-Cough (lag 1), adherence (lag 2), day number.	NA	Adherence Predictor-Cough (lag 1), Adherence (lag 6), day number.	NA	Cough predictor-adherence (1 day) and cough (3 day lag) predict adherence	Cough-Predictor-Adherence (lag 1), cough (lag 1).	NA
Wheeze	NA.	Wheeze Predictors-Wheeze (lag 4), adherence (lag 1), day number	NA	Wheeze Predictors-Wheeze (lag 5), day number, periodicity, adherence (lag 1).	Adherence Predictor-Adherence (lag 1), wheeze (lag 1), day number.	NA	Adherence Predictor-Wheeze (lag 16), adherence (lag 1), day number;	NA	NA	NA	NA	Adherence Predictor-Day number, adherence (lag 6), wheeze (lag 1).	NA	NA	NA	NA
Difficulty breathing	NA	Difficulty breathing Predictors-difficulty breathing (lag 4), adherence (lag 1), day number.	NA	Difficulty breathing Predictors-Difficulty breathing (lag 2), adherence (lag 1), day number, periodicity.	Difficulty breathing Predictor-Difficulty breathing (lag 2), adherence (lag 1) day number.	NA	Difficulty breathing Predictor-Adherence (lag 1), trouble breathing (lag 5), day number.	NA	NA	NA	Difficulty breathing Predictor-Difficulty breathing (lag 4), adherence (lag 9).	Adherence Predictor-Difficulty breathing (lag 2), adherence (lag 1), day number.	NA	NA	NA	NA
Pain	Adherence Predictors-Adherence (lag 7), pain (lag	NA	NA	NA	Pain Predictor-Pain, Adherence (lag 1),	Pain Predictors-Adherence (lag 8), pain.	NA	NA	NA	NA	Pain Predictor-Pain (lag 3),	Pain Predictor-Adherence (lag 2), pain (lag	Pain Predictors-Pain (lag 3), Adherence	Pain Predictor-Pain (lag 2), adherence.	NA	NA

	1), day number				day number.						adherence (lag 9).	2) day number.	(lag 1), day number.			
Tiredness	NA	NA	NA	Tiredness Predictors-tiredness (lag 5), adherence (lag 1), day number and periodicity.	NA	NA	NA	Tiredness Predictor-Tiredness (lag 1), adherence.	Adherence Predictor-Tiredness (lag 1), adherence (lag 3).	NA	NA	Adherence Predictor-Tiredness (lag 1), adherence (lag 7), day number.	Tiredness Predictors-Tiredness, adherence (lag 1), day number.	Tiredness Predictors-Adherence (lag 1), tiredness (lag 3), day number.	NA	Tiredness Predictor-Tiredness (lag 4), adherence (lag 1), day number.
Mucus	NA	NA	NA	NA	Mucus Predictor-Mucus (lag 6), adherence (lag 1), day number	Adherence. Predictors-Mucus, adherence (lag 3).	Mucus Predictor-Adherence (lag 1), mucus (lag 1), day number	NA	NA	NA	NA	Adherence Predictor-Mucus (lag 2), adherence (lag 4), day number	NA	Mucus Predictors-Mucus (lag 3), adherence (lag 1), day number.	NA	NA

Occurs 11 times	Relationship A: Adherence Predictor & Positive Relationship
Occurs 3 times	Relationship B: Adherence Predictor & Negative Relationship
Occurs 13 times	Relationship C: Symptom Predictor & Negative Relationship
Occurs 13 times	Relationship D: Symptom Predictor & Positive Relationship

5.7.6 Autocorrelation

As explained within step 5 of the method sub-section variables must be lagged sufficiently to ensure there is no evidence of autocorrelation within the outcome variables which will be analysed. Within this sub-section the step taken to address autocorrelation for each symptom for each participant will be summarised. The way in which autocorrelation was addressed was different for each participant and each variable. Please see Appendix I for further detail relating to autocorrelation.

5.7.7 The relationship between symptoms of Cystic Fibrosis and adherence to nebuliser treatments

Nominated Symptom

Participants were provided with the option of choosing an additional symptom to track during the four-month period. In total eight participants chose to select a symptom to nominate. Participants 8,9, 10,11,13,14,15,16,17,18,20,22,25 either chose not to nominate a symptom, did not record enough data or their cross-correlation chart was not indicative of a relationship and therefore no analysis was undertaken. Cross-correlation charts for participants 12, 19 and 21 were indicative of a potential relationship with adherence and therefore this was investigated further.

Participant 12

The cross-correlation chart for nominated symptom (motivation) and adherence for participant 12 suggested that there was a potential relationship in which higher adherence potentially predicted higher levels of motivation in 7 days. Therefore adherence was the predictor variable and motivation was the outcome variable. Within the final regression model motivation was the outcome and the predictor variables were: motivation lagged by 10, adherence lagged by 7 and day number. The model revealed that motivation predicted motivation in 10 days time significantly (B=.247 95% CI= .083-412.; R^2 =.140; P=.004). However, the regression revealed

that high adherence in 7 days time was not able to significantly predict high motivation (B=.007 95% CI=.00-.013 -.; R^2 =.140; P=.056.). Furthermore the relationship between day number and motivation was not statistically significant (B=-.003; 95% CI -.011-.004; R^2 =.140; P=.369).

Participant 19

The cross-correlation chart for nominated symptom (fatigue) and adherence for participant 19 suggested that there was a potential relationship in which higher adherence predicted higher fatigue in 3 days time. Therefore a linear regression was conducted to investigate this further in which the predictors were: adherence lagged by 3 (to investigate the relationship shown on the cross-correlation chart), fatigue lagged by 1 (to investigate the relationship shown on the autocorrelation chart) and day number. Fatigue significantly predicts fatigue in one day (B=. 694 95% CI= .562-.825 -.; R^2 =.559; P=.000). Adherence significantly predicts fatigue in 3 days time(B= 003 95% CI=.000-.005; R^2 =.559; P=.021).However the relationship between day number and fatigue was not significant (B=-. 95% CI=-.004-.003 -.; R^2 =.559; P=.626).

Participant 21

The cross-correlation chart for nominated symptom (fatigue) and medication adherence for participant 21 suggested there was potentially a negative relationship in which low levels of fatigue predicted high levels of adherence the next day. This was therefore tested using a linear regression in which adherence was the outcome variable and the predictors were: adherence lagged by 1 (as per the auto-correlation chart), fatigue lagged by 1 (as per the cross-correlation chart) and day number (as per step 4b of the analysis method). The regression revealed that adherence was a significant predictor of adherence the next day (B=.647 95% CI=.513-.782.; R^2 =.490; P=.000). Also low levels of fatigue was a significant predictor of high adherence the next day (B=-4.846 95% CI=-9.684- -.008; R^2 =.490; P=.050). However day number was not

a significant predictor of medication adherence for this participant (B=.039 95% CI= -.036-.114 R^2 =.490; P=309.).

Cough

For two participants (15 and 20) there was too much missing data and therefore the symptom 'cough' could be not be analysed. For participants; 9, 10, 11 13,16, 18, 25 there was no evidence of a relationship between cough and objective adherence on the cross-correlation charts, therefore no further analysis was undertaken. The cross-correlation charts of participants: 8,12,14, 17,19, 21, 22 revealed there was evidence of a potential relationship between cough and objective nebuliser adherence, this was further investigated.

Participant 8

The cross-correlation chart for participant 8 demonstrated there was potentially a positive same day relationship for cough and adherence for this participant. However for the regression one variable must be the outcome and therefore the next closest relationship on the cross-correlation chart suggested adherence predicted cough. Therefore, within the regression cough was the outcome variable and the predictors were: adherence, cough lagged by 1 (as per auto-correlation) and day number.

The regression revealed that the relationship between cough and adherence on the same day was not significant (B=.005; 95% CI= -.002-.011; R^2 =.112; P=.183) and the relationship between day number and cough was not significant either (B=-.003; 95% CI= -.009-.002; R^2 =.112; P=.225). However the relationship between cough on one day and cough the next was significant (B=.209; 95% CI= .035-.384; R^2 =.112; P=.019).

Participant 12

The cross-correlation chart for participant 12 demonstrated that there was potentially a positive relationship in which cough could potentially predict adherence in 6 days time. This was investigated using a linear regression in which the outcome variable was adherence and the predictors were: adherence lagged by 1 (as per auto-correlation chart), cough lagged by 6 (as per cross-correlation chart), day number (see step 4b of the method). The regression revealed that cough was a statistically significant predictor of adherence in 6 days time (B=9.515; 95% CI= 5.423-13.607; R^2 =.229; P=.000).However adherence at one day was not able to significantly predict adherence the next day (B=.125; 95% CI=-.047-.298; R^2 =.229; P=.153) and day number was not able to significantly predict medication adherence (B=-. 074; 95% CI=-.232-.085; R^2 =.229; P=.359).

Participant 14

The cross-correlation chart for participant 14 demonstrated that there was potentially a positive relationship in which higher cough could potentially predict higher adherence in 7 days time. This was investigated using a linear regression in which the outcome variable was adherence and the predictors were: adherence lagged by 1 (as per auto-correlation chart), cough lagged by 7 (as per cross-correlation chart) and day number (see step 4b of the method). The regression revealed adherence one day could predict adherence the next day (B=-.836; 95% CI=.745-.927; R^2 =.804.; P=.000). Also high cough was able to predict high adherence in 7 days (B=4.570; 95% CI=.791-8.349; R^2 =.804.; P=.018).However day number was not a significant predictor of adherence for this participant (B=-. 060; 95% CI=-.019-.139.; R^2 =.804.; P=.135).

Participant 17

The cross-correlation chart for participant 17 suggested that there was a potential relationship in which high adherence could predict high cough in 2 days time. This was investigated using a linear

regression in which the outcome variable was cough and the predictors were: adherence lagged by 2 (as per cross-correlation), cough lagged by 1 (as per auto-correlation) and finally day number (as per step 4 of the analysis). The regression revealed that for this participant cough one day was able to significantly predict cough the next (B=.285 95% CI=.109-.458; R^2 =.236; P=.002), furthermore day number was a significant predictor of cough for this participant (B=-.008 95% CI= -.014- -.003; R^2 =.236; P=.004). However adherence was not a significant predictor of cough in 2 days time for this participant (B=.004; 95% CI=-.001-.008; R^2 =.236; P=.119).

Participant 19

The cross-correlation chart for participant 19 demonstrated a potentially positive relationship between cough and adherence, more specifically a positive relationship in which high adherence predicts high cough in 6 days time. This relationship was tested using a linear regression in which the predictor variables were: adherence lagged by 6 (to investigate the relationship shown on the cross-correlation chart), cough lagged by 1 (to investigate the relationship shown on the auto-correlation chart) and day number (as step 4b of the analysis demonstrated a possible relationship between day number and cough). The regression revealed that cough was able to predict cough in 1 days time (B=.586; 95% CI=.440-.731; R^2=.487.; P=.000).Furthermore adherence was a significant predictor of cough in 6 days time (B=.005; 95% CI=.002-.008; R^2=.487; P=.002). However, the relationship between day number and cough was not significant (B=7.797 95% CI=-.005-.005; R^2=.487.; P=.998).

Participant 21

The cross-correlation chart for participant 21 demonstrated that there was potentially a negative relationship in which low cough predicted high adherence in 3 days time for this participant. Therefore this was investigated using a linear regression in which adherence was the outcome variable and the predictors were:

cough lagged by 3 day (as per cross-correlation chart), adherence lagged by 1 (as per auto-correlation) and day number. The regression revealed that adherence was able to predict adherence the next day for this participant (B=.425; 95% CI= .283-.566; R^2 =.603; P=.000). Also cough lagged by 3 days was able to predict adherence (B=-10.565; 95% CI=-13.956- -7.174; R^2 =.603; P=.000), meaning low cough predicted high adherence in 3 days for this participant. However day number was not a significant predictor of adherence for this participant (B=-.012; 95% CI= -.083- .059; R^2 =.603; P=.737).

Participant 22

The cross-correlation for participant 22 demonstrated that there was a potential negative relationship between cough and adherence for this participant, in which low cough potentially predicts high adherence the next day. This was investigated using a linear regression in which adherence was the outcome and the predictors were: adherence lagged by 1 day (as per auto-correlation), cough lagged by 1 day (as per cross-correlation) and day number (as per step 4 of the analysis). Adherence was able to significantly predict adherence the next day (B=.309; 95% CI=.138-.481; R^2 =.142; P=.001) However, day number was not a significant predictor of adherence for this participant (B=-.061; 95% CI= -.315-.192; $R^{2=}$ .142; P=.633) and cough was also not a significant predictor of adherence the next day too (B=-15.109; 95% CI= -31.751- 1.532; R^2 =.142; P=.075).

Wheeze

For participants; 8, 13,10, 15, 16, 17, 18, 20, 21, 22 and 25 data was either analysed and cross-correlation charts revealed no evidence of a relationship, missing data was over 40% or participants rated the symptom as a constant 0 and therefore no analysis could be undertaken. However, the cross-correlation charts of participants; 9, 11,12,14 and 19 revealed there was evidence of a

potential relationship between wheeze and objective nebuliser adherence which was further investigated.

Participant 9

The cross-correlation chart for participant 9 suggested that there was potentially a positive relationship in which high wheeze predicted high adherence in four days time. This was therefore further investigated using a linear regression in which adherence was the outcome and the predictors were: adherence lagged by 1 (as per auto-correlation), wheeze lagged by 4 (as per the cross-correlation) and day number (due to evidence of time-trends). The regression revealed that the relationship between adherence at one day and adherence the next day was significant (B=.228; 95% CI= .020-.437; R^2 =.112; P=.032). However day number was not a significant predictor of adherence (B=.019; 95% CI= -.070-.109; R^2 =.112; P=.670), nor was wheeze lagged by 4 days (B=1.881; 95% CI=-.093-3.855; R^2 =.112 P=.062).

Participant 11

The cross-correlation chart for participant 11 suggested that there was a potential negative relationship between wheeze and adherence, in which low wheeze predicted high adherence in 5 days time. This was investigated in a linear regression in which the outcome variable was adherence and the predictors were: wheeze lagged by 5 (as per cross-correlation), adherence lagged by 1 (as per auto-correlation), day number and periodicity due to evidence of a potential relationship at step 4 of the analysis. The linear regression revealed that wheeze lagged by 5 days was a significant predictor of adherence (B=.342; 95% CI=-19.431- -.649; R^2 =.258; P=.036), adherence one day also significantly predicted adherence the next day (B=-10.040; 95% CI=.176-.507; R^2 =.258; P=.000) and

finally periodicity (the difference between weekdays and days at the weekend) was a significant predictor of adherence (B=-30.546; 95% CI=-52533- -8.559; R^2 =.258; P=.007). Study day was the only variable which was not a significant predictor of adherence for this participant (B=-.192 95% CI= -.488-.103; R^2 =.258; P=.200).

Participant 12

The cross-correlation chart for participant 12 suggested that there was potentially a positive relationship in which high adherence predicted high wheeze on the next day. This was therefore further investigated using a linear regression in which wheeze was the outcome variable and the predictor variables were: wheeze lagged by 1 (as per auto-correlation chart,) adherence lagged by 1 (as per cross-correlation chart) and day number (due to evidence of time-trends see 4b of the method). The regression revealed that adherence was able to predict wheeze the next day for this participant (B=.009; 95% CI=.003-.014; R^2 =.465; P=.002). Furthermore, wheeze one day was also a significant predictor of wheeze the next day (B=.565; 95% CI=.422-.707; R^2 =.465; P=.000). However day number was not a significant predictor of wheeze for this participant (B=.002 95% CI=-.004-.007; R^2 =.465; P=523.).

Participant 14

The cross-correlation chart for participant 14 suggested that there was potentially a negative relationship in which high adherence predicted low wheeze in 4 days time. This was investigated using a linear regression in which the predictor variables were adherence lagged by 4 (as per cross-correlation), wheeze lagged by 16 (as per auto-correlation) and day number (as per step 4b of the method). The regression revealed that high adherence was a significant predictor of low wheeze in four days time (B=-.005; 95% CI=-.009--.001; R^2 =.059.; P=.019). However, wheeze was not a significant

predictor of wheeze in 16 days time (B=.059 95% CI=-.130-.249; R^2 =.059.; P=.536) and day number was not a significant predictor of wheeze also (B=.002; 95% CI=-.002-.006; R^2 =.059.; P=.404).

Participant 19

The cross-correlation chart for participant 19 suggested that there was potentially a positive relationship in which high adherence could predict high wheeze in 6 days time. This was investigated using a linear regression in which the predictors were: adherence lagged by 6 (as per the cross-correlation), wheeze lagged by 1 (as per the auto-correlation) and day number (as per step 4b of the method). The results of the regression shown that wheeze 1 day is able to significantly predict wheeze the next day (B=.806; 95% CI=.700-.912; R^2 =.759.; P=.00). Furthermore, high adherence is able to statistically significantly predict high wheeze in 6 days time(B=.003. 95% CI=.000-.006; R^2 =.759.; P=.042). However day number was not able to significantly predict wheeze for this participant (B=-.005 95% CI=-.011-.000-.; R^2 =.759.; P=.055).

Difficulty Breathing

For the following participants 15,16,17, 20, 21 and 25 there was over 40% of missing data therefore no further analysis was computed. Participant 22 reported difficulty breathing as being 0 for the duration of the study therefore no further analysis was undertaken. Following the inspection of cross-correlation charts there was no evidence of a relationship between difficulty breathing and objective nebuliser adherence for participants; 8, 10 and 13. For participants 9, 11,12, 14, 18 and 19 cross-correlation charts indicated there was a potential relationship between difficulty breathing and objective adherence.

Participant 9

The cross-correlation chart for participant 9 indicated that there was potentially a positive relationship in which high difficulty breathing predicted high adherence in four days time. This was investigated using a regression in which adherence was the outcome and the predictors were difficulty breathing lagged by 4 (as per cross-correlation chart), adherence lagged by 1 (as per auto-correlation chart) and day number (as per section 4b of the method). The regression revealed that the relationship between trouble breathing and adherence in four days time was significant (B=2.900; 95% CI=.834-4.966; R^2 =.152; P=.007). However the relationship between day number and adherence was not significant (B.021; 95% CI=-.063-.104; R^2 =.152; P=.622), the relationship between adherence one day and adherence the next day (B=.198; 95% CI= -.008-.404; R^2 =.152; P=.060) was also not significant.

Participant 11

The cross-correlation chart for participant 11 suggested that there was a potential relationship between difficulty breathing and adherence, in which high trouble breathing could potentially predict high adherence in 2 days time. This was investigated using a linear regression the outcome variable was adherence and the predictors were: difficulty breathing lagged by two days (as per cross-correlation chart), adherence lagged by one day (as per auto-correlation chart), day number and periodic patterns (as per step 4 of the analysis). The regression revealed trouble breathing was a significant predictor of adherence in 2 days time (B=13.433; 95% CI=3.679-23.188; R^2 =.266; P=.007), further more adherence one day was a significant predictor of adherence the next day (B=.380; 95% CI -.220-.540; R^2 =.266; P=.000), periodic patterns is also a significant predictor of adherence for this participant (B=-.29.706; 95% CI=-50.914- -8.497; R^2 =.266; P=.006). However, study day was not a significant predictor of adherence for this participant (B=-.177; 95% CI -.458-.103; R^2 =.266; P=.213).

Participant 12

The cross-correlation chart for participant 12 indicated that there could be a potential relationship in which high difficulty breathing could predict high adherence in 2 days time. This was further investigated using a regression in which adherence was the outcome and the predictors were: adherence lagged by 1 (as per auto-correlation chart), troubled breathing lagged by 2 (as per cross-correlation chart) and day number (as they was evidence of time trends at step 4b of the analysis).

The regression revealed that adherence at 1 day was a significant predictor of adherence the next day (B=-.229; 95% CI=.059-.399; R^2 =.194.; P=.009) and also that trouble breathing was able to predict adherence in 2 days time (B=9.833; 95% CI=4.064-15.602; R^2 =.194; P=.001).However, day number was not a significant predictor of adherence for this participant (B=-.096; 95% CI=-.261-.068; R^2 =.194; P=.249).

Participant 14

The cross-correlation chart for participant 14 indicated that there could be a potential relationship in which high difficulty breathing could predict high adherence in 5 days time. This possible relationship was investigated using a linear regression in which trouble breathing lagged by 5 days (as a per cross-correlation), adherence lagged by 1 day (as per auto-correlation) and day number were the predictors variables and adherence was the outcome variable. The regression revealed that the relationship between adherence in the current day and adherence in one days time was significant (B=.835; 95% CI=.746-.924; R^2 =.810; P=.000), as was the relationship between high difficulty breathing and high adherence in 5 days time (B=3.068; 95% CI=.804-5.331; R^2 =.810; P=.008) However day number was not a significant predictor of adherence for this participant (B=.058; 95% CI=-.015-.132; R^2 =.810; P=.117).

Participant 18

The cross-correlation chart for participant 18 suggested that there was a possible negative relationship between difficulty breathing and adherence for this participant, in that low difficulty breathing could predict high adherence in four days time. This was investigated using a linear regression in which adherence was the outcome and the predictors were: difficulty breathing lagged by 4 (as per auto-correlation) and adherence lagged by 9 (as per auto-correlation).The regression demonstrates that low difficulty breathing was a significant predictor of high adherence in four days time (B=.236 95% CI=.023-.446; R^2 =.114; P=.031) and adherence was a significant predictor of adherence in 9 days time (B=-2.178 95% CI=-4.151--.204 R^2 =.114; P=.030).

Participant 19

The cross-correlation chart for participant 19 suggested that there was a potentially a relationship in which high adherence one day predicted high difficulty breathing the next. Therefore a regression was conducted to investigate this in which adherence lagged by 1 (as shown on the cross-correlation chart), difficulty breathing lagged by 1 (as shown on the autocorrelation chart) and day number (as per step 4b) was the predictor variables and difficulty breathing was the outcome. There was a significant relationship between difficulty breathing and difficulty breathing in 2 days time (B=.467 95% CI=.321-.621; R^2 =.381; P=.000). Adherence lagged by 1 was able to significantly predict difficulty breathing (B=.005 95% CI=.002-.007; R^2 =.381; P=.001). Day number was not able to significantly predict difficulty breathing (B=-.003; 95% CI=-.007-.001; R^2 =.381; P=.151).

Pain

For the following participants- 9,10,14,15,16 and 17 missing data was over 40% and therefore no further analysis was undertaken for these participants. The cross-correlation charts of participants 11, 22 and 25 revealed that there was no evidence of a relationship between pain and objective nebuliser adherence, therefore no further analysis was undertaken. For participants 8, 12, 13, 18, 19, 20, 21 there was evidence of a potential relationship between pain and adherence, therefore this was further investigated.

Participant 8

The cross-correlation chart for participant 8 suggested that there was potentially a positive relationship in which high adherence predicted high pain in 7 days. This was investigated using a linear regression in which pain was the outcome and the predictors were: adherence lagged by 7 (as per cross-correlation chart), pain lagged by 1 (as per auto-correlation chart) and day number (as per section 4b of the method). The regressions revealed pain was a significant predictor of pain the next day (B=.400; 95% CI=.235- .564; R^2 =.351; P=.000), adherence in 7 days time was a significant predictor and pain (B=.011; 95% CI= .003- .018; R^2 =.351; P=.005). However, day number was not a significant predictor of pain (B=-.004; 95% CI= -.011-.002; R^2 =.351; P=.169).

Participant 12

The cross-correlation chart for participant 12 suggested that there was potentially a positive same day relationship pain and adherence for this participant. However for the purpose of the regression as one variable must be the outcome, the next closest relationship on cross-correlation chart suggested high pain predicts high adherence. Therefore within the regression pain would not be lagged to investigate this same day relationship and adherence would be lagged by 1 (as per the auto-correlation chart). Day number was also used as a predictor in the regression due to

evidence of time trends at step 4b of the analysis. The regression revealed that all of the predictors were able to significantly predict adherence for this participant; day number (B=-. 237; 95% CI= -.414--.060; R^2=.247; P=.009), adherence lagged by 1 (B=.271; 95% CI=.109-.432; R^2 =.; P=.001) and pain which suggests a same day relationship for high pain and high adherence for this participant (B=6.228; 95% CI=3.204-9.252; R^2 =.; P=.000).

Participant 13

The cross-correlation chart for participant 13 suggested that there was potentially a negative same day relationship for pain and adherence for this participant. However for the purpose of the regression as one variable must be the outcome variable, therefore the next closest relationship on cross-correlation chart suggested adherence would be the outcome. Therefore within the regression pain would not be lagged to investigate this same day relationship, however the outcome variable (adherence) was lagged by 8 to investigate relationships within this variable. The regression demonstrated the relationship between adherence and pain on the same day is statistically significant (B=-1.680; 95% CI= -3.229- -.132; R^2 =-.088; P=.034), meaning low pain predicts high adherence on the same day for this participants. Furthermore the relationship between adherence now and adherence in 8 days time was also significant (B=.216 95% CI=.037-.395; R^2 =.088; P=.018).

Participant 18

The cross-correlation chart for participant 18 suggested that there was a possible negative relationship between pain and adherence for this participant in which low pain predicted high adherence in 3 days time. This was investigated using a linear regression in which adherence was the outcome and the predictors were: pain lagged by 3 (as per cross-correlation) and adherence lagged by 9 (as per

auto-correlation). The regression revealed that both pain lagged by 3 (B=-3.003; 95% CI= -5.687- -.319; R^2 = 116.; P=.029).and adherence lagged by 9 (B=.238; 95% CI=.026-.449; R^2 = 116.; P=.028) were significant predictors of adherence for this participant. Suggesting pain predicted high adherence in 3 days time and adherence predicted adherence in 9 days time.

Participant 19

The cross-correlation chart for participant 19 suggested that there was potentially a negative relationship in which low pain predicted high adherence in 2 days time. Therefore a linear regression was conducted to investigate this further in which the predictors were: pain lagged by 2 (as shown on the cross-correlation chart), adherence lagged by 2 (as shown on the autocorrelation chart) and day number (as per step 4), and the outcome variable was adherence. The regression revealed that the relationship in which low pain predicted high adherence in 2 days time was statistically significant (B=-6.342 95% CI=-10.434- -2.251;R^2 =.444; P=.003). Furthermore the relationship between adherence on one day and adherence in 2 days time was statistically significant (B=.574 95% CI= .431-.716; R^2 =.444; P=.000). However the relationship between day number and adherence was not statistically significant (B=-.292 95% CI=-.590-.005; R^2 =.444; P=.054).

Participant 20

The cross-correlation chart for participant 20 suggested there was potentially a relationship in which high pain could predict high adherence in 3 days time. This was investigated using a linear regression in which adherence was the outcome variable and the predictor variables were: adherence lagged by 1 day (as per autocorrelation chart), pain lagged by 3 days (as per cross-correlation chart) and day number (as step 4b of the analysis). The regression revealed that the only significant predictor of adherence

for this participant was adherence in one day time (B=. 720; 95% CI= .592-.847; R^2 =.584; P=.000). Pain was not a significant predictor of adherence in 3 days time (B=7.954 95% CI= -.257-16.166; R^2 =.584; P=.057) and day number was not a predictor of adherence for this participant (B=.034 95% CI= -.162-.230; R^2 =.584; P=.734).

Participant 21

The cross-correlation chart for participant 21 suggested that there was potentially a negative same day relationship for pain and adherence for this participant. However for the purpose of the regression as one variable must be outcome, therefore the next closest relationship on cross-correlation chart suggest pain would be the outcome. Therefore within the regression adherence would not be lagged to investigate this same day relationship and pain would be lagged by 2 to investigate variation within the outcome (as suggested on the autocorrelation chart). The results of the regression demonstrated that there is a significant negative same day relationship for high adherence and low pain for this participant (B=-.007 95% CI=-.012--.003; R^2 =.142; P=.001). There is also a significant relationship in which pain predicts pain in 2 days time for this participant (B=-. 240; 95% CI=.072-.408; R^2 =.142; P=.006).

Tiredness

There were no participants who had over 40% of missing data for tiredness. Therefore cross-correlation charts were inspected for all participants. The cross-correlation charts for the following participants (8,9,10,12,13,14,17,18,22) demonstrated that there was no evidence of a relationship between the variables and therefore no further analysis was undertaken. However for participants: 11, 15, 16, 19, 20, 21, 25, there was evidence of a potential relationship based charts which was investigated further using linear regressions.

Participant 11

The cross-correlation chart for participant 11 suggested that there was a potential relationship between tiredness and adherence, in which high tiredness could lead to high adherence in 5 days time for this participant. This was investigated using a linear regression the outcome variable adherence was and the predictors were: tiredness lagged by 5 (as per cross-correlation chart), adherence lagged by 1 day (as per auto-correlation chart), day number and periodic patterns (due to evidence of a potential relationship at step 4 of the analysis). The regression revealed adherence was able to predict adherence the next day for this participant (B=.349; 95% CI=.184-.514;R^2 =.253; P=.000), furthermore periodic patterns were able to predict adherence for this participant (B=-29.989; 95% CI=-52.108--7.870; R^2 =.253; P=.008). However tiredness was not a significant predictor of adherence in 5 days time for this participant (B=9.268; 95% CI=-.198-18.733; R^2 =.253; P=.055), also day number was not a significant predictor of adherence for this participant (B=-.211; 95% CI=-.507-.084; R^2 =.253; P=.159).

Participant 15

The cross-correlation chart for participant 15 suggested there was a potential negative relationship between tiredness and adherence for this participant in which low tiredness potentially predicted high adherence the next day. This was investigated using a linear regression the outcome variable was adherence and the predictor variable was tiredness lagged by 1 day. Adherence showed no evidence of autocorrelation and therefore a lagged version of the variable was not included. The regression revealed that low tiredness was able to predict high adherence the next day (B=-7.920; 95% CI= -12.059- -3.782; R^2 =.106; P=000.).

Participant 16

The cross-correlation chart for participant 16 suggested there was a potential relationship between tiredness and adherence for this participant, in which high adherence could lead to low tiredness in 3

days time. This was investigated using a linear regression the outcome variable was tiredness and the predictor variables were: adherence lagged by 3 (as per cross-correlation) and tiredness lagged by 1 (as per auto-correlation). The regression revealed that tiredness was able to predict tiredness the next day for this participant (B=.318 95% CI=.148-.489; R^2 =.148; P=.000) and also low adherence could predict low tiredness in 3 days time (B=-.016; 95% CI= -.029- -.003; R^2 =.148; P=.015).

Participant 19

The cross-correlation chart for participant 19 suggested that there was a potentially a positive relationship in which high adherence could predict high tiredness in 7 days time. Therefore a linear regression was conducted to investigate this further in which the predictor variables were; adherence lagged by 7 (as per cross-correlation chart), tiredness lagged by 1 (as shown on the autocorrelation chart), day number (as per step 4b of the method), and the outcome variable was tiredness. Tiredness at 1 day was able to significantly predict tiredness at the next day (B=.565 95% CI=.417-.713.; R^2 =.484; P=.000). Adherence was able to statistically significantly predict tiredness in 7 days time (B=.004 95% CI=.001=.007; R^2 =.484; P=.003). However the relationship between tiredness and day number was not statistically significant (B=.001 95% CI -.; R^2 =.484;CI =-.003-.006.; P=.542).

Participant 20

The cross-correlation chart for participant 20 suggested that there was potentially a positive same day relationship for tiredness and adherence for this participant. However for the purpose of the regression as one variable must be outcome, therefore the next closest relationship on cross-correlation chart suggested high tiredness predicts high adherence. Tiredness was therefore the predictor along with adherence lagged by 1 (as per autocorrelation) and day number, adherence was the outcome.

This was investigated using a linear regression, the model demonstrated that adherence was a significant predictor of adherence the next day (B=.72995% CI=.608-.851.; R^2 =.609; P=.000). Also the tiredness was a significant predictor of adherence on the same day (B=9.845 95% CI=2.923-16.767; R^2 =.609; P=.006). However, the relationship between day number and adherence was not significant (B=-.012; 95% CI=-.203-.178; R^2 =.609; P=.897).

Participant 21

The cross-correlation chart for participant 21 suggested that there was potentially a negative relationship in which low tiredness could predict high adherence in 3 days time for this participant. This was investigated using a linear regression in which adherence was the outcome and the predictors were: adherence lagged by 1 (as per auto-correlation chart), tiredness lagged by 3 (as per cross-correlation chart) and day number (see step 4b of the method).The regression revealed that adherence was able to significantly predict adherence the next day for this participant (B=. 626; 95% CI=.493-.760; R^2 =.515; P=.00).Furthermore, low tiredness was able to significantly predict high adherence in 3 days time for this participant (B=-6.896 95% CI=-11.238- -2.554; R^2 =.515; P=.002).However day number was not a significant predictor of adherence for this participant (B=.038 95% CI=-.038-.114; R^2 =.515; P=.323).

Participant 25

The cross-correlation chart for participant 25 suggested there was a potential negative relationship between tiredness and adherence for this participant in which low tiredness could potentially predict high adherence in four days time for this participant. This was investigated using a linear regression the outcome variable was adherence and the predictor variables were tiredness lagged by 4 (as per cross-correlation), adherence lagged by 1 (as per auto-correlation) and finally day number (as per step 4 of the method

section). The regression revealed none of the predictors were significant; adherence at 1 day was not able to predict adherence the next (B=.187; 95% CI=-.025-.399; R^2 =.110; P=.082). Tiredness lagged by 4 was not a significant predictor or adherence (B=-3.913; 95% CI= -8.954- 1.127; R^2 =.110; P=.126), and neither was day number (B=-.161; 95% CI= -.428-.106; R^2 =.110; P=.235).

Mucus

Participants 11,15, 20 and 25 had over 40% missing data and therefore their mucus data was not analysed. Cross-correlation charts were inspected for remaining participants, for participants; 8,9,10,16,17 18, 22 there was no evidence of a relationship, therefore no further analysis was undertaken for these participants. For participants 12,13,14,19 and 21 there was evidence of a potential relationship between variables which was investigated further.

Participant 12

The cross-correlation chart for participant 12 suggested that there was potentially a relationship in which high mucus potentially predicted high adherence in 6 days time. This was therefore investigated using a linear regression in which adherence was the outcome and the predictors were: mucus lagged by 6 (as per cross-correlation), adherence lagged by 1 (as per auto-correlation) and day number as per step 4b of the analysis. The regression revealed that adherence was a significant predictor of adherence the next day (B=.178; 95% CI=.011-.345; R^2 =.218; P=.037)and also high mucus was a significant predictor of high adherence in 6 days (B=10.051; 95% CI=5.533-14.569; R^2 =.218 P=.000).However, day number (time-trends) was not a significant predictor of adherence (B=-.092 95% CI=-.254-.070 R^2 =.218; P=.263).

Participant 13

For participant 13 the cross-correlation chart for mucus and adherence demonstrated there was a potential negative relationship in which adherence could predict mucus in 3 days time. This was investigated using a linear regression in which mucus was the outcome and the predictor was adherence lagged by 3 (as per cross-correlation) the lagged outcome variable was not included here as there was no evidence of autocorrelation. The regression revealed a significant relationship between the variables (B=-.02595% CI=-.043- -.008; R^2 =.064; P=.005), therefore low adherence predicts low mucus in 3 days time for this participant.

Participant 14

The cross-correlation chart for participant 14 suggested that there was a potentially a relationship in which high mucus could predict high adherence the next day. This was investigated using a linear regression in which adherence was the outcome variable and the predictor variables were: Mucus lagged by 1 (as per cross-correlation), adherence lagged by 1 (as per auto-correlation) and day number (as per section 4b of the method). The relationship between mucus and adherence the next day was significant (B=5.699; 95% CI= 1.278-10.119; R^2 =.818; P=.012), furthermore adherence at one day as able to predict adherence the next (B=.871; 95% CI=.791-.951; R^2 =.818; P=.000).However, the relationship between day number and adherence was not statistically significant (B=.033; 95% CI= -.036-.102; R^2 =.818; P=.346).

Participant 19

The cross-correlation chart for participant 19 suggested that there was a potentially a relationship in which high adherence could predict high mucus in 4 days time. This was investigated using a regression in which mucus was the outcome variable and the predictors were: adherence lagged by 4 (as per the cross-correlation chart), mucus lagged by 2 (as per the auto-correlation

chart) and day number (as per step 4b of the method).The regression revealed that mucus was a predictor of mucus in 2 days time for this participant (B=.514 95% CI=.361-.666.; R^2 =.499; P=.000.). Adherence lagged by 4 was a statistically significant predictor of mucus for this participant (B=.008 95% CI=.003-.012.; R^2 =.499; P=.000).However day number was not able to significantly predict mucus was this participant (B=.005; 95% CI=-.001-.012; R^2 =.499; P=104.).

Participant 21

The cross-correlation chart for participant 21 suggested that there was potentially a negative relationship in which low mucus predicted high adherence in 3 days time for this participant. This investigated using a linear regression in which adherence was the outcome and the predictors were: mucus lagged by 3 (as per the cross-correlation chart), adherence lagged by 1 (as per the auto-correlation chart) and day number (see step 4b of the method). The results of the linear regression were as followed: Adherence during one day was able to significantly able to predict adherence the next day for this participant (B=.474 95% CI=.334-.613; R^2=.582; P=.000).Mucus low was able to significantly predict high adherence in 3 days time for this participant (B=-11.586; 95% CI=-15.75-7.42; R^2=.582; P=.000).However day number was not a significant predictor of adherence for this participant (B=.031 95% CI=-.040-.102; R^2=.582; P=.388).

Summary of significant relationships

The outcome of the analysis is different for all participants which underpins the importance of looking at these relationship on an individual level. There are a number of participants (five) who were found to have only one significant relationship between their symptoms and adherence or simply did not provide enough data to enable inferential statistical investigation. There was one participant who was found to have significant relationships between all

symptoms and adherence. As the data led the development of the hypotheses for each participant, the outcome and main predictor variable changed. However, in terms of the significant relationships it was found that more commonly the symptom was the predictor. In regards to symptoms cough, pain and tiredness were most commonly found to be in significant relationships across all participants.

5.8 Discussion

The current study aimed to explore the relationship/s between adherence to nebuliser treatment and symptoms of Cystic Fibrosis (CF). To address this a pilot and feasibility study was conducted to explore how the methods would be received given the lack of information about this. The pilot study was positively received but did not appear to be long enough to detect relationships, therefore a longer modified version was conducted. The findings of which will be discussed below.

Research question 4 for of the thesis (Is symptom monitoring in patients with CF acceptable and feasible?), was reviewed within the mini discussion of this chapter for the pilot study. However in terms of the feasibility of tracking for the four month period, the findings demonstrate that 11/19 participants had less than 33% missing data overall. Which suggests good engagement with the study. Although, three participants did not provide enough data across the period and therefore their data was not analysed. There were no participants which withdrew from the study. Interestingly this differs from the work of Sarafaraz et al. (2010), who reported that only 37.2% completed their symptom monitoring study with patients living with CF. The value of using symptom tracking as a longer term tool will be discussed in further detail the next study of this thesis.

In relation to RQ 5 (Do CF patients understand feedback graphs, which display the relationship between their adherence and

symptom data?) In qualitative aspect of the pilot study there was a mixed response in relation to how participants received the graphs, some participants offered suggestions of how they felt they could be improved. For example using a similar format to those on the CFHH. Previous evidence has highlighted the importance of being graph literate due to the impact this can have on health outcomes (Shah et al., 2019). However graph literacy in both the UK and the US is poor (Cutilli and Bennett, 2009; Rowlands et al., 2015). However, only one participant within the study reported clearly that they have some difficulty reading and interpreting the graphs.

The body of evidence which investigates perceptions of graphs using symptom and adherence data is limited, specifically in terms of how participants can identity relationships between variables and within the CF population. However, this was something that was explored in study 1 (chapter 4) of this thesis.

In relation to RQ 6 ‘are there any barriers that prevent CF patients from understanding symptom tracking?’ within the qualitative aspect of this study there were some barriers to symptom tracking reported, for example difficulty remembering whether an entry had been completed on a particular day. Some participants suggested that including a reminder or the opportunity for them to look at results retrospectively to check if they had submitted a response that day would be useful.

Although not reported as a barrier, a number of participants in the main study were tracking symptoms during the COVID-19 pandemic. This obviously impacted upon participants routine and their priorities during this difficult period of time. During the pandemic patients living with CF in the UK were advised to shield which meant not having contact with anyone outside their household, according to Collaco et al. (2021) this impacted upon routine, work, education and social lives amongst other factors. This will be explored in more detail in the next chapter of the thesis.

Participants were not specifically asked to report if they were admitted to hospital during the study, however some participants did refer to this within the qualitative study It is important to highlight that this data was still analysed. However, if the participant was receiving other treatments during this time (e.g. intravenous antibiotics) this may have impacted upon both their symptoms. Hoo et al. (2019) found that increased symptoms and lower FEV1 scores are a predictor of clinicians advising intravenous antibiotics and patients expecting them. Although, the hospitalisation and other factors (e.g. illness, holidays, Christmas) are a reflection of events which occur throughout life and would occur if symptom tracking to be used on a long-term basis. Therefore acknowledging this in future symptom tracking work would perhaps be useful.

Research question 7 investigated ‘What is the relationship between self-monitored symptoms and adherence in CF patients?’ the quantitative aspect of the pilot study offers mixed findings; for three participants, there was no evidence of a relationship between symptoms and adherence. For the remaining three participants, there was evidence that higher levels of cough, pain and tiredness related to lower levels of adherence on the same day. Given that these relationships occurred on the same day it was not possible to determine the direction of these associations i.e. did low adherence cause increased symptoms or did higher symptoms mean that people were less likely to adhere.

The lack of a relationship between symptoms and adherence over a six-week period for some participants is surprising. Previous studies have concluded that treatments such as tobramycin and hypertonic saline can work during this period of time and will often lead to an improvement in FEV1 (lung function) after an average time of four weeks (Ramsay at al., 2011). However, it is not clear how much adherence is necessary and for how long, in order to produce symptom changes, and there could be individual differences in the response. It might be that changes in lung function are not associated with noticeable changes in perceived symptoms.

Although the relationship between adherence and symptoms in patients with CF is complex, previous findings have highlighted the importance of symptom tracking within the population. Van Horck et al. (2017) and Sarafaraz et al. (2010) suggest that symptom tracking can be used to help participants predict forthcoming exacerbations. This is important for patients living with CF as exacerbations are associated with a decline in lung function and in serious cases mortality (Ferkol et al., 2006). However it can be difficult to understand exactly how long patients need to track symptoms for in order for this to be beneficial.

In relation to the four month symptom tracking study there are four outcomes which can help explain the relationship between symptoms and adherence and adherence and symptoms. For clarity they will be referred to as relationship A, B, C and D. Relationship A: Adherence is the predictor of a positive relationship for example adherence is high and the symptom high. Relationship B:Adherence is the predictor of a negative relationship for example adherence is high and symptom is low. Relationship C: The symptom is the predictor of a negative relationship for example the symptom is low and adherence is high. Relationship D: The symptom is the predictor of a positive relationship for example the symptom is high and adherence is also high.

Relationship A occurred a total of 11 times across four different participants. As this relationship would suggest that adherence can predict an increase in the level of the symptom experienced, this would be linked to possible side-effects from nebuliser treatments. For example particular nebulisers such as hypertonic saline can break down mucus causing increased coughing (Elkins, 2011).

Relationship B occurred a total of 3 times across four different participants. Based upon drug trial studies (Ramsey et al., 2011; Wark et al.,2018), this would be an expected outcome for the relationship, for example a patient takes their nebuliser as prescribed and their symptoms improve.

Relationship C occurred a total of 13 times across seven different participants. Previous literature has suggested that experiencing symptoms such as tiredness and fatigue can be a barrier to adherence (Eaton et al., 2020). Tiredness was a symptom identified within this study by three different participants, however other symptoms include: wheeze, pain, difficulty breathing, mucus and nominated symptom (fatigue). Arden et al. (2019) reported that tiredness can make adherence more difficult for some patients living with CF, therefore this could be the opposite in that in patients are feeling well enough to adhere they will.

Relationship D occurred a total of 13 times across six different participants. This relationship can be explained using the NCF (Horne and Weinman, 1999), if a patients feels unwell then they are more likely to take the treatment as prescribed because their symptoms indicate the necessity of treatment-taking, and this higher perceived necessity is more likely to outweigh their concerns (Goodfellow et al., 2015; Horne et al., 2004).

Following on from this the findings show that all of the symptoms (cough, wheeze, difficulty breathing, pain, tiredness, mucus and nominated symptom where applicable) were all able to predict adherence for at least one participant in the study. However not all symptoms for all participants demonstrated a significant relationship and it is difficult to suggest there is particular pattern for example after X number of days of adherence cough will improve.

It was anticipated after the findings of the first phase that extending the time period would help to identify more relationships, this has been the case, however as discussed above there is no consistent pattern shown. It could be that limited relationships have been found because in fact there is no relationship present for some participants, or at least this relationship is weak. Although this is surprising as nebulisers are licensed and recommended by NICE to improve symptoms for patients with respiratory conditions (NICE, 2024). It could be that the way in which the improvement is measured within the drug trials differs to the way in which the

symptoms are measured within this study. For example Wark et al. (2023) found that measures of sputum clearance were reported more regularly than symptoms in a Cochrane review nebulised hypertonic saline trials for CF.

Therefore, based on the findings from this study it is clear that a large-scale intervention using feedback about how treatment adherence is related to patient's symptoms may not be useful for helping people understand the benefits of treatment. As for many individuals there is no clear evidence that adherence will lead to clear noticeable improvements in their symptoms in the short to mid-term.

5.8.1 Strengths and Weaknesses

In relation to the positive aspects of this study the unique mixed-method design of the study enabled participants to explain the relationships between symptom and adherence data using individualised graphs created with their data. This provided them with the opportunity to discuss data during data prompted interviews. The addition of this qualitative data helped to enrich the quantitative data collected over the study period. For example if there was a period of extreme symptom severity or low adherence this could be discussed further with the participant, providing them with the opportunity to explain possible reasons for this. Additionally, participants physical activity data was also discussed during the interviews. In turn this provides an enriched approach and understanding to the quantitative data collected. Although previous studies involving patients with CF have used objective adherence data in data prompted interviews to prompt discussion (Arden et al., 2019), it is anticipated that this is the first study to present objective adherence and self-reported symptoms to further understand this relationship. Additionally, given the small size of the CF population it may have been difficult to power a traditional study, whereas an N-of-1 study was able to be fully powered. Both studies had well over the suggested 50 data points power (Tabachnick and Fidell, 2007) with main study including 11,572. Furthermore, a traditional study

could have missed the important differences between participants, a clear finding of the study.

Using an observational N-of-1 design of course has limitations, for example as this is not an experimental design there is no manipulation so causality cannot be determined (McDonald., 2020).However, this design is enables researchers to better understand potential temporal links in data which is time ordered, therefore ensuring the research questions associated with this study to be addressed (Hobbs et al., 2013).

In addition, it is possible that the concept of medication adherence is being overly individualised due to the chosen methodology (N-of-1) and broader patterns have not been detected. However, evidence from a randomised controlled trial (RCT) from the CFHealthHub (n=608) has reported evidence that adherence should be looked at on an individual basis (Wildman et al., 2021). As it was reported that normative adherence improved by an average of 10% for each participant recruited into the trial. Participants in the intervention worked with an interventionist as well as an app which displayed adherence data and problem solving information. The RCT did not utilise N-of-1 methods, highlighting that this finding is not specific to the methods and can be applied to traditional methods. Therefore, this perhaps provides insight into medication adherence which has previously been missed when using a ‘one size fits all’ approach, when there are so many possible barriers and facilitators to medication adherence specific to each drug and condition. This suggestion was also made within the work of Easthall and Barnett (2017) who suggested that this ‘one size fits all’ approach should be abandoned and appropriate behaviour change techniques should be employed where possible to translate theory into practice.

Previous adherence literature and theory, such as the NCF (Horne & Weinman, 1999) has provided a clear framework around the mechanisms and factors which are influence adherence. Traditional

adherence research has offered an understanding into population level trends, across numerous conditions, for example Asthma (Axelsson et al., 2013), Cystic Fibrosis (Bucks et al., 2009), HIV (Gonzalez et al., 2007), depression (Aikens et al., 2005) and cancer (Horne et al., 1999). This group-level research provides a useful foundation for understanding the kinds of factors that are likely to be relevant for adherence and suggests some potential targets for intervention. However, the work from this thesis offers a more personalised (individualised) approach to understanding patterns in behaviour (Lillie et al., 2011) and aims to understand the relationship (between symptoms and adherence) and the behaviour of adherence at an individual level. While for some this might mirror group effects this is not likely to be universal. Although there are challenges, using individualised approaches, because they are more time consuming, they could be especially useful for those who are struggling to manage their adherence, for whom previous (group based) approaches have been unsuccessful. What is clear is that the approach within adherence should not be ‘one size fits all’, for example factors which may motivate one person are likely to be different for another. Langendoen-Gort et al. (2022) suggested that this approach to intervention development should be discarded. The relationship between symptoms and adherence is complex and unique for all patients and likely conditions too. Taking an individualised approach does not diminish the traditional previous literature, rather it offers an alternative perspective when attempting to implement the best possible support for patients living with long term conditions and where resources allow. It might be possible for example to triage patients who are struggling with maintaining adherence (for example see Robinson, 2023) and who are experiencing significant symptoms to access a more individualised approach to care.

Within the current study, although a total of 19 participants were recruited across three different sites within the UK, three participants were excluded due having over 40% missing data for

all symptoms. Attrition and missing-data is unfortunately expected within all research, however specifically when participants are encouraged to engage with the programme on a daily basis for a prolonged period of time. McDonald et al. (2017b), suggests that missing data is common issue when adopting N-of-1 methods. Although the attrition and missing data was recorded for this study it should be acknowledged that participant recruitment and response rates were not recorded for the main study. This is due to the complexities of recruiting across three sites, in addition due to ethical reasons HCP's lead recruitment activities which meant unfortunately this data was not recorded.

Additionally, McDonald et al. (2020) has highlighted limitations of the 'pre-whitening' method used in this study. The method was used to remove any autocorrelations within the data, however McDonald et al. (2020) suggest that the method should be used with caution as it has the potential to obstruct the identification of periodic and weekly trends within the data. Which could mean that relationships between specific symptoms (e.g. cough) and objective adherence occurring due to weekly trends may have not been detected within this analysis. However, due to this study including a pilot study and a larger scale study within the second part the method analysis was changed and the pre-whitening step was removed to enable the analysis of periodic patterns and weekly trends.

5.8.2 Practical suggestions for future research

Practical changes which could be incorporated into future studies include asking participants to select the date in which the answers (data) they are providing correspond to. This would add additional clarity to which points relate to which day, for example if a participant submits data at 12.01am it is likely they are submitting for the day before and not that day. In the current study the use of the 'additional comments' box where they could include any qualitative information as often participants would specify if this was the case. However to add additional clarity asking participants to include the date would be helpful.

Furthermore, providing participants with the option to look back retrospectively at the days they have tracked previously may have been useful. Adding this function would help participants monitor their condition over a period of time and also help add some calibration to their scoring system. An older study conducted in 1997 (Collins et al., 1997) found that based on translating the findings of a 100mm Visual Analogue Scale to a four point scale, a rating of 30mm corresponds to moderate pain and 54mm corresponds to severe pain. It is possible that these findings suggest that within the current work a rating of 3 is moderate pain and a rating of 5 is severe pain, however it is not clear if these findings can be applied in this way. In relation to providing participants the opportunity to look back at data retrospectively this was not an option due to funding. Qualtrics © (https://www.qualtrics.com) the university's chosen survey design website was used and exploring saved previous responses was not an option was not seen to be an obvious option.

The final practical change which could be made based on the findings of this study is to frame questions slightly differently to encourage participants to rate a symptom as '0' rather than missing a day if they are not presenting with a specific symptom. This could possibly help to reduce the amount of missing data there would be and encourage participants to record a even if symptoms are minimal.

5.8.3 Conclusion

To summarise, the findings of this chapter highlight the need for a more individualised approach to be taken when understanding medication adherence to nebuliser treatments in CF. There was no consistent relationship between adherence and symptoms across participants and the relationship between symptoms and adherence differed between symptoms within individuals. Within the pilot study

symptom tracking for this population was viewed to be acceptable and feasible and overall feedback data could be understood by participants.

5.8.4 The Next Steps

The findings from the main N-o-f1 study revealed there was no clear pattern and relationship between adherence and symptoms for people with CF. To further understand people's unique experiences and perspectives related to their symptoms and treatment adherence, qualitative interviews were undertaken with a sub-sample of individuals from the main N-of-1 study. Feedback data from the main N-of-1 study was presented to individuals within these interviews to further explore how people interpreted and made sense of this data and provide participants with an opportunity to share their experiences engaging with the four month symptom monitoring study. Study 3/chapter 6 presents the findings from this study.

Chapter 6- A qualitative study to investigate the feasibility and perceived value of using symptom monitoring and adherence feedback data with patients with Cystic Fibrosis (Study 3)

6.1 Chapter overview

As outlined within previous chapters of this thesis the relationship between symptoms of Cystic Fibrosis and adherence to nebulised treatments is complex and individualised. Chapter 5 of the thesis have described studies that monitored the relationship between these variables for periods of six weeks and four months. Understanding the relationship between adherence and symptoms could be valuable for both patients and healthcare practitioners. However, for this to happen participants need to be able to record/monitor their symptom and adherence information in a way which is feasible and be able to accurately understand the relationship between these variables when they receive feedback on this data.. Participants' health data therefore needs displayed in a way which enables them to identify any trends or relationships between symptoms and adherence with relative ease. If these criteria are met then there is the potential to further an individuals' understanding of their condition and how their treatment taking behaviour can impact on their day-to-day experience of living with CF and its associated symptoms. If this type of feedback data helps patients identify the benefits of treatment taking then this information could, in turn, be used to promote adherence.

This study aimed to explore participants' understanding of their own adherence and symptom data and explore participants' experiences of using daily diaries, to record this data. The qualitative design used in this study also allowed for the exploration of participants' understanding of how their adherence to treatment was related to their CF symptoms more generally. According to Wisdom (2013) mixed methods research provides participants with the opportunity to share their experiences and enables the researcher to better understand quantitative data obtained.

6.2 Introduction

Monitoring symptoms and treatment taking can provide insight into the complex relationship between adherence to medication and symptoms of CF. This may provide further understanding of the factors which influence adherence in patients with CF. The Necessity-Concerns Framework (NCF) (Horne and Weinman, 1999), theorises that those who have stronger perceptions relating to the necessity of an action are more likely to undertake the behaviour. Adherence to medication could lead to a reduction in CF symptoms which could highlight the perceived necessity (e.g. benefits) of treatment taking. In support of the NCF Sawicki et al. (2015) found in a qualitative study of adolescents with CF and their parents, that one of the reasons for poor adherence was related to the lack of perceived consequences of not taking the treatment i.e. lower perceived necessity or concerns about the efficacy of treatment. Sawicki et al. (2015) reported that some participants were unable to recognise the value of the nebuliser treatment and also believed that if they felt well at the time the treatment was not required. Conversely, Mohamed et al. (2016) found that an improvement in symptoms (i.e. improvement in dry cough) can on occasions lead to an improvement in adherence. It could be that when participants notice improvements this reinforces the necessity of the treatments and counterbalances any concerns relating to side-effects or the overall effectiveness of the medicines. Therefore understanding not only the extent and the direction of the relationship but also patient underlying beliefs underpinning that relationship is key, using mixed-method research could enable this investigation.

Nebulisers often require long-term adherence before there will be a noticeable improvement in symptoms. Trials which investigated the use of hypertonic saline in patients with CF found it can take at least four weeks to notice improvements in patients' symptoms (Amin et al., 2010; Elkins., 2006). This could therefore mean that

adherence may not lead to an immediate noticeable change in symptoms and therefore limit the identification of relationships between adherence and symptoms. The findings from study 3 have revealed that the relationship between symptoms and adherence behaviour is complex and appears to be bi-directional. Previous literature has reported that particular symptoms of CF can negatively impact on treatment adherence directly. Drabble et al. (2019), for example, found symptoms such as tiredness can cause temporary lapses in treatment taking, in otherwise high adherers.

The findings from study chapter 2 revealed that temporal relationships between symptoms and adherence are likely to be different for each patient and therefore providing patients with simple and generic messages about how adherence may ‘improve symptoms’ may not always be accurate or helpful. For example, some people may only notice improvements in some certain symptoms as a result of high levels of adherence. Other individuals may find that adherence is influenced by how they are feeling (e.g. symptoms such as tiredness may impact on whether they adhere to treatment). However, helping patients better understand their condition and how treatment taking and symptoms are related for them could have real benefits to developing better awareness of their CF and successful self-management strategies. According to Proudfoot et al. (2014) monitoring can also support clinicians to treat symptoms in the timely manner to ensure the patient receives the best treatment possible.

Prior to the development of such work it is important that the feasibility and acceptability is assessed within patients who live with the condition. According to the NIHR (2019, p2) ‘Feasibility studies are pieces of research done before a main study in order to answer the question "Can this study be done?". They are used to estimate important parameters that are needed to design the main study’. Acceptability (which is also called adoptability) focuses on how well the intervention is received by and meets the needs of the target

population and the organisation which will deliver it (Green & Kreuter, 1999; Steckler & Linnan, 2002).

The aim of this research programme is to investigate the feasibility and potential usefulness of symptom monitoring and using feedback data (illustrating links between adherence and health outcomes/symptoms) for patients with CF. Previous studies have investigated the feasibility of symptom tracking in patient living with a number of different conditions including Parkinsons (Heijmans et al., 2019), Bipolar disorder (Schwartz et al., 2016) and Cystic Fibrosis (Sarafaraz et al., 2009).

The work of Heijmans et al. (2019) and Schwartz et al. (2016) suggested that short-term symptom monitoring was acceptable in patients with Parkinsons and Biopolar. However Sarafaraz et al. (2009) found that over six months only 37.2% of patients with CF completed the symptom monitoring study. These findings differ with previous work within this thesis (chapter 5) which found that symptom tracking for a period of six weeks was both acceptable and feasible for patients with CF.

Although the work of Heijmans et al. (2019) and Schwartz et al. (2016) would suggest that symptom tracking is a helpful tool and something accepted by different patient groups, the poor response rates in Sarafaraz et al's (2010) study could suggest that either the length of time participants were asked to monitor for or the at home spirometer devices were a potential barrier and an additional burden for participants. Interestingly the work conducted by Heijmans with Parkinsons patients (Heijmans et al., 2019) had better levels of compliance despite asking participants to complete a survey several times per day as well as wearing sensors.

This study will look at feasibility and potential value of self monitoring and using feedback data with patients. The next study within this thesis will look at the feasibility of using symptom tracking in a clinical setting from the perspective of Healthcare Professionals who work with patients with Cystic Fibrosis.

The present study

This study will use data prompted interviews (please see chapter 3 for more information on this) to present participants with graphs of their objective nebuliser adherence and self-reported symptom data collected over the four-month study period in order to explore participants understanding of the data and explore the participants perspectives around the feasibility of self monitoring and usefulness of this feedback data.

This qualitative study addressed two main research questions, which focused mainly on further exploring the relationship between symptoms of Cystic Fibrosis and objective nebuliser adherence. The current study will aim to address the following research questions: How valuable did participants find symptom tracking using daily diaries (RQ 8)? and how did participants understand the relationship between their treatment adherence and symptoms of CF (RQ 9)? This study was a sub-study of the four month symptom tracking study (please refer to chapter 5 of the thesis).

6.3 Method

6.3.1 Recruitment

Participants were recruited from three Cystic Fibrosis centres across the UK. These sites used CFHealthHub which was where participants objective adherence data was collected from.

All participants who were recruited into N-of-1 trial were invited to participate in this qualitative study at the end of the four-month symptom monitoring period.

In total 13 participants agreed to participate in this study. In total there was four females and nine males, at least one participant from each site agreed to take part in the study. Adherence for the four month symptom tracking period ranged from 29.33%-96.15%. The remaining participants did not respond to the email invitation.

6.3.2 Inclusion/Exclusion criteria

The inclusion criteria for the recruitment of participants were as followed:

VI. Patients were 16 years or older and being treated by adult services within the NHS in England (in one of the three sites selected)

VII. Participants were part of the CFHealthHub Data observatory (see section 3.5) and had agreed they were happy to be contacted about future research.

VIII. Participants were receiving treatment, using an eTrack® (Pari GmbH, Stanberg, Germany) nebuliser system.

IX. Translation was not available so participants must speak English to ensure consent could be obtained accordingly and the study could be completed.

X. Participants were required to own a smartphone to complete the online survey each day.

XI. Participants must have taken part in the N-of-1 trial.

The exclusion criteria for the recruitment of participants were as followed:

V. CF patients who were under the age of 16 (the change of transition into adult services in the NHS in England).

VI. Patients who were not using nebuliser as a part of their daily treatment and not receiving treatment through one of the three selected sites.

VII. Patients who were in the late palliative phase of treatment (i.e., people in the end stage of their illness for whom the emphasis of care was comfort).

VIII. Patients who were pregnant or on the transplant list at the start of the study were also excluded from taking part in the study due to the stress likely to be experienced in such experiences.

IX. Patients who had taken part in the pilot study were not permitted to take part.

6.3.3 Procedure

During the symptom monitoring period participants were asked to score their cough, wheeze, difficulty breathing, pain, tiredness, mucus amount (and had the option of monitoring a symptom of their choice) on a visual analogue scale which ranged from 1 (minimal) to 10 (maximum). Prior to the interview participants individual data sets consisting of objective adherence data (taken from the CFHH) and symptom data (taken from the daily questionnaire) were analysed using N-of-1 methods (please see section 3.3) in the programme SPSS[1]. The complete analysis was not presented to participants however statistically significant relationships (if these existed) were displayed using graphs (information relating to the specific graphs used will follow within this section).

The purpose of the interview was to present participants with their personal adherence and symptom charts from the study period and to discuss the participants' interpretation of this data and examine whether they could accurately identify relationships between these variables and whether this information was of value and interest to them. Participants were also asked questions relating to the feasibility of tracking symptoms and their thoughts on using the tool to monitor their condition in the future. The interviews followed a semi-structured format and the topic guide for the interviews can be seen in Appendix J.

The graphs were discussed in detail during the interview. According to Kwasnicka et al. (2015) using graphical representation in qualitative interviews (i.e. data-prompted interviews) allows researchers to discuss more complex issues that without the data would be difficult to explain. Therefore presenting healthcare data to

[1] Please see chapter 5 – for full details of how this analysis was conducted and the corresponding results.

participants during an interview creates the opportunity to discuss these complex relationships.

The findings from the first study chapter fed into the design of the graphs used to provide feedback data to participants. Graphs of all symptoms with adherence were presented over the 4-month period of data collection (where sufficient data had been provided by participants). Where there had been missing data for specific symptoms participants were asked about the reasons behind not monitoring/recording specific symptoms. All graphs were emailed to participants in advance to ensure they had chance to look at the graphs in detail and ask any questions if necessary. The graphs were all double line graphs, in which adherence was presented in a red line and the symptom in blue (see Appendix K for examples of the graphs).

The analysis was conducted prior to the interview to ensure that any statistically significant findings could be presented to participants. The analysis focused on the relationship between the symptom scores recorded by patients and their objective nebuliser adherence. If there was evidence of a significant relationship participants were presented with a one-month graph of the specific symptom and adherence as shown in figure 12 in an attempt to present the relationship at a more detailed level. Where there was no evidence of a significant relationship participants were presented with a graph of the full four-month period as shown in figure 13.

Figure 12.

Tiredness and adherence data for one month, as presented to participants

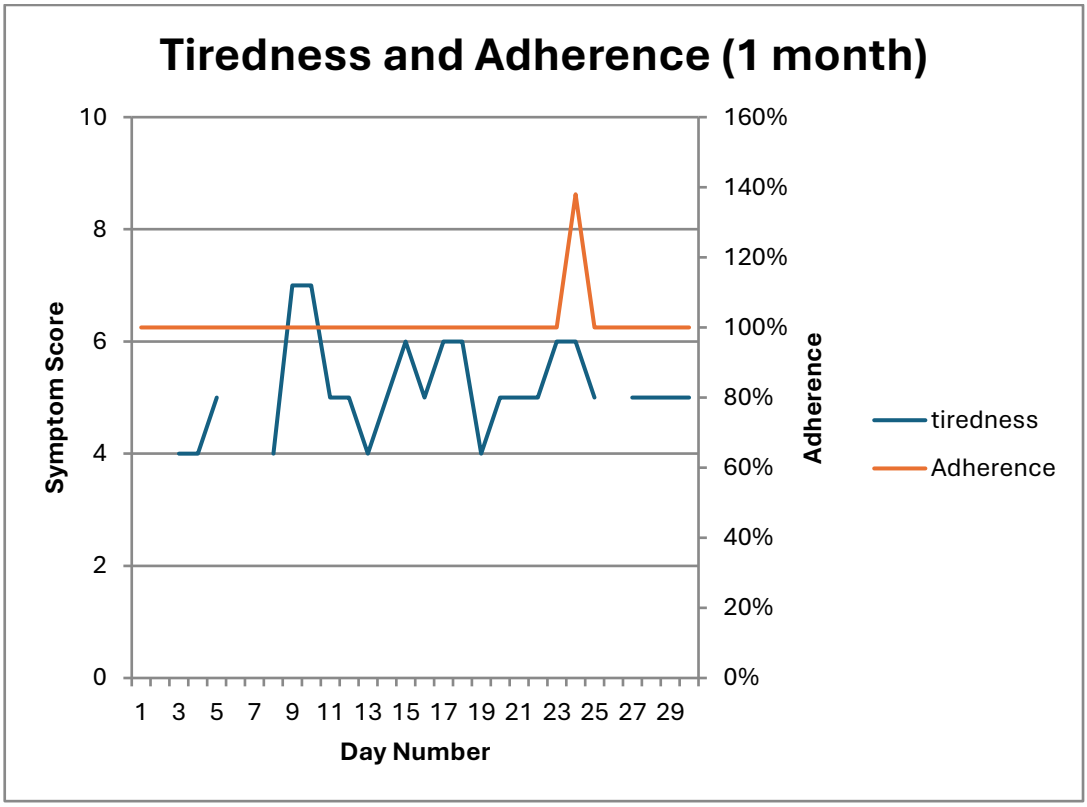
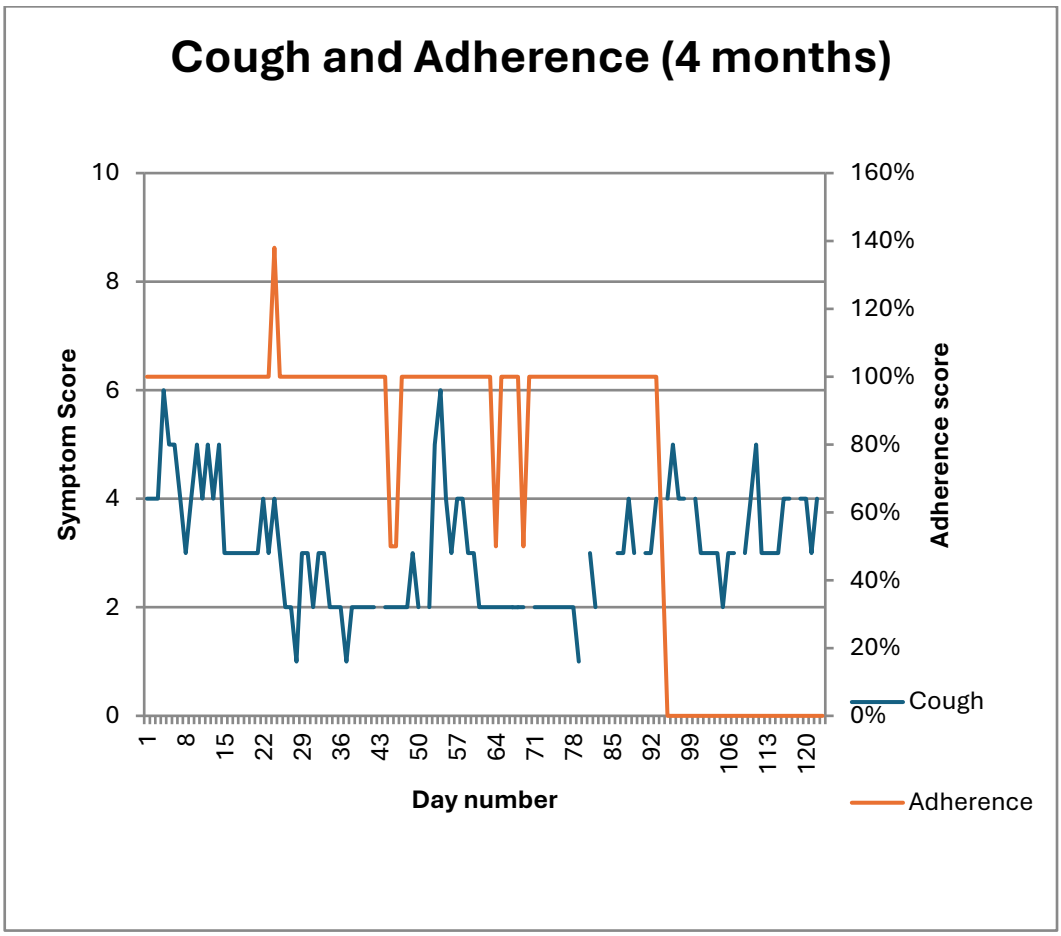


Figure 13.
Cough and adherence data for four months, as presented to participants



It is important to note that the interviews were conducted during the COVID-19 pandemic (17th April-26th April 2020), therefore interviews were not conducted face to face. Instead they were conducted via Zoom. Recordings of the interviews were transcribed by a University recommended private transcription company. The length of the interviews ranged from 25-58 minutes.

6.3.4 Ethics

The study received ethical approval from Sheffield Hallam University Research Ethics Committee (Ethic Review ID: ER12789084). Following this the study received ethical approval from London Bromley Research Ethics Committee (17/LO/1769) on the 16th November 2017, and the Health Research Authority (12th December 2017). Informed consent was taken from all participants

who were involved in the study (for participant information sheet and consent form see appendix F).

6.3.5 Analysis

The data was transcribed verbatim and analysed using Braun and Clarke's (2006,2012, 2022) thematic analysis. The thematic analysis was conducted using the following six-phase process, please see table 21.

Table 21.
Stages of analysis

Stage of analysis	**Explanation**	**Who was involved?**
Familiarisation with the data	Reading and rereading the data to encourage familiarity with the data before progressing to coding.	RM and JP
Generation of initial codes	Key words and phrases which summarise small pieces of data were selected and documented on the transcripts.	RM whole data set JP a sample of data
Searching for themes	In relation to the research questions, time was spent looking through the codes and grouping them into themes.	RM whole data set JP a sample of data
Reviewing the themes	In a group supervision meeting the themes were	RM, MA and JP

	presented and discussed.	
Defining and naming of themes	There were some minor changes made to ensure each the findings were represented by the most appropriate theme.	RM
Producing the written report	The written report was produced by RM with the support supervisors.	RM, MA and JP

Developing themes

When developing themes the research questions were used to ensure the analysis was relevant, RM spent time becoming emerged within the data and reviewing codes, all coding and analysis was conducted using pen and paper. Codes were grouped together with similar or opposing codes using sticky notes. A selection of the data was selected and during an online meeting RM and JP worked together to ensure codes were similar.

Following this the whole data set was completed and the groups of codes were given working (theme) names and transferred into diagrams in a word document, this was then presented at a supervision meeting, discussed and amended were appropriate.

Visual mapping was used as an aid to help develop the themes as advised Braun and Clarke (2013) to help visual the connection between themes and also the data supporting the themes.

Field Notes

This data was collected during March and April 2020, at this point the UK were in lockdown due to the COVID-19 pandemic. As a result of this participants with CF were told hey were ‘clinically

extremely vulnerable' and told not to leave the house. As a results of this participants were interviewed at home via Zoom. During the interview some of the participants were waiting for food and medical deliveries. Some participants were living separately to family members or staying confined to a room. The pandemic was mentioned informally at the start of all of the interviews and because the interviews were early in terms of the whole lockdown period it was still very much the unknown for everybody. Please see below for field note extracts, recorded after interviews with participants which are relevant to the pandemic and context:

'X seemed really grateful for this opportunity and the chance to discuss adherence with somebody different/new during this time'.

'As we are in the pandemic/ lockdown period I would ask if participants have more time to engage with the study and think about their medication adherence'.

'This participant explained that normally they would not have time to participate in an interview due to a busy work life and hobbies, however due to the lockdown they have more time and are happy to participate'

Here are some general field notes:

'There was an error with adherence data for this participant, I have informed X. The participant was a little frustrated by this . I also will only be able to analyse data up to this point'

'This participant explained that taking part in the study had encouraged them to adhere and feel motivated to continue to do so'

Reflexivity

The following reflexivity statement will be written in first person:

As the patients recruited into this study had previously been recruited into the 4 month symptom tracking study I had met most of them before or at least spoken to them. In addition to this I had sent emails to all participants each day for 4 months, some had completed the study with little contact and others had questions or technical concerns throughout. I felt like when it came to the

interviews I was more familiar with them than previous participants I had interviewed in other studies outside of the PhD. I also felt like having the data was a nice resource that I could use to encourage discussion with participants.

In terms of my positionality in this research I still had distance from the patients in that I was not involved in their clinical appointments in anyway as this study sat separately to that. I had obviously spent a lot of time researching CF and discussing CF with HCP's but the patients knew their condition better than I did. It is possible that participants could be more open and honest when speaking to me as I was not a member of their clinical team. I have no judgement of participants and their level of adherence and my job is not to help improve adherence but to understand this further. However I do feel like my work could help patients with CF in the future and this is what drives me.

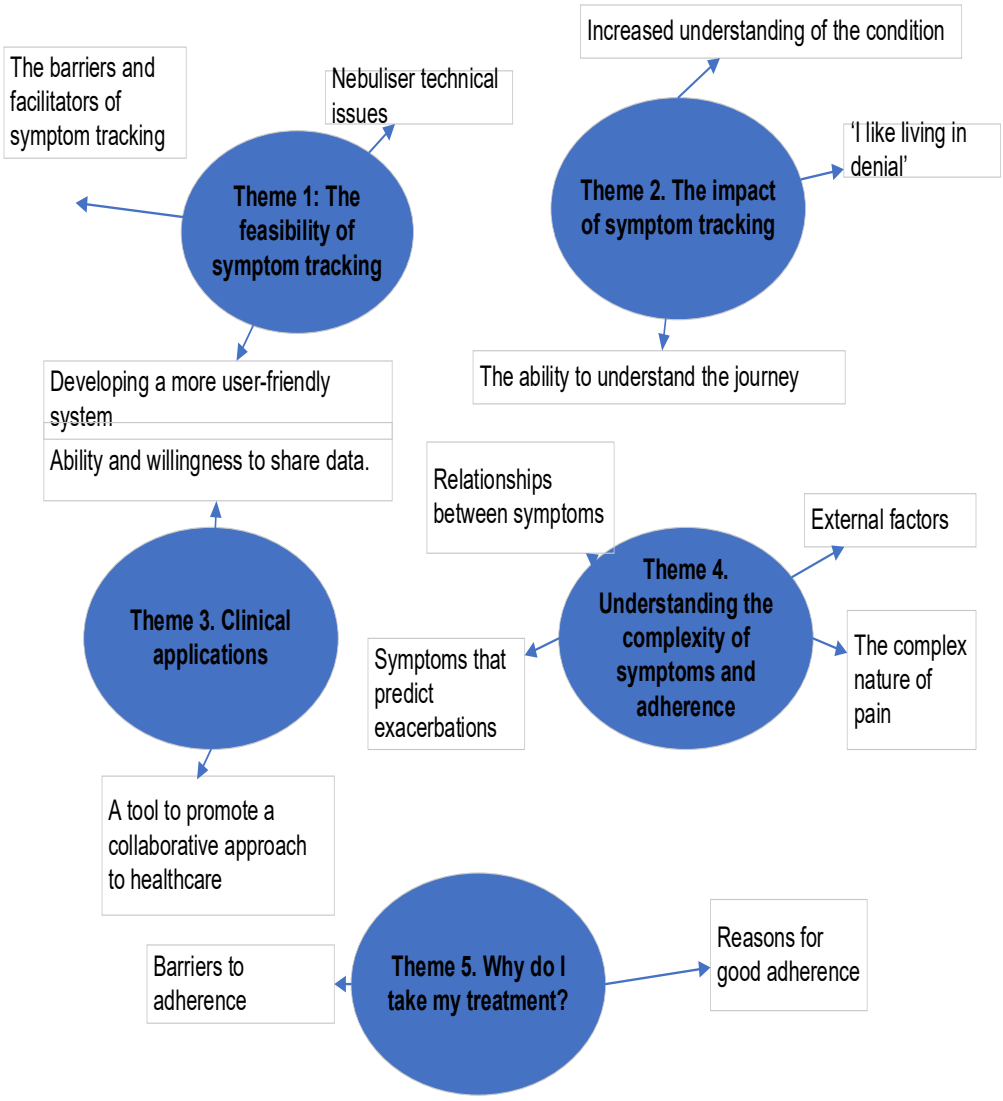
As aforementioned in the field notes the interviews were conducted at the start of the COVID-19 pandemic. For some of the participants it felt as though they enjoyed taking part in the study as it was something 'pass time' during a strange time. A number of participants I spoke with were currently furloughed or not working and were experiencing large changes to their routine. Perhaps it gave some participants time to think and reflect on this, something they might not normally have done if their day to day lives had been more routinised.

Please see research paradigm section of methodology chapter (chapter 3) for a full reflexivity statement.

6.4 Results

The themes that were identified following this analysis process included: 'The feasibility of symptom tracking, 'The impact of symptom tracking', 'Clinical applications', 'Understanding the complexity of symptoms and adherence' and 'Why do I take my treatment?' The themes can be seen below in figure 14, presented in the form of a thematic map.

Figure 14.
Thematic map



Theme 1- The feasibility of symptom tracking

Participants spoke of how the process could be improved and the existing aspects of the symptom tracking tool that they enjoyed or found useful. Within this theme there are three subthemes firstly;

‘Developing a more user-friendly system’, secondly, ‘The barriers and facilitators’ and finally ‘Nebuliser technical difficulties’.

Developing a more user-friendly system

Participants referred to the visual analogue scoring system used in the study (see method section of this chapter for further detail) and suggested that attempting to remember retrospectively what they had reported on previous days was challenging. Some participants felt it was important to be aware of this so they could make a clear comparison to how they felt the previous day to rate symptoms accordingly. Therefore the ability to view their previous data would aid the development of a more user-friendly system.

> ‘just because I wasn’t able to see what I had put previously and I just couldn’t remember what I had put previously really’ Line 747-750 Interview 390 (Male)

> ‘Yes. It was like, when I was doing it, I couldn’t remember like how I’d marked it against each other kind of thing, but now I can see it in front of me, its like ‘oh yes’. Line 29-31 Interview 391 (Male)

Furthermore, the visual analogue scale caused some confusion for some participants. One area of confusion was that there was no differentiation between rating a symptom as a zero and the system inputting a zero if the symptom or questionnaire was missed on a specific day.

> ‘maybe have a zero would be useful if you were going to do it again, because then you would actually have it tracking down zero as opposed to just looking like a missed.’ Line 783-785 interview 390 (Male)

In addition to this the participant below emphasises the ease of the survey, specifically after the first few initial days as the scoring system starts to become more familiar.

> ‘It was just easy to use, to be honest. It wasn’t particularly tricky. And once I’ve done it two or three times, that’s had a bit of an idea of the benchmark of the numbers that I was using, it was just really easy to use. In terms of what I really liked about it, it wasn’t too onerous; there weren't too many questions. Sliding scale of 1 to 10; it’s pretty easy to …, isn't it?’ Line 18-23 interview 398 (Male)

An additional point in relation to the scoring system was that some participants felt finding a baseline was something that they required to help them complete the questions accurately and use the visual analogue scale in the most effective way. Some participants spoke of how they chose to rate all of their symptoms at five on the first day and work from that as a central point, as evidenced below.

> ‘So that’s why the first one I did was like a five on most.. well it was on most of them, or it was dead centre because I used that as base point.’ Line 359-365 Interview 391 (Male)

The barriers and facilitators of symptom tracking

There were several factors identified by the participants that acted as either a barrier or facilitator to them completing the symptom tracking survey. For example, the emails which were sent to participants’ phone each day acted as a facilitator.

> ‘I used to do it in an evening because I did it so that I got the email to my phone and so then that reminded me when it buzzed to just fill it in straight away and then it was done, so I didn’t forget very often’ Line 23-26 Interview 395 (Female)

The use of technology provided participants with the opportunity to complete their symptom tracking anywhere, providing they had connection to the Internet. For many this was another facilitator that helped them to complete the survey each day. One of the participants completed the survey whilst on holiday in America; this highlights the flexibility of the tool and the compatibility with a busy modern lifestyle.

> ‘I mean, we were on holiday in the middle of it, we were doing it in America, I was doing it in America as well, so, when I was in the hotel that I could pick up, you know, my emails up on, yes, no problem at all.’ Line 7-10 interview 393 (Male)

Similarly, participants spoke of the convenience of tracking symptoms electronically, explaining that this fits in well with everyday life.

> ‘I think it was quite handy being able to do it electronically because, I suppose, it’s kind of reached the stage now where so much of our lives generally is done online and done sort of, you know.’ Line 45-48 Interview 401 (Female)

However, tracking symptoms electronically is reliant on WIFI, therefore having no connection would mean there is no way of tracking symptoms via the daily email link. For the participant below this was the only reason they were unable to track.

> ‘No, nothing at all really. I mean, there may have been the odd day when I didn’t have the internet and it didn’t get to me but apart from that no, it wasn’t an issue, it was just another job really’ Line 15-17 P393 (Male)

It was reported that the symptom tracking was easy to complete, with many participants reporting that they missed only some days over the four-month period. This was mainly due to forgetting as demonstrated in the quotes below.

> ‘I found it alright, yes. I definitely missed a few, but I think I got most of them. I mean the chart seems to, seems to be fairly consistent’ P390 Lines 60-61 (Male)

> ‘All the days that I missed it, it was just that I had forgot to check my email sort of thing.’ P390 Line 108-109 (Male)

> ‘I mean, once I got into a routine it was fairly easy. It was just the routine itself.’ P391 Line 19-20 (Male)

Nebuliser technical Issues

Although there are clear applications of the use of technology some participants experienced technical issues specifically relating to the nebuliser. These issues with the nebuliser system seemed to be a cause of stress and frustration for some.

> '…unfortunately at the moment my nebuliser's playing up so recently we changed the – because I'm using the, God what's the name of it? But changed over the wire and that seemed to make some difference but then there seems to be a problem with my actual nebuliser' P401 Line 110-116 (Female)

> 'mean aside from the fact the nebuliser drives me nuts at the moment because it's not working properly and it's really frustrating, I find that really frustrating but – ' P401 Line 256-257 (Female)

Within this theme, participants spoke of the symptom tracking procedure being easy to use and access, especially as participants were able to complete the survey anywhere with connection to WiFi. However, there were some challenges associated with adapting to the use of the visual analogue scale and also the nebuliser system as discussed here.

Theme 2- The impact of symptom tracking

Within the second theme, participants spoke of their experience of symptom monitoring- for some this was useful and helped them to better their understanding of their condition, whereas for others this was an unhelpful reminder of the condition they live with. In order for the experience to be useful in terms of potentially promoting adherence it was important participants could understand the data presented to them. Subthemes within this theme included; 'Increased understanding of their condition', 'I like living in denial' and 'The ability to understand the journey'.

Increased understanding of their condition

Participants spoke of symptom tracking as a tool that enabled self-management which came under the sub-theme of increased understanding of their condition. For some participants there was a notable difference each day and the survey helped them understand that one bad day does not necessarily mean the following day will be the same.

> ‘It helped me sort of- it just helped track how I was feeling and knew its something I can look back on and say, oh I didn’t feel so good yesterday but I’m alright today’ P399 Line 522-524 (Female)

> ‘So yes, so yes, I think, you know, being able to have that opportunity to think about how you’re feeling means that you are – I was much, much more able to work out how I was, how my health was whereas previously, I suppose it’s quite reactive in the sense that you wake up, you feel okay, you know, the day goes well. Other days you wake up it’s a bad day.’ P401 Line 92-95 (Female)

Additionally, participant 400 explains how she felt more aware of her condition prior to receiving IV treatment in hospital, although she was aware of changes in her condition symptom tracking added additional confirmation to this.

> ‘Yes, no it was good especially like I say before I went to hospital to have the IV's. I knew that I was poorly anyway but answering that question sort of confirmed it for me if that makes sense.’ P400 Lines 40-42 (Female)

For some symptom tracking was an opportunity to be more aware of the changes in their condition, for this participant it helped make an incredibly important decision in relation to having a lung transplant.

> ‘It sort of gave me a bit of an idea of where I was feeling in general with my health I think which was kind of good for me based on the fact that I’m, like, deciding whether I need a transplant right

away or not but – yes, it gave me a decent idea of how I was feeling in general. It sort of made me be more honest with myself I suppose.' P392 Line 48-52 (Male)

However being more aware of their conditions and associated symptoms was not something that all participants perceived to be positive all of the time. The participant below used the word 'denial' to describe how they approach living with their condition.

> 'I like living in denial so I like to forget about CF until my appointment and things… I just put it to the back of my mind and get on with my life kind of thing, I don't like to think about it everyday if you like'. P389 Line 152-160 Interview (Male)

Similarly, a different participant explained that they try to 'minimalise' symptoms and symptom tracking can prompt thoughts relating to the severity of symptoms which some participants may chose to ignore.

> 'So like the coughing up stuff and all that, because, you know, I just didn't think that really happened. It turns out it does just I kind of minimalize it.' P391 Line 90-92 (Male)

This suggests the complexity of self-monitoring and awareness of chronic conditions and the idea that it may not be something all participants would want to use as a long-term tool. In particular, patients who may adopt more avoidant coping strategies to live with this serious condition (Abbott, 2003).

The ability to understand the journey

The final subtheme within this theme is 'the usefulness depends on the ability to understand journey'. The usefulness of self monitoring appeared to be dependent for some people on their ability to interpret the data and understand what it was telling them about how their symptoms/adherence were related and how their experiences were changing over time. The interviews suggested that not all participants in the study had the ability to understand the graphs presented to them.

> ‘Q: So did you manage to get the graphs up on your phone?
>
> P: I did, yes. Not that I really understood them but hey.’ P401 Lines 316-317 (Female)

This suggests that despite the graphs being designed in a way to maximise understanding and interpretation (based on the findings of study 1) some participants were unable to understand or found it difficult to interpret the graphs without an explanation.

However other participants referred to the graphs during their interview, to help identify and explain trends in the data presented. For the participant below this demonstrated the ability to confidently interpret graphs and also identify changes in symptoms as a result of an infection.

> ‘I got an infection halfway through doing it and think that actually shows, only on the graph because what happens with me is a lot of my CF condition is in my nasal cavity.’ P396 Line 87-89 (Male)

Theme 3- Clinical applications

Within this theme participants spoke about the practical uses of the data collected and how using the data could aid treatment plans and help create a more collaborative approach to their care. Subthemes within this theme include; ‘Ability and willingness to share data’ and ‘A tool to promote a collaborative approach to healthcare’.

Ability and willingness to share

A willingness to share data with healthcare professionals was common across all of the participants interviewed suggesting that the symptom-monitoring tool is something that could potentially be shared with healthcare professionals to support and aid the care of patients with CF. Participants suggested that by sharing data it is likely to be more useful and helpful when treating their condition as demonstrated below.

> ‘Yes, because then they can give me like obviously, they don’t, well without testing obviously, they can’t say if I have got an infection or anything, but I think if they can see it and then see that I’ve been coughing up blood for the, for the three days or whatever, they could phone me and say well, do you want this appointment, we have got this going this free? You know.’ Line 582-590 Interview 397 (Female)

When asked if they would feel comfortable sharing data with HCP’s and CF teams participants responded positively. For this participant it was important to be open and honest with the team so they could receive the best care possible.

> ‘I think it’s much better for me to be open and honest with them because their job is – they’re genuinely trying to help me so the more information I can give them then hopefully the better they can help me.’ Line 986-988 Interview 401 (Female)

A tool for promoting a collaborative approach to healthcare

The symptom-monitoring survey was a tool, which captured changes of symptoms on a daily basis. The survey was almost a vehicle, which encouraged and aided self-management of CF and also promoted discussion during clinical appointments.

> ‘Yes and I think it's useful for them as well to, I know often before clinic they will look on the health hub and see how the nebuliser has been going and then if there is any like dips or anything we can talk through them so it's always useful to.’ Lines 345-348 Interview 400 (Female)

> ‘I’m used to tracking how I feel and knowing when I need to call the nurses and stuff like that so in terms of that it was just a tool to help me write it down really and track it that way which was quite handy for me so- and like I say it helped because it was at the same time’ Line 506- 509 Interview 392 (Male)

By sharing their data some participants felt they had the opportunity to feel more empowered to make decisions with their HCP about their health.

> ‘if I was to have access to this particular tool then it probably would mean that and also because obviously the Physios at my hospital can obviously pick it up as well that even if I only looked at it every three months when I went for a hospital appointment, we sat and looked at the charts together, because my adherence is much better than it was so hopefully I won’t have those huge problems with, you know, awful symptoms’ Line 946-953 Interview 401 (Female)

The quote below highlights how much this participant valued the opportunity to discuss their symptoms and condition, as this really helped their understanding. This demonstrates that the data collected through symptom tracking could help some patients further understand their complex condition with the support of HCP’s.

> ‘That’s right, yes, anything that anybody else has an opinion on, I’m not the smartest person so it helps when somebody says something to me and discusses things with me so that’s what I prefer really’ Line 547-549 Interview 392 (Male)

However, some participants had experienced clinicians who may have questioned or queried the symptoms reported during previous consultations. Therefore, symptom charts and tracked symptom data can be taken into appointments to facilitate useful discussion between patients and clinicians.

> ‘when I first moved to adults it was because one of the doctors in children’s wouldn’t believe what I saying kind of thing, so it kind of provides that evidence for it in some ways, so like they can, its easy to do it for that so its like a back up kind of thing, for what you’re saying if that makes sense.’ Line 372-376 Interview 391 (Male)

For some participants the symptom tracking was so useful during the study they discussed the possible further applications such as the development of an app which would allow patients to view symptoms (e.g. pain) and step count.

> ‘And things like that, so I think at the minute obviously looking at my phone and looking at my stepper that way, then it would be nice to have an app to like to correspond, you know with the pain and things like that, just to and then I know obviously if I’ve overdone it by my stepping on me phone’ Lines 545-549 Interview 397 (Female)

Theme 4 – Understanding the complexity of symptoms and adherence

This theme highlights the complexity of symptoms and the relationship of symptoms and adherence. Within this theme there are four subthemes; ‘External factors’, ‘Relationships between symptoms’, ‘The complex nature of pain’ and ‘Symptoms that predict exacerbations’.

External Factors

The interviews revealed that the relationships between adherence and symptoms are complex, different for all patients and affected by a range of different external factors.

Participants cited a range of different factors, which influenced their symptoms and adherence behaviour over the course of the study. One of the participants discussed the impact of the season/weather as one of these factors.

> ‘I think that was in a kind of, you know, winter, the peak of winter, which is generally when I get coughs and things because, obviously, 99% of the time I get it as well, having CF, so you always pick something up’. Line 172-175 Interview 398 (Male)

The participant below felt adherence was different at weekend due to a change in routine and in particular, wake up time which makes it more difficult to take all of the prescribed medication on particular days.

> ‘Sometimes weekends are harder because I’m not up at six and I’m not doing the things I would normally do- on a daily basis so that throws my body out of sync with all the medicine that I take so then it just becomes a bit harder to get mas much up as I normally would’ Lines 381-388 Interview 392 (Male)

Furthermore, there is also evidence to suggest that the change in context can impact upon the symptoms experienced by the participant. As suggested in the quote below the participant experiences less tiredness at the weekend when they have the opportunity to sleep more.

> ‘Yes, so like on the weekends I normally… I’m not as tired because I’m sleeping a lot more’. Line 256-257 Interview 391 (Male)

Change of routine was highlighted as an important factor by a number of participants. The participant below spoke of how having time off work due to the COVID pandemic caused disruption to her routine and as a result she found it more difficult to adhere, despite having more time than she usually would.

> ‘P: Yes. So I am obviously not working at the minute so it sounds silly but I have still got into this routine in the day where going to work was easier because I would have to get up and I would have to do it
>
> Q: Yes.
>
> P: and then go to work whereas now I can get up as late a day, the other day I did walk into the Kitchen and it was like, oh it's because I set it up the night before just so it's like as a reminder’ Lines 69-75 Interview 400 (Female)

On this occasion routine and the support of a spouse is a facilitator which helps this participant take his treatment as prescribed.

> ‘P: No, no by my wife, she reminds me if I have forgot to do my nebuliser.
>
> Q. Yes, oh that’s a help.
>
> P: I have a little daily routine anyway’ Lines 179-183 Interview 396 (Male)

Relationships between symptoms

For many of the participants there was a discussion relating to the overlap of symptoms and how a set of symptoms will influence each other and/or present together depending on the health of the patient.

> ‘I’ve got quite a high cough and then it matches with like joint pains, I know that’s kind of like when I’ve been doing fitness at college or something because that’s a killer’ Line 164-166 Interview 391 (Male)

The participant below spoke of occasions where symptoms presented together and other times where symptoms seemed separate.

> ‘I mean I can definitely see periods of time where a lot of the symptoms seem to overlap each other and then there’s obviously different times where they almost seem sort of disembodied where you get one symptom and maybe not another’ Line 663-663 Interview 401 (Female)

Additionally, participants spoke of symptoms that can impact on the development of further symptoms or perhaps even present as a cluster. For example a wheeze causing a cough as demonstrated in the quote below.

> ‘Where I’ve had a wheeze and that’s caused a bit of a cough as you’d expect it would but it wasn’t something I really

> suffered with until about a year or so ago'. Lines 232-234 Interview 392 (Male)

The complexity of the symptoms of CF is something that patients are continually attempting to understand, the participant below talked about how a symptom can be a predictor of another issue for example a wheeze predicting underlying mucus. This suggests that spending time unpicking these complex relationships could help patients be more in tune with their symptoms and what this means for them and their condition.

> 'Bit of a weird one so for me if I've got a day where I was feeling wheezy or tight chested or both it made me realise that there was some underlying mucus that I hadn't been able to shift for whatever reason. Some days it was because I felt quite dry so I was quite surprised when I was kind of wheezy and a bit tight chested but then later that day or even the next day I suddenly would be very, very productive'. Lines 70-74 Interview 401 (Female)

Participants spoke of the changes in symptoms from one day to the next, which became clear as a result of the symptom tracking survey. For this participant it was the mucus in particularly that could change on a daily basis.

> 'Yes it does change quite often (amount of mucus) because if you bring the lot up one day, the next you don't bring a lot up because you have already kind of cleared it the day before' Line 614-616 Interview 390 (Male)

Although not all participants were able to identify clear relationships between different symptoms of their condition. Participant 394 demonstrates this, however he acknowledges the possibility of using symptom patterning to draw such conclusions.

> 'it's a good thing actually, yes because then you're more likely to look, notice changes and I suppose if you're, I

> didn't see any parallels between sort of days I'm tired and days I'm sort of more productive in coughing up mucus. I suppose without thinking about those details and looking back on how you'd been that particular day you wouldn't spot patterns, that saying I didn't spot any patterns.' Line 65-70 Interview 394 (Male)

The complex nature of pain

Pain was a specific symptom which appeared to have raised complexities of its own within the self-monitoring study. When discussed during the interviews it was clear that participants had different perceptions and experiences of how pain may be related to their condition.

For some participants the source of pain was clearly linked to CF, for example the participant below suggested the pain came directly from their lungs.

> 'Its like a stabbing pain, mainly mines in my left side like in my rib, like where me lung is a bit like directly where my rib is'. Line 416-416 Interview

Additionally, for some pain was linked to their condition but because of a secondary complication which impacted upon a different area of the body. For example the participant below refers to pain as a result of a feeding tube.

> 'Yes because I was suffering all this pain and then like within minutes they took this tube out and the pain was gone and I had been whinging and complaining about it for months and months and months.' Lines 341-343 Interview 399 (Female)

Whereas for others pain was not overtly linked to their symptoms of CF, as demonstrated in the quote below.

> ‘I think it was pain possible because it was kind of like, that’s a bit- I don’t really get pain as such but it was kind of like does that include headaches’ Lines 106-108 interview 389 (Male)

Symptoms that predict exacerbation

The predictors in terms of symptoms that presented prior to an infection differed for each participant. For some it was closely related to respiratory symptoms such as mucus and for others the symptoms were more general such as tiredness.

> ‘my nose starts to run bad, I start bringing up loads of mucus, and then I feel tired and run down as if I’ve got the flu. That’s the sign I get, and then I, and then my breathing gets bad.’ Lines 76-79 Interview 393 (Male)

> 'If I am starting to get more tired and heavier breathing without doing anything, that usually means there’s something going on.’ Line 412-413 Interview 390 (Male)

Although the symptoms were different for all participants, one thing participants had in common was that they were aware of oncoming infections due to the change in symptom patterns. For the participant below experiencing cold-like symptoms and hunger pangs can be an indication of a forthcoming exacerbation.

> ‘Well you get the other symptoms of getting a cold, you know, I always know if I'm going to get a cold I feel very hungry in advance and I want to eat loads of food all the time and then I get symptoms after that, I suppose it's the body saying fatten yourself up.’ Lines 317-320 Interview 394 (Male)

Whereas coughing through the night is a symptom, which often predicts an exacerbation in the patient below.

> ‘Yes, yes, when I’ve been coughing like through the night and then my chest gets sore from coughing a lot, and then because that makes me cough more it’s a bit

> of vicious circle sort of thing sometimes.' Line 109-110 Interview 395 (Female)

Although the majority of participants were able to recognise the symptoms which for them are a predictor of an exacerbation, the predictors differed greatly from person to person. This highlights once again the differences between each patient and the need for individualised care plans.

Theme 5- Why I take my treatment?

The subthemes within this section include: reasons for good adherence and barriers to adherence. Within this theme there are two subthemes, firstly, 'reasons for good adherence' participants speak of the factors which encourage and promote good adherence. The second subtheme is 'barriers to adherence' within this subtheme participants refer to the factors which prevent good levels of adherence.

Reasons for good adherence

Participants cited different factors which influenced their adherence to treatment. For the participant below, good adherence to them related to the concept of being healthy.

> 'its just to keep you healthy really, as healthy as you can be' Line 159-160 Interview 392 (Male)

Similarly this participant spoke about how they chose to take their treatment everyday so they can avoid being treated in hospital.

> 'I just don't want to experience being ill and ending up in hospital so that's a reason to do my drugs everyday' Line 119-120 Interview 393 (Male)

Others spoke about the difference between the long-term and short-term benefits of adherence. Although the perceived benefits may not be immediate there was an obvious long-term gain of adhering to nebuliser treatments for some patients.

> ‘So they work- they do work and long term benefits to having them is a lot- is more than just the short term benefit so they will work slowly over time I think is the best way of looking at it’ Line 459-461 Interview 392 (Male)

It was acknowledged by participants that sometimes good levels of adherence can be difficult and some days are especially hard and frustrating in comparison to others.

> ‘I do it every day, every day, I get… sometimes I get fed up with doing it, and sometimes I say to my wife, ‘I’m pissed off with this, I don’t know why I bother’, and I say that to them at the hospital, but then it’s like, you know, being not, being punched in the mouth, falling down, and then ‘oh I can’t be bothered to get up and fight’. I get up at, and you know, I think ‘oh [unclear word 00:28:27], oh no, no, it’s no good, I’ve got to get up and have another go’, so you just put it to the back of your mind, you get up and start doing it again.’ Lines 383-390 Interview 393 (Male)

The influence of the hospital staff and receiving motivation from the HCP’s was a factor that encouraged the participant below the take their treatment is prescribed.

> ‘When I talk to them at the hospital about it they say ‘well you know, because youre doing the drugs, that’s whats keeping you well, we only wish all our patients would’ Lines 133-135 Interview 393 (Male)

Barriers to adherence

There were also a number of barriers cited in the interviews with participants, which suggest reasons that may prevent them from taking their nebuliser as prescribed.

One barrier identified in the interviews was specific symptoms, which can make it more difficult to adhere. Symptoms such as

cough and tiredness were specifically identified as evidenced below.

> ‘when I’ve got a really bad cough and I’m coughing all of the time, which isn’t very often, but it puts me off doing my nebuliser because I’m coughing more when I’m already sore in my chest’ Line 21-23 Interview 395 (Female)

Some participants made it clear that it is very unusual for them to miss their treatment but if they are feeling particularly tired there may be occasions when they are missed.

> ‘the only time I might have a problem doing it is if I go out for the day and then when I come home at night, I’m too tired and I don’t bother’ Line 12-124 Interview 393 (Male)

Finally, there was evidence in the interviews of participants bargaining when it came to missing treatments, for the participant below it was not an option for a specific type of nebuliser treatment, dornase alpha (DNase).

> ‘sometimes I might miss the, I never miss DNAse but the other one, maybe every so often if I’m really tired and at work. But it depends how busy it is at work to how tired I get really’ Line 24-26 Interview 395 (Female)

6.5 Discussion

This qualitative study aimed to explore the feasibility and perceived value of using self-monitoring/daily diaries from the participant’s perspective and investigate their ability to interpret feedback data on the relationship between adherence and symptoms.

There was a total of five themes that were identified; ‘The feasibility of symptom tracking’, ‘The impact of symptom tracking’, ‘Clinical

applications', 'Understanding the complexity of symptoms and adherence' and finally 'Why I take my treatment'.

This qualitative study addressed two research questions, the first being how valuable did participants find symptom tracking using daily diaries (research question 8 of the thesis)? and how did participants understand the relationship between their treatment adherence and symptoms of CF (research question 9 of the thesis)?

In terms of the feasibility of symptom monitoring participants reported that there could be changes made to the technology which could improve their experience, this includes have the opportunity to look at their responses retrospectively to review how they have been rating symptoms and make comparisons. Participants liked that their survey was completed online which gave them the flexibility to complete this anytime, anywhere with the requirement that they had their phone and access to the internet. Furthermore, the email reminders were valued by participants and helped prompt them to complete their daily survey.

Prior to the pilot study (reported in chapter 5) it was a concern that daily symptom tracking would not feasible for participants and a potential additional burden, however on the whole findings were positive which provided a strong rationale for the longer tracking period. The findings of this contrast with Sarafaraz et al.'s (2010) study which reported poor levels of compliance from a six-month study which asked patients with CF to measure symptoms and spirometer readings at home. This could suggest that the easily accessible and short survey sent to participants each day in the current study was perhaps more acceptable than the at-home spirometer kit used to test lung function and also the use of an additional device (participants were not able to track symptoms on their phone). Although Sarafaraz et al. (2010) suggest that it is not clear exactly why there was poor engagement and high levels of attrition associated with the study, out of the 51 participants who started the study 19 completed it with an average of 63.9% of data

recorded. Therefore rather than low levels of data reported it could be that symptom tracking was not useful for some of the participants which is why they decided to withdraw.

There are a number of clinical applications associated with symptom tracking which have been reported prior to this study (Proudfoot et al., 2014). Participants in the current study suggested that one of the applications of symptom tracking is that the data and graphs produced can be shared with healthcare professionals and used as a point of discussion at appointments. Additionally, participants suggested that the data could be used within consultations as proof that they were experiencing specific symptoms, even if this may not be clear upon assessment. A recently published paper by Lumley et al. (2022), found that participants felt objective adherence data could be used as proof of adherence within consultations with Health Care Professional's (HCP's). This could suggest that patients can feel as though their reports of adherence and also symptoms are not believed and could be a lack of trust between the HCP and patient. Suggesting that data of both kinds could be used within consultations to provide the patient with a useful tool and possibly help develop trust in the health professional-patient relationship.

Some participants attributed good levels of adherence to support from healthcare professionals who helped to keep them motivated. Drabble et al. (2020) found in a complex intervention with CF patients (the CFHealthHub) that having the opportunity to talk about their adherence with an interventionist helped keep them motivated. An Italian study reported similar findings that participants who had a good relationship with HCP's reported this to be the most important facilitator of good adherence (Colombo et al., 2018). These findings highlight the importance of patients receiving support from specialised healthcare professionals, and also the openness of participants in relation to sharing data with HCP's and using this information to support consultations.

In terms of the second research question ‘How do participants understand the relationship between treatment adherence and symptoms of CF?’, participants reported unique patterns in symptoms, however all participants were aware of oncoming exacerbations through the recognition of changes in their condition. A number of participants reported that self monitoring helped them to better their understanding of their condition and provide an opportunity to think about how they are feeling (as discussed within theme 2). These findings support previous findings in the area, such as the work of Calthorpe et al. (2020) who suggested that self-monitoring can help patients with CF better understand and manage their own condition. In addition to this a small trial in Australia piloted the use of an app to monitor symptoms in patients with CF in an attempt to increase their self-efficacy and improve medication adherence and disease self-management. It was concluded that the use of the app was feasible and aided the development of self-efficacy in adults and adolescents with CF. However it is important to note that the findings of this study are limited due to a small sample size of 20 participants.

Key symptoms were recognised as barriers preventing good levels of adherence, this aids understanding of quantitative data which revealed that certain symptoms can influence adherence behaviours in specific individuals. For example cough, for some coughing was a barrier and the idea that the nebuliser could increase levels of coughing (in breaking down the mucus) was something which prevented adherence. Tiredness was also reported as a barrier, this was also found in the work of Drabble et al. (2019) who reported that good adherers who do not normally miss taking their nebuliser treatment can experience lapses when tired. Santuzzi et al. (2020) also recruited patients with CF but focused on adherence to general and respiratory exercises, it was reported the main barriers included tiredness and motivation.

Previous literature has reported that competing life demands (Hogan et al., 2015) and busy periods (Dzuiban et al., 2010) are

barriers which prevent participants from being adherent to medication. Changes to routine were also reported as a barrier to adherence in the current study, with some participants reporting that specifically during lockdown when they were unable to work, doses of treatment were more frequently missed. This supports the work of Jones et al. (2015) and Hoo et al. (2019b) who reported the importance of habit formation and routine. Hoo et al. (2019b) found that those with stronger habit formation were higher adherers, perhaps due to having a stronger routine, this is something which could have been disrupted during the pandemic. Whereas poor adherers can often rely on becoming unwell as a prompt to take their nebuliser (Hoo et al. 2017). Often competing life demands such as holidays, social life and travel have previously been reported as a barrier to adherence (Arden et al. 2019) which could all be linked to change is usual routine and habit.

Midão et al. (2022) conducted a study around the impact of medication adherence during the COVID pandemic, using an online study with 476 participants in Portugal. Midão et al. (2022) suggested that poor medication adherence was an important issue prior to the pandemic, however the pandemic exacerbated this issue in participants (5.9%) who already had lower levels of medication adherence. For some participants (8.2%) the pandemic improve their levels of medication adherence. Although habit was not reported as a specific barrier to adherence, other changes of habit were cited such as healthy lifestyle habits in order to control associated fear and danger of the pandemic.

As reported within the medical field (Rubin, 2015), some nebuliser treatments such as hypertonic saline can in-fact increase the amount of coughing a patient will experience, however the cough will be more productive and efficient which helps break down the build up of mucus in the lungs. According to Henke and Ratjen (2007) side effects are rare, less common side effects include respiratory symptoms such as: increased cough, dyspnea (tightening of the chest), rhinitis and sinusitis. However the findings

from other drug trials differ, Dentice et al. (2016) found that hypertonic saline reduced the severity of exacerbation symptoms in a group of patients who were hospitalised due to symptoms of CF. The current study can build upon this and helps bridge the knowledge gap between how side effects of treatment can impact on adherence to treatment, as some participants who experienced the increased cough reported that this did in fact impact upon medication adherence as some felt this could increase a symptom (cough) that they were already experiencing. This could be explained using the Necessity Concerns Framework (Horne et al.,1999), as experiencing severe side-effects could impact upon the concerns in relation to treatment taking and cause patients to lower adherence or not adhere at all.

In the current study participants were aware that although adhering to treatment may not have any immediate impact upon symptoms there are long-term benefits of adhering to treatments as prescribed. Within theme 5: 'Why I take my treatment' participants suggested that motivation from HCP, the concept of being healthy/healthier and understanding both the short term and long term implications encourage adherence. In relation to the NCF (Horne and Weinman, 1999) it could be that long-term impacts are motivating some participants to adhere because of the associated benefits of this. Therefore perhaps the long term rewards have a different level of motivational value compared to short term goals for these participants.

Hogan et al. (2015) reported in an Australian study that one of the barriers to adherence was the perceived lack of importance of the nebuliser treatments. Both the current findings and those of Hogan et al. (2015) provide support for the Necessity Concerns Framework which would suggest that those who chose to adhere to medication have stronger perceptions regarding the necessity of the treatment and fewer concerns relating to their treatment (e.g. side effects). Furthermore, this relates to the COM-B (Michie et al., 2011) for example if patients are able to detect differences in their symptoms

as a result of adhering, this would sit within the reflective motivation aspect of the framework.

Participants highlighted how one of the benefits of self monitoring was that it provided them with the opportunity to sit and think about the symptoms they were experiencing on a specific day and why changes could be occurring. One of the participants described themselves as being ‘reactive’ prior to symptom tracking, responding to their condition depending on how they felt each day, rather than being consistent with care and treatments. This change in approach highlights the possible benefits and clinical applications of tracking symptoms. However, because the results showed that symptom tracking could result in some patients feeling more aware about their symptoms in a negative way, it is important that patients have autonomy about whether they use symptom tracking in their care plan. For some thinking about their condition each day may not be something which is beneficial.

In relation to reading the graphs and observing the relationships presented, there were mixed findings. Some participants were able to understand the graphs and identify important pieces of information such as periods of increased symptoms however, others were less confident in their ability to interpret the graphs correctly and required support with this. It was not always easy for participants to notice the relationship between symptoms and adherence, however one of the participants was able to clearly identify where on the graph they were experiencing an infection and the associated symptoms. One implication of this could be that it should not be assumed that patients can understand data presented to them and there should be an option of HCP support to aid patients understand data they are presented with. This understanding may help participants to better monitor their condition and also help them calibrate the visual analogue scale scoring system.

Study strengths and limitations

The methodology used within this study provided participants with the opportunity to discuss their own symptom and treatment data, which had been collected over a four-month period and presented back to them in the form of graphs. This is the first study to have employed this methodology to explore how individuals with CF understand this complex relationship. This qualitative research design enabled more in-depth exploration of the quantitative data obtained in study 2.

There are however limitations of the study, for example all of the patients who were recruited into the symptom tracking period were invited to an interview, however an interview was not arranged with all participants. Those who did not participate could have had different experiences to those individuals who did take part in the interviews. For example, they may have had more negative experiences of symptom tracking, which could have created a potential sample bias in the study.

However, it is important to acknowledge that this invite was sent in March 2020. During this time England entered the first national lockdown and the CF patients were included in the 'clinically extremely vulnerable' group and initially told not to leave their house for at least 12 weeks, which was ultimately extended (Cystic Fibrosis Trust, 2021. As this was such an unsettled period of time for the participants it was important to be sensitive when contacting participants to invite them to an interview, therefore participants were sent just one invite to the interview and one follow-up email.

Following on from this, due to the pandemic it was not possible to collect data in person and interviews were conducted online. Therefore it can be difficult to build rapport with participants and can limit the depth of the interview (Irvine et al., 2013). Furthermore, because this was early on in the pandemic, perhaps some participants were less familiar with using video-call platforms and this was a factor which lead to them not taking part in the interview. However Keen et al. (2022) argue that using technology can increase accessibility- participants can be in the comfort of their

home and do not need to consider travel arrangements. Ultimately there was no choice for this study.

Study implications

The findings of the current study support data from study 2 and reveal that the four-month symptom-tracking period was an acceptable timeframe for this patient group and that it was feasible for people to monitor there symptoms using the software and technology used in the study. There are a number of clinical applications based on the findings of the study.

For some participants the act of self-monitoring had been useful in that it had prompted them to reflect on their condition and how they had felt that day. However there was data which suggested that for some people symptom monitoring could be an unhelpful reminder of symptoms and the impacts of CF.

In terms of the usefulness of feedback data the findings suggest that the graphs and statistical analyses alone might not be enough to help further their understanding of the relationship between adherence and symptoms for some participants. Which highlights the importance of using the graphs in clinical practice as an additional source of information to prompt discussion, as for some of the participants recruited into the study looking at the graphs alone was not as helpful as using them in discussion.

The participants in the current study were monitoring adherence via CFHH until the closure of this in October 2024. Although it would no longer be possible to add the addition of a symptom tracking option to the smartphone application of CFHH, the findings of this study suggest that for some participants using a similar tool could be useful. However, if there is the intention to use this data to help patients identify the impact adherence has on their symptoms (and promote future adherence) then clinician or perhaps Artificial Intelligence (AI) input may be required to help patients fully understand this relationship. As highlighted in the work of Majekodunmi (2024) although extensive testing and training would

be required, there are a number of possible applications of AI in primary care including triaging patients and possibly the detection of disease through the use modelling. Therefore it could be possible to use AI to help explain the trends in the data or graphs and summarise the findings to participants in a way which is useful and understandable.

7.6 Conclusion

To conclude the participants recruited into this study had previously been asked to monitor their symptoms of CF for four months. This qualitative data-prompted interview was an opportunity to discuss their experience of symptom tracking and talk through their feedback adherence and symptom data with the researcher.

The majority of the participants in the study found the symptom-tracking experience to be one of merit which provided them with useful materials that could be shared with healthcare professionals both to help inform decisions made relating to their treatment and also to provide professionals with an insight into their symptoms in the months between reviews. However, the findings from this study highlight individual differences in relation to the perceived benefits of self monitoring and also the patients ability to understand feedback graphs because of the complexity of data. This identifies the need for additional support being provided to patients who do want to see their feedback data to help these individuals understand the complex relationships between their symptoms and adherence data. There are areas that require improvement to maximise the feasibility of symptom monitoring for patients, specifically related to the development of a user-friendly system and using appropriate scoring systems. It is also important to investigate the feasibility and acceptability of using symptom tracking in clinical practice with Healthcare Professionals.

7.7 Next steps

The next chapters of the thesis will adopt qualitative research methods to explore the perceived feasibility and benefits of

symptom tracking from the perspective of clinicians who care for people with CF.

Chapter 7- Understanding Healthcare Professional's (HCP's) perceptions of the factors which influence adherence to nebuliser treatments in patients with Cystic Fibrosis

7.1 Chapter Overview

This study aimed to further understand Healthcare Professionals' (HCP) perception of the factors which influence adherence to nebuliser treatment in Cystic Fibrosis (CF) and also to investigate how useful symptom tracking could be in clinical practice. This study utilised previous findings from studies 2 and 3 of this thesis to facilitate discussion with HCP's, in particularly around the relationship between symptoms and adherence and the feasibility of symptom tracking. This study adopted a qualitative design to ensure the findings and the HCPs' experiences could be discussed in depth. This study is the final study chapter of this thesis.

7.2 Introduction

Healthcare Professionals (HCP's) play a vital role in the support of medication adherence in patients with long term conditions. There has been a shift over time in the way medication adherence is discussed with patients and a move towards a more collaborative approach to facilitate honest discussions (Koplin et al., 2024). According to Schneider and Burnier (2023) adherence is a collaborative effort between two parities: the patient and the healthcare provider.

Something which has supported this collaborative approach in the care for those with Cystic Fibrosis (CF) is the CFHealthHub (CFHH)(Wildman et al., 2021). Data from the CFHH has allowed and encouraged objective adherence data to be used in clinical appointments (permitting the patient provides consent) (Wildman et al., 2021). However, although the programme allowed the monitoring of objective nebuliser adherence in real time there was no function related to symptom tracking or monitoring for both the patient and HCP to use. It is important to note that the CFHH platform was closed in October 2024 due to lack of NHS funding.

Calthorpe et al. (2020) reported that 98% of HCPs recruited into their study reported adherence is commonly discussed in clinical practice, even when facing time constraints. The same study also recruited patients living with CF and found that 85% of patients felt comfortable talking honestly with their team about adherence (Calthorpe, 2020). Arden et al. (2019) also reported that a number of patients were happy to have their adherence monitored in real-time by HCP's. These findings suggest that the majority of patients and professionals are happy to discuss adherence to CF treatments. An Italian study conducted in 2018 found that a good relationship between the patient and HCP is one of the most important facilitators relating to good adherence in patients with CF (Colombo et al., 2018). The importance of this relationship was also highlighted in the work of Sawicki et al. (2015).

However, evidence from qualitative data with 12 patients with CF (Dawson et al., 2023) has found that often patients with CF feel that discussions around adherence can be 'infantilising' which can make talking about low levels of adherence difficult. Dawson et al. (2023) concluded that a culture shift in CF care is required and a more open and non-judgemental approach should be adopted by HCP's. Research has found that HCP's and patient's do not always share the same opinion relating to how adherence such be approached and strategies to use, which can add further complications (Calthorpe et al., 2020). Calthorpe et al. (2020) concluded that strategies found to be valued more by HCP's include the use of technology and short-term goal setting, whereas patients valued education and the importance of being well informed.

Both HCP's and patients living with CF reported that one of the barriers to adherence to nebuliser treatment is beliefs about the necessity of the treatment i.e. that adherence is not a necessity (Arden et al., 2021; Hoo et al.,2017). Currently, there is a lack of research exploring HCP's understanding of the factors which influence CF patients adherence to nebuliser treatment and the

perceived impact treatment can have on CF symptoms, and this will be explored in the current study.

There is also a paucity of information about how useful (e.g. benefits and problems) HCP's feel it would be to use patients' health data (e.g. adherence and symptom experience) with them in an attempt to help them better understand their condition, the relationships between symptoms and treatment-taking and to promote adherence. A patient's adherence and symptom data could be used to prompt discussion between HCP's and patients to help both parties better understand the individual's experience of CF and highlight the potential benefits of treatment (the impact adherence has on symptoms). This could have similar effects as Data Prompted Interviews, according to Kwasnicka et al. (2015) there are three main aims of DPI's which include: encouraging discussion through the use of data-driven prompts, to explore contrasts between the participant's experience and the data and to discuss participants opinion of their personal data.

Lumley et al. (2022) concluded that using objective adherence data in discussion between HCP's and patients living with CF can be seen by patients as 'proof of adherence' and can be used to facilitate honest and open discussion. Furthermore, Sharp et al. (2021) explored the use of smart phone applications to remotely monitor patients and reported that this can help contribute towards shared decision-making whilst providing HCP's with enhanced information about patients' conditions. This could promote the use of patient centred care which could be useful to encourage the cultural shift referred to in the work of Dawson et al. (2023) in which patients struggling with adherence would not be viewed as disobeying guidance from authority figures (HCP's). However the benefits and limitations of this approach in the management of a long term condition should be carefully considered because there are some potential negative impacts.

In other conditions such as rheumatoid arthritis (RA) the use of symptom tracking has been reported to provoke beneficial

discussion in clinical appointments for both HCP's and patients, to help improve this relationship and aid decision making (Skyrme et al., 2024). However, some concerns were raised by HCP's in the study about patients struggling to record data, which could limit the usefulness of the discussions. Laverty et al. (2022) looked at the use of symptom tracking in people living with RA and concluded that ultimately HCP's have the power to decide when or when not data is used and whilst this can be selected carefully to fit with their narratives around symptoms and treatment, asking patients to collect data that is then not discussed could be creating additional unnecessary burden for patients. As previously discussed within study 3 of this thesis symptom tracking can also increase the amount of time patients are thinking about their condition which is not always a positive thing. Therefore it is important to acknowledge that there may be some challenges associated with the tool. Further work is required to understand the perceived benefits and disadvantages of using symptom tracking and feedback data for the management of CF in both patients and healthcare professionals.

In addition to considering the benefits and challenges of symptom tracking, both for patients and healthcare professionals, the actual feasibility of using this approach in practice and incorporating symptom monitoring and feedback into CF management needs to be explored. Keyworth et al. (2020) conducted a systematic review of 36 systematic reviews that looked at the barriers and enablers to HCP's providing behaviour change interventions during clinical appointments. In total there were four themes reported: perceptions of the knowledge or skills needed to support behaviour change with patients, perceptions of the healthcare professional role, beliefs about resources and support needed and healthcare professionals own behaviour. An earlier study conducted by Keyworth et al. (2019) also focusing on the use of behaviour change interventions in healthcare professionals found that not understanding the complex mechanisms of the intervention can be a barrier to delivery.

Girling et al. (2024) found some of the initial concerns about using data from CFHH in clinical appointments included the lack of support from other team members and not being confident in interpreting data. As these concerns are relating to using data in clinical appointments it could be that some HCP's have similar feelings in relation to using symptom tracking data in clinical appointments with CF patients. However, to date, there is a lack of information on how HCP's feel about the feasibility of using self monitoring and adherence data with their patients in CF care.

Rationale and Aims

This study aimed to explore health professionals' perceptions of the factors that influence adherence to CF treatment in their patients, how they feel treatment can benefit patients' symptoms, and the perceived feasibility and usefulness of using adherence and symptom data as part of clinical management of CF.

The study had three specific research questions: To further understand HCP's perception of the factors which influence adherence to nebuliser treatment in CF patients and their understanding of how treatment influences symptom experience and management (RQ 10) How feasible is it to use self-monitoring data alongside adherence data within the management CF (RQ 11)? How useful is it to use self-monitoring data alongside adherence data within the management CF (RQ 12)?

7.3 Method

7.3.1 Recruitment

Following ethical approval clinical staff members working at Cystic Fibrosis centres (recruited into the CFHealthHub programme) were sent an email invitation to take part in the study from a lead research physiotherapist, who at that time worked on the CFHealthHub programme. The invitation included details of the study and also the Participant Information Sheet (PIS). Those interested in taking part in the study were asked to contact the lead

researcher for the study (RM) directly. Following this snowball sampling was used, so participants were asked to share the study information with colleagues and those interested were asked to contact the lead researcher for the study (RM).

Participants were recruited from three Cystic Fibrosis centres across the UK (Newcastle, Oxford and Plymouth), where they worked as Healthcare Professionals. All of the participants were recruited from sites which were all part of the CFHealthHub trial i.e. they were routinely using charts of objective adherence data inform conversations with their patients about adherence

7.3.2 Participants

In total 8 participants agreed to participate in this study, table 22 below provides information relating to job role and length of time people had worked in roles for. Job roles include a diverse range including: a dietitian, physiotherapists, nurses and consultants. All but two of the professionals had over 10 years of experience in their role.

Table 22.
Participants pseudonym, job role and reported time in role

Pseudonym	Role	Reported time in role
Harry	CF Specialist Nurse (Band 7)	Over 10 years
Sandra	CF Physiotherapist	Around 18 years
Jamie	Consultant physician at a CF centre	Around 30 years
Ben	Respiratory Physiotherapist (Band 6)	6 years in respiratory 7 years in NHS
Gabriella	CF nurse	6 months in CF role

Idris	Consultant physician at a CF centre	Around 20 years
Ria	CF physiotherapist and interventionist	Over 10 years
Eva	CF dietitian	Over 10 years

To protect the anonymity of participants in a small population the centre/area participants were associated with has not been disclosed. Furthermore, quotes provided in the analysis section will not be associated with the pseudonym to further guard against their identity being revealed.

7.3.3 Inclusion/Exclusion criteria

The inclusion criteria for the study was that participants work for the NHS, participants work with patients with Cystic Fibrosis, spoke English and be aged 18 or over.

7.3.4 Procedure

Participants who contacted the lead researcher (RM) expressing an interested in participating in the study were re-sent the PIS and the consent form (to see participant facing documents for this study please see appendix M). Participants completed the consent form using their computer or signed and scanned if printing was available and returned via email, no consent forms were physically transferred. RM was responsible for the consent procedure. Participants were provided with the opportunity to ask questions before taking part in the study.

The interview was arranged at a time convenient for the participants and an email containing a Microsoft Teams link was sent to their NHS email address. All of the interviews were hosted via Teams. All of the interviews were conducted in usual working hours (between 9am-5pm).

Following the interview participants were sent a debrief form via email (to see participant facing documents for this study please see appendix M). Participants were given 7 days to withdraw their data if they wished to do so after participation.

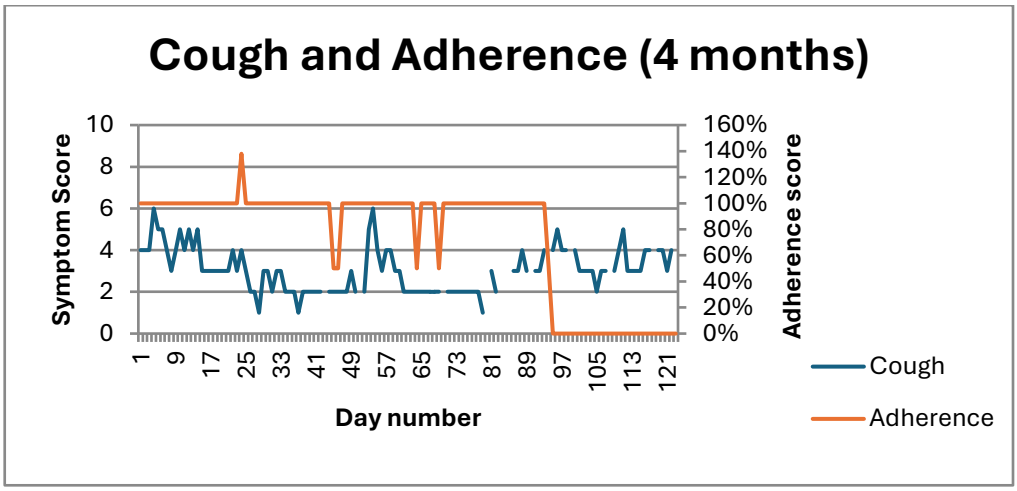
7.3.5 Interviews

During the interview participants were asked about their role and experience of working with patients with CF and questions which addressed the three research questions. Such as: ‘What factors do you think influence adherence in your CF patients?’ ‘Do your patients notice improvements in their symptoms (i.e. cough, wheeze, difficulty breathing) as a result of taking their medication?’ ‘What symptoms do you think they will notice changes in as a result of taking their treatment?’ Some of the questions were informed by the COM-B model for example: ‘How do you feel about the idea of discussing patients’ symptom and adherence data with them?’ (motivation) ‘To what extent do you feel you have the skills, understanding and/or knowledge to be able to discuss symptom and adherence data with patients in a useful way?’ (Capability) ‘To what extent do you feel that you have the necessary resources and support to discuss symptom and adherence data with patients in a useful way?’ (Opportunity). The topic guide can be found in Appendix M.

Participants were also provided with a summary of the findings of study 2 and 3 from this thesis and asked to respond to a series of associated questions (see topic guide questions in block 2). These included questions such as ‘have the findings discussed influenced how you understand the impact treatment has on people’s experiences of symptoms associated with CF?’ and ‘do these findings support your experiences of working with patients with CF?’. Such questions helped to address RQ11 and RQ12 of the thesis. During this part of the interview participants were also presented with a graph to give them insight into the data that was collected and how this was presented to CF patients who were

recruited into previous studies within this thesis. Please see figure 15.

Figure 15.
An example of the charts used in participant interviews



7.3.6 Ethics

The study received ethical approval (ID: AA64736224) from Sheffield Hallam University Research Ethics Committee via CONVERIS. The study was then submitted via IRAS (IRAS ID: 342379) and received HRA approval. This study was REC exempt as it recruited NHS staff members, rather than patients. Pseudonyms are used to protect participants identity as much as possible and the information provided by participants is confidential. All participants provided informed consent and participants were able to withdraw data up to seven days after the study, however no participants withdrew their data.

7.3.7 Analysis

The data was transcribed and analysed using Braun and Clarke's (2006,2012, 2022) thematic analysis.

The thematic analysis was conducted using the following six-phase process (please see table 23).

Table 23.

Stages of analysis

Stage of analysis	Explanation	Who was involved?
Familiarisation with the data	Reading and rereading the data to encourage familiarity with the data before progressing to coding.	RM
Generation of initial codes	Key words and phrases which summarise small pieces of data were selected and documented on the transcripts.	RM whole data set MA and JP a sample of data
Searching for themes	In relation to the research questions, time was spent looking through the codes and grouping them into themes.	RM whole data set MA and JP a sample of data
Reviewing/ refinement the themes	In a group supervision meeting the themes were presented and discussed. Further refinement and	RM, MA and JP

	development was then required.	
Defining and naming of themes	There were some changes made to ensure that themes were clear.	RM
Producing the written report	The written report was produced by RM with the support from supervisors.	RM, MA and JP

Developing themes

When developing themes the research questions were used to ensure the analysis was relevant, RM spent time becoming emerged within the data and reviewing codes, all coding and analysis was conducted using pen and paper. Software was not used to aid the analysis. Codes were grouped together with similar or opposing codes. Once this process was completed the groups of codes were given working names and transferred into diagrams in a word document.

Visual mapping was used as an aid to help develop the themes as advised Braun and Clarke (2013) to help visual the connection between themes and also the data supporting the themes. During a supervision meeting this visual aid was explained and discussed, aspects were moved around and renamed to ensure the themes were as clear as possible and relevant when to answering the research questions.

Reflexivity

According to Olmos-Vega et al. (2023, p. 242) reflexivity is ‘a set of continuous, collaborative, and multifaceted practices through which researchers self-consciously critique, appraise, and evaluate how their subjectivity and context influence the research processes’.

The following reflexivity statement will be written in first person:

I have spent some time reflecting on my personal and interpersonal reflexivity prior to the data collection for this study, I was guided by the paper written by Olmos-Vega et al. (2023), which suggested asking yourself the following question 'how are our unique perspectives influencing the research?' and 'what relationships exist and how are they influencing the research and the people involved? What power dynamics are at play?'

I am not a healthcare professional and have no experience of working clinically with patients with CF. I do not know the participants recruited into this study. I understand that the healthcare professionals may feel this study is almost like this study is enquiring about how well they do their job, however I feel because I have a different job role (non clinical) and also do not work with these participants it may be a chance for them to be honest and open. Although, this could influence the way in which people discuss the subject and their experiences with me and I am not an expert in this area. In relation to the power dynamic I am aware of this and have/will consider this during data collection, however I feel the people I will interview have likely participated in research and conducted research prior to this and are leading experts in this area.

In terms of my perspective I have a good amount of prior knowledge about CF, however I may not be familiar with acronyms or hospital specific language. I have worked closely with a number of patients living with CF and feel I have an insight into how they live with the condition and the impact this has on their life. CF patients have referred to interactions with HCP's in my previous studies and conversation but not in a large amount of detail.

Something to note here is prior to the interviews taking place funding of the CFHealthHub was not extended by NHS England and therefore interventionists were informed that the programme would stop at the end of October 2024. I feel now this be

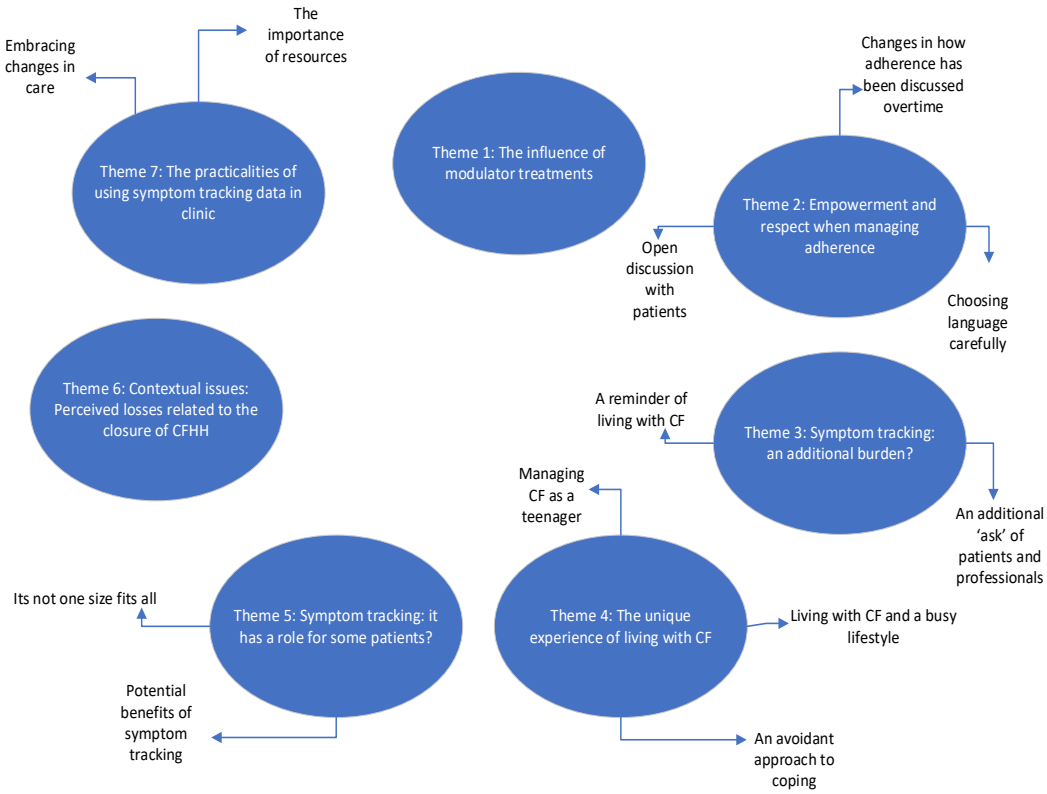
something which will be discussed in the interviews due to this important change in CF care.

Additional field notes were recorded after each interview using the guidance of Phillippi et al. (2018), the notes include observations around: demographics, participants, the interview and anything else of note. Please see Appendix N for a sample of the field notes.

7.4 Findings

A thematic analysis was conducted and identified seven themes: 'The influence of modulator treatments', 'Empowerment and respect when managing adherence', 'Symptom tracking an additional burden?' 'The unique experience of living with CF', 'HCP's understanding of the usefulness of symptom tracking', 'Contextual issues: the closure of CFHH and the practicalities of using symptom tracking data in clinic'. Each of the themes are discussed in more detail below. Please see figure 16 for a thematic summary.

Figure 16.
Thematic summary



Theme 1: The influence of modulator treatments

Healthcare professionals recruited into the study referred to changes in the care of CF specifically those linked to the development and prescribing of modulator treatments (please see treatment section in the introduction chapter for more information about modulator treatments). Not all patients can be prescribed with modulator treatments but for those who are the treatments often lead to better outcomes for those patients (Taylor Cousar et al., 2023), according to HCP's this contextual change had led to changes in adherence for other treatments and more recently changes in symptoms. This will be discussed with this theme.

HCP's spoke of how adherence for some patients has changed since taking modulator treatments. Some believed improvements in symptoms caused by modulator treatment had reduced the perceived need to take nebulisers for some CF patients. Previously patients could identify the link between symptom and adherence and now post-modulator treatments they cannot see this connection which has reduced the perceived need for treatment.

> 'A guide for them on when to do their nebulisers or to do their nebulisers because they felt their chest's bubbling or producing sputum and they could see the impact. A direct impact on doing their nebulisers there you know, either their sputum was less, they were able to move it more easily, they could breathe easier. And they had that direct correlation. With doing the nebulisers and how their chest felt and the modulators changed all of that.'

Some of the HCP's also discussed how for some patients' symptoms are now returning to taking nebuliser treatments after a period of low adherence when they have begun to notice an impact on symptoms such as wheeze and chest tightness.

‘we have had some patients that really dropped off their treatments (since taking modulators) and they’re starting to get unwell and then they've actually said I'm starting to notice that I've got a little bit more... my chest is a bit tighter again or I've got a bit of a cough’

It was suggested that even if patients had experienced new symptoms, this was not always enough to increase adherence to nebuliser treatments.

‘ back after a period of low adherence and needing to prioritise. But just because they have new symptoms doesn’t mean they are going to adhere as well as they did (before modulator treatments).’

The data extract below highlights how difficult it can be for patients to start adhering again once they have perhaps had a period of lower levels of adherence due to focusing on or prioritising new treatments.

‘Not enjoying quite as good health as they did when they first went on modulator treatment, actually having to go back on it is really hard and having to pick those things up again.’

Not only can it be difficult to re-establish routine and habits but for some patients it is a deeper shift which relates to their beliefs around wanting to take the medication. Re-starting medication can be difficult for patients as it can be an indication that their condition has declined.

‘It is really. It's kind of seen as a really negative and I stepped back and I think actually, emotionally and psychologically, that's really difficult for people. And that's before you've even addressed the same barriers that they had before, around time. But a lot more, a lot more. Now, I think it's the I actually don't want to do it. I don't think I need to do it.’

For some patients living with CF taking a modulator treatment such as Kaftrio has been an opportunity to take a break from taking nebulisers and other treatments. Although, there could be

consequences to this, and there is evidence to suggest that patients should continue taking all treatments with the addition of the modulator treatments (Tong Song et al., 2022). The quote below highlights an example of an adolescent patient who wanted to ‘feel normal for a period’ and decided to stop other treatments during this time.

‘There are still some people who have been pretty rough as early teenagers.
And who have taken Kaftrio and deliberately chosen not to take some of the normal treatments. And and they've said I just want to feel normal for a period and I know it's wrong.. I don't remember. They used the word wrong, but they essentially said I know it's wrong. I should be doing these other things, but I what I really want out of Kaftrio is a couple of years of not taking CF drugs and not feeling like I've got CF, even if that means that I'm back feeling rough sooner than I would be. So they really they really just wanted a break.’

The quote below highlights that it can be difficult to advise or direct patients when the guidelines are not clear. According to this HCP their role is to present the arguments to patients as to why continuing adherence is best for their health, however ultimately the decision relating to *if* they take the treatment falls to the patient.

‘It's difficult. No one's really got the answers at the moment and I think it is much more led by what the patient wants to do. We can, you know, set out the the arguments and then they have to make the decision at the end of the day, what's what's right, what's right for them.’

Furthermore, the lack of evidence relating to continuing nebulised therapies whilst taking Kaftrio can add further complications from the healthcare professionals perspective. Ensuring the are giving the best advice to patients can be difficult when there is no evidence from the best practice guidelines at this time.

‘And I guess it also from our side, the evidence for continuing therapies like hypertonic, saline and DN as isn't completely out there yet for those patients that are on Kaftrio. You know, should they continue? Should they not continue? Is there more of a drop in lung function for those patients that rationalise their therapies and stop their therapies? I think if we had the data to say, look, if you continued with this then it will, you know, preserve your lung function a lot longer that that's also something that patients listen to.’

It is clear from this theme that there are changes in CF symptoms and adherence to treatments which are related to the development and use of modulator treatments in CF care.

Theme 2: Empowerment and respect when managing adherence

HCP’s shared insight into how adherence is discussed with patients, emphasising that they are there to guide and advise patients and not tell them what to do. Within this theme there are three subthemes: ‘*Changes in how adherence has been discussed overtime’, ‘Open discussion with patients’* and *‘Carefully choosing language’.*

Changes in how adherence is discussed overtime

Some of the experienced HCP’s reflected on the differences in how adherence is discussed now in comparison with several years ago. Noting that patients are now seen as the expert and are empowered to make their own decisions about adherence with the support of HCPs, rather than ‘told’ how to manage their condition as they may have previously.

‘You've got to be so flexible with them, in my opinion, and you cannot drill things, so it's not. It's not 30 years ago. You know, you must have this because if not, you know you're going to not do very well. They know this, they're experts.’

Again the data below emphasises the change in approaches to discussing medication with patients over time and the movement towards a more collaborative approach.

‘I've over that time I've kind of seen.
The way that or I think I've changed my practise in the way that we have communicated with patients from being a ‘do this’ approach to ‘how can we work together approach?’

For some HCP’s the CFHealthHub, and the ability to look at objective adherence data with patients, had been the driver behind change related to how adherence is discussed with patients.

‘It kind of gave us. It showed us a way of kind of supporting people a bit more actively and using that platform. And that's certainly changed how effective we were. I think with our conversations with patients and it was much more patient led and focusing on the positives and and those kind of things’

Patient Led Discussion

When asked how nebuliser adherence is discussed in the clinical setting a number of the HCP’s referred to having open discussions to encourage patients to be honest and also feel empowered to make decisions relating to their health.

‘No one's really got the answers at the moment and I think it is much more led by what the patient wants to do. We can, you know, set out the arguments and then they have to make the decision at the end of the day, about what's right, what's right for them.’

The HCP below suggests that taking a paternal approach to discussions around adherence or ‘telling’ patients what to do can in fact create more barriers to open and honest discussion.

‘Everybody's so different. So I will put it down to the patient. You know, if they're struggling, I'll go in and say right, like I said earlier, what can we do to help not you know, you you're doing this because they don't need the finger wag. It doesn't help. It just puts a barriers. So we'll sit down, we'll go through what's been happening.’

Also being mindful that patients may not want to discuss adherence in each appointment, with each HCP they see (often patients will see a number of multi-disciplinary team members in one clinic) as this can be overwhelming for patients and again could increase barriers.

‘How much they would like to do if they'd like to discuss it, if they'd like to talk about it. If they don't want to. If they want to call in a few days or a few weeks, that's fine.
And be very flexible to what their needs and their wants are.’

Carefully choosing language

HCP’s spoke of the importance of language and how this must be carefully selected to ensure that patients do not feel like they are being judged by their clinician.

‘So how can we make those other days as successful as what you've already achieved rather than that's really poor? You should be so disappointed in yourself?
Why can't you just do it on the other days? So I think the language that we use is really important and it's really hard when when you, when you are really worried about somebody and they're not doing their treatments.’

A number of HCP’s explained that when discussing adherence they carefully consider their language and framed their question to ensure helpful discussion can be facilitated. Specifically when asking patients how much of their medicine they have been taking and giving them ‘permission’ to be honest.

‘ I'll often say in an average week how often would you miss one of those doses in the hope that counting it that way is then permission to say I I do miss the odd one and then I'll sometimes sort of. Say if they say maybe two days a week, I'll say, you know, two or three or maybe four and just give them an opportunity to say, oh, yeah, maybe it is a bit less. So it'll always come up.’

Furthermore, the HCP below emphasises the importance of changing language when discussing adherence and symptoms with patients, suggesting that it might not always be something time consuming that is required.

‘I think we always just try and find it (time).
Because sometimes it's not about finding extra time, it's just about changing the language that you use.’

The findings from this theme suggest that HCP’s recruited into this study respect their patients and use techniques to facilitate an open and honest discussion which is useful for their care.

Theme 3: Symptom tracking: an additional burden?

Perhaps the most major concern relating to symptom tracking for the HCP’s was that completing a daily questionnaire is another reminder for patients that they are living with a condition, for some an unwelcome reminder or an additional burden. There are two subthemes within this theme: *‘A reminder of living with CF’ and ‘An additional ‘ask’ of patients and professionals’.*

A reminder of living with CF

One of the concerns relating to symptom tracking was it could act as a reminder of their condition which could negatively impact them.

‘Sometimes a lot of our patients, they don’t want the constant reminder of something. And I think if there’s a constant reminder of, OK, I’ve, you know, I’m coughing or I’m not coughing, it’s sort of detaches them from just their general everyday life that they’re just trying to get on with’

The reminder of the illness is not just isolated to symptom tracking and can also be related to taking medication such as nebuliser treatments.

‘It’s also, again, as we said, for some patients you know a reminder that they are that they’ve got cystic fibrosis, there’s a you know proportion of patients that are on Kaftrio feeling so much better, significantly better than they were prior to to you know’

For patients who are feeling well due to modulator treatments the symptom questionnaire could be difficult for them as it is possible that they do not experience symptoms each day. However it could remind them of the symptoms they could experience.

‘Certainly our younger children or younger adults. Have never experienced being poorly and therefore again, it just makes adherence. Not as relatable, because they’ve not seen the difference it makes. So asking them to monitor something that they don’t see as an issue and don’t see a problem so it might be tricky’

An additional ‘ask’ of patients and professionals

There was a concern for some that incorporating symptom tracking into self-management routines could be overwhelming for some patients who perhaps already feel like they have lots to do.

‘And other people would just be like, I’m so overwhelmed because you’re asking me to do another thing. So I think I think like most things, it’s personality dependent. But I think that’s also why we have lots of different.’

‘When we try and get them to approach things or adapt things and some people really buy into something and really take it on board and other people just like I just, I can’t think about something else like I just can’t add in something else there.’

In terms of clinical appointments it was clear from the HCPs that they are happy to incorporate the discussion of symptom into appointments with patients. Some actually felt that it was something that they already do.

‘I think yeah, it could definitely be used and and there would be time because we are already talking about it.
Something that’s relatable and and you know, for some pictorial for some.
Kind of it includes some in the conversation’

For this HCP adding in anything which is likely to help patients it worthwhile.

‘I’ll open my arms out to anything and embrace anything if I think it’s going to benefit patients. And I think our team are like that. But it depends on how much time you’re talking because we do a lot of questionnaires.’

Overall, it should be recognised that symptom tracking could be an additional reminder of living with CF for patients and an additional task for both patients to complete the questionnaire and HCP’s to use the data.

Theme 4: The unique experience of living with CF

Patients have often lived with the condition since birth which means that they know their condition and medicines very well. Furthermore, often patients with CF are younger which can be associated with challenges such as puberty, independence and studying. The subthemes within this theme include: ‘*Managing CF as a teenager’, ‘Living with CF and a busy lifestyle’* and *‘An avoidant approach to coping’*.

Managing CF as a teenager

A number of healthcare professionals discussed the fact that they often work with young adults or teenagers who are living with CF. The data below relates to the burden that living with CF can add to life as an 18 year old and empathising with this.

‘Yes, they're so young. That's just mad. Like, you know. How can their brains, even when you're told, oh, you've got cystic fibrosis, like I sit in with like the newly diagnosed patients I was only with a an 18 year old the other week just finding out for the first time.’

Furthermore, the HCP below discussed how young people can be supported, even when they feel as if they no longer care about their health or condition.

‘She's a teenager, but she doesn't really care about anything and she doesn't really care about how she feels. So I just asked her what her memories of being an early teenager were like, and she said I hated it. I hated being ill. I said all right, so I said, well, you don't feel like you care about your health. Actually, you do remember caring when it felt bad and and just leaving it there in the hope that that will kind of burrow away in a brain little bit and she'll think, actually, I didn't like being ill maybe I do care a bit.’

For some young patients planning for the future or looking after themselves now so they will benefit from it in the long-term is difficult to consider as they are more focused on living in the moment.

‘Sometimes we talk about the long term kind of trajectory and goals. But particularly with some of our younger adults, that's it's just too far away. It's not relatable. You know, they don't, you know, with our 19 year olds, they're not really thinking about when they're 35/40, they want to go out partying tomorrow’

Living with CF and a busy lifestyle

HCP’s in the current study acknowledged that patients are not simply living and managing their condition they have complex lives filled with different factors, this can lead to changes in adherence.

‘But it's almost like this is a real life person. Like you can see there's up and down how adherent it's like, you know, we know everyone's not perfect. Like you're not going to take it, but especially if you're going out to uni like you're going to have a late night and not get up for that thing first thing in the morning.’

Similarly the quote below suggests that even patients who are generally good adherers will experience events in life which can impact upon the management of their condition.

‘People just have busy lifestyles and once people are into the health hub as was or into their adherence, then you find that they do pretty well in the quite successful over the time, but you'll always get the

ones who are really successful or some dipping because something's happened, you know they've lost a parent or you know, there's been a life trauma, which is generally when you get the hiccup in the road.'

An avoidant approach to coping

The data below suggests that to the surprise of HCP's and some CF patients, others will try to forget about their CF between clinical appointments as a way of coping with the condition.

'Understandably and much to the surprise of healthcare professionals,
so you have patients want to forget about their CF, between clinic appointments.
This amazes people, people who don't know anything about this sort of thing that they'd love to measure their lung function every day of the week and measure their weight and document all their symptoms and be really on top of their CF all the time'

Furthermore, the way in which patients cope with their condition and their attitudes towards the disease can impact upon interactions with HCP's and the type of support they are provided with. The HCP below demonstrates awareness of different coping strategies.

'Avoidance. Optimistic acceptance. Their attitude towards their disease.
Then possibly the severity. If we start saying, actually, unfortunately you're getting worse. Things are going badly. Your lung function is falling. You've had multiple exacerbations. You're not doing well. We need to step up your treatment…so you come down to who is your patient'

Some professionals suggested the avoidance coping can pose problems due to negatively impacting on treatment taking and

resulting in health problems over time. As demonstrated in the two quotes below:

‘Yeah. The first thing to do, they still need that reminder and that prompting that that actually they have got CF.’

‘ I mean, sometimes we do, we sometimes want them to remember that they've got CF’

To summarise, within this theme participants discussed the unique experience of living with CF. Often patients are managing busy lives or social activities and do not always want to be faced with a reminder of their condition. This should be considered when developing symptom tracking tools.

Theme 5: Symptom tracking: It has a role for some patients?

HCP’s were asked questions relating to how useful they felt symptom tracking would be when used in clinical practice and if they had any concerns around this. Within this theme there are two subthemes: ‘*Its not one size fits all’* and the *‘Potential benefits of symptom tracking’.*

Its not one size fits all

Throughout the interviews the HCP’s emphasised how patients must be treated at an individual level and a tool or plan which could be helpful to one is likely to not help others.

‘That’s why we have lots of different tool kits and things and ways of approaching things for people differently. Because we, because we know not one thing fits everybody.’

In the data there was a real emphasis on the fact patients need to be seen as an individual and there is not a ‘one size fits all’ approach, this covered a range of areas such as the management of their condition, medication adherence and symptom monitoring.

This suggests that some patients are more open to trying new things to manage their condition than others.

‘Some patients are quite open and they're really they actually want to improve their adherence to therapies. They're aware of the benefits they give and they're gen, they genuinely have difficulty with motivation and you know, finding time for it or, you know, and for those patients we sometimes try and see them, you know, for maybe a few weeks once a week to just help sort of establish those.’

Therefore symptom tracking would be down to each individual to decide if it would be something they would find useful. Some of the healthcare professionals gave examples of patients who are aware of measures such as their lung function and change their medicines accordingly, in theory perhaps already monitoring symptoms.

‘So I think it's, yeah, I think that's probably it depends on what patient you were really speaking to. Some are very much more attentive of their lung functions and they're already on top of their, you know they'll increase the amount of clearance that they're doing because their lung function's a bit lower and there's a bit more sputum and you know, so it depends on the patient's psychology, I guess.’

The HCP below suggested that having a use in clinic could provide additional motivation for patients to engage with symptom tracking, and furthermore potentially using the tool for a short period of time could be useful and again encourage more engagement.

‘Its got to have a roll in clinics because if not people won’t use it, but how you implement that when CF’s changing with the modulators is beyond me of what would be successful in doing that. But I think as a short term tool or when you’re working with somebody that might actually… you could get a good use for that to be fair’.

Some individuals are more engaged with data and enjoy tracking things whereas others will be less keen, the addition of anything

overwhelming or time-consuming will not be helpful for some patients.

‘Can't be overwhelming. Can't be time consuming and for some people who love to track data and things, that's absolutely fine, you know. So I'll, for example, to help adherence, I should try and match what's better, what's best for the patient. So for example, and not everybody needs these. But some of my patients are saying, can you do me a treatment plan?’

When presented with the findings from previous studies with the thesis, some of the HCP explained that they found the summary helpful and for some participants explaining the relationship between symptoms and adherence could be helpful, however not for all.

‘I actually think that that's quite helpful. Yeah, to sort of tap in the moment that they've got more symptoms. To start their therapies, I mean, we're always gonna have a population of patients that, regardless of symptoms, they're not gonna do it. But we might be able to hold on to the ones that will. So yeah, I think that's helpful.’

Potential benefits of symptom tracking

The potential benefits of symptom tracking were discussed by all HCP’s, in the main HCP’s felt that could be useful to help better understand the relationship between adherence to treatment and patients’ symptoms.

‘Yeah, I mean, I couldn't agree more really. I think that's the time where we can push adherence and help for them to actually start their therapy. Sometimes some patients, they'll go for, you know, weeks or even months without anything. And it's only at the moment that they actually get an exacerbation, that they restart and at the point that they restart, we're able to sort of develop that new new pattern and routine. So, yeah, I I I actually think that that's quite helpful. Yeah, to sort of tap in the moment that they've got more symptoms. To start their therapies, I mean, we're always gonna

have a population of patients that, regardless of symptoms, they're not gonna do it. But we might be able to hold on to the ones that will. So yeah, I think that's helpful.'

'I I think on a yeah, practical level, I think it would, they would, they would, the patients would struggle to do it on a daily basis. And I think their fatigue would wear off. So I think we'd have to be quite careful about the frequency and the amount of time that they were having to put into it. But I think they would definitely.
I think there's a time and a place for it, definitely'

It was suggested that it would be helpful to use symptom tracking now that some patients are experiencing new symptoms after taking modulator treatments and reducing their adherence to nebulisers. As some of the HCPs felt this could provide patients with motivation to re-start their old treatments.

'Now that people are starting to get a few symptoms, having been on Kafrio for a few years. So you're saying you need to do treatments in order to stay well, and they're thinking, actually, I have started to get a bit more symptomatic. Perhaps they're right. Perhaps that perhaps that helps to motivate them.'

When presented with the data from the thesis and an example graph, some of the HCP's felt that the data would be useful to point out improvements in symptoms and possible relationships which could be useful in encouraging patients to adhere.

'Once they get into that, that would be quite useful, I think to say, actually look, your symptoms are starting to improve when you take your treatment'

'I guess that's the it's making it something more tangible to discuss, I suppose.
Where otherwise it's just is it just adherence for adherence sake or some arbitrary goal of what my lung function is in five years? Actually, if it's something a bit more tangible and meaningful.'

However, other HCP's had concerns about how useful it could be, especially if they are already completing other questionnaires in clinic.

'And I think having the patient fill in lots of symptoms scores. Is probably not terribly useful. We in clinic sometimes use it where we use several additional patient reported outcome measures is the term we sometimes use PROM's. So we'd often ask them to do a depression score and anxiety scores or something like APH Q9 and GADS 7 for example'

A small number of HCP's expressed concerns about symptom tracking not showing an improvement in symptoms, something which could potentially provide negative reinforcement to patients as highlighted below.

'There's a little bit of a worry about the green light phenomenon when people choose a bad behaviour and then you do some data and it looks like they've got away with bad behaviour and it makes them think go good. I guess I can carry on. So I it looks like it'd be really helpful, particularly when there's that little, you know, drop off in adherence and the cough goes up. That's quite useful. But you'd worry that if they're adherence drops, their symptoms remains pretty similar.'

However, it was suggested that having a record of symptoms/adherence to look at if required could overcome the recall and accuracy issues that can occur when asking patients to remember retrospectively at the clinical appointment how they have felt over a period of time.

'So recording it may be more helpful because it's a proper reminder of what you felt that particular day, not what you think you felt a month ago when someone's trying to talk to you about it. So I think terms of accuracy, it's going to be a massive step forward.'

To summarise, if the symptom tracking tool was to be developed it should be something which is different for all patients and flexible so

that patients can chose how and when they would like to use it. Furthermore, most of the HCP's felt there was a potential benefit to symptom tracking, although it could be additional burden for patients, this is something which must be considered.

Theme 6: Contextual issues: Perceived losses related to the closure of CFHealthHub

A number of HCP's spoke about the closure of the CFHealthHub within their interview. The platform has been used to support patients with nebuliser adherence for several years and was closed in October 2024. One of the of main factors which was discussed was the future of adherence without CFHealthHub and also how to discuss adherence without objective data.

One HCP emphasised how CFHealthHub has been used within both their clinical assessment as an outpatient and also in their letter which is sent off to their GP. Therefore the importance of this adherence data is evident.

'We've incorporated CF health hub adherence to patients who are participating. The CF health hub adherence, you know, percentage doses taken over say the last month or so into their standard clinical assessment and we've included that on their CF letter'

Disappointment related to the closure of the platform was also highlighted by the HCP below.

'It's difficult to know how that will go forwards now without the data. That we're getting. But I think just that whole just knowing a bit, understanding a bit more about the, the things that impact adherence and really spending that having that time to actually talk to patients and find out what it is for them and what may make the difference for them.'

HCP's spoke of how it will be difficult to discuss adherence without the objective data collected by CFHealthHub.

‘The thing is gonna make things much more challenging. Especially to ascertain whether or not so often we use health hub, but not only to encourage them with their therapies, but to identify whether or not that's the reason why they're getting unwell. And so if a patient says, well, I'm doing 100% therapies when they're not and they get in unwell more, more frequently.’

However for some there are skills and approaches which they learnt about during the CFHH intervention which they will continue to use in their practice.

‘Those were definitely things that I learnt from health hub, the language and how we approach it is very different. Having the objective data is well was game changing because I think when you can see it’

One of the HCP’s suggested that since using the CFHH they are so used to using adherence data in clinical appointments as this provides useful information relating to the patient. The data can also provide support for patients if they are adhering but not feeling as well as they should.

‘I suppose kind of more on because we've become more used to using adherence and having data on the nebuliser. We're using it in more areas now as well in terms of trying to get the information that we can use for if there's doubt, well.
If there's either doubt or we're seeing differences of opinion in terms of what the patient's reporting to what we suspect.’

One of the HCP’s highlighted that the CFHH data provided more structure and formality to clinical appointments.

‘Well, it had become much more structured and formal, so to speak….So there was objective data. Which one could incorporate into the role, so it might be sort of typical clinic who obviously as well as how they are and all the usual clinical stuff you'd end up with.’

Based upon the findings from this theme it is evident that HCP's found the CFHH useful and now without the programme there will be changes in care and discussions around adherence to nebuliser treatments. However, the legacy from the CFHH is that HCP's have developed new skills which can still be applied to relevant discussions.

Theme 7: The practicalities of using symptom tracking data in clinic.

Within this theme HCP's spoke about the practicalities and considerations which would be required to use symptom tracking in clinical work. Within this theme there are two sub-themes: **'***Embracing changes in care'* and '*The importance of resources'*

Embracing changes in care

Many HCPs said they would be willing to make adaptions and incorporate the discussion of symptom and adherence feedback data with patients if they felt this was likely to help their patients achieve better outcomes.

'But I think you know, I would say I don't think I've ever worked with a team that isn't open. You know, things move forward all the time. Things change all the time. We adapt to approach all the time just because it's all about just kind of trying to work to get the best care for our patients.'

'I'll open my arms out to anything and embrace anything if I think it's going to benefit patients. And I think our team are like that'

The HCP below emphasises the important of embracing changes and keeping 'up to date' with advances which could potentially help patients live healthier lives.

'And if we all just sat back on what we were doing, you know, 10-20 years ago, that's not in the best interest. That's not why people get

into healthcare. So yeah, I think it's, yeah, it's just about we try and keep up to date with things and change our approaches of ways of doing things so that we, you know our patients have better outcomes.'

This demonstrates some alignment with reflective motivation as the HCP's suggest that their goal is to ensure that patients are receiving the best possible care and to deliver this they must embrace changes.

The importance of resources

When asked about opportunity to use symptom tracking data in clinical appointments some of the HCP's recruited into the study highlighted the need for further support, specifically in terms of admin teams to ensure that the information is ready and can be accessed prior to the appointment with the patient.

'Get all the information together during the appointment. Sometimes you find you've only got 5 minutes left to do any talking, so I can't see much of a barrier apart from just needing the admin support to get everything together before someone with CF is seen in clinic'

One of the HCP's suggested that if this information was readily available then burden and time constraints in clinic could in fact be reduced.

'It might theoretically, it might reduce. I guess if you had something that was even prior to the clinic'

When discussing capacity and burden some of the HCP's suggest that they were already using data in clinical appointments to aid discussion, such as CFHealthHub adherence data or data from the 'Neva' platform. The HCP below suggests that with the information available before clinic, burden could be reduced, highlighting again the importance of when/how information is made available to clinicians.

'It might theoretically, it might reduce. I guess if you had something that was even prior to the clinic. So on our Neva where platform, we

would send our prompts that for them to do a lung function, if if it came up as lung function, you know they and maybe I don't know, really arbitrary figure, but maybe 70% of patients would probably do their lung function before coming to their clinic 70-80%.'

In regards to capability and additional training which may be required to ensure HCP's can use symptom and adherence data to have meaningful discussion with patients, some of the HCP's felt that additional training would be useful.

'I think it you'd need some. I guess it's understanding of what you're trying to get out, what you're trying to teach the patient. And I think there's some, some of us that would find that quite easy to make that link, whereas other people make might need. You know a bit more support to see why. It's why it's relevant, why these smaller symptoms are relevant, and then the impact that it can have on.'

Whereas others felt that those who have had training relating to the CFHealthHub may already have the skills required to use adherence and symptom data in clinic.

'I'd say there's lots of things that teams have developed, like toolkits and stuff themselves of like check things. So I think it's just a different another process. So I don't think it would need massive training. The bit that's quite hard is if you haven't had the training.'

To summarise, if symptom tracking was to be used in practice it is important to ensure that the relevant resources are available to HCP's. This could include additional administrative support or training. It is clear from the findings however that the HCP's are willing to implement changes if they are useful to patients.

7.5 Discussion

This qualitative study aimed to further understand HCP's perceptions of the factors which influence adherence to nebuliser treatment in CF patients and their understanding of how treatment influences symptom experience. Furthermore, the feasibility and usefulness of using self-monitoring was explored.

A total of 7 themes were identified: The influence of modulator treatments, Empowerment and respect when managing adherence, Symptom tracking: an additional burden? The unique experience of living with CF. Symptom tracking: It has a role for some patients? Contextual issues: Perceived losses related to the closure of CFHealthHub. The practicalities of using symptom tracking data in clinic.

Themes 1 (the influence of modulator treatments), 2 (empowerment and respect when managing adherence) and 4 (Symptom tracking: It has a role for some patients?) addressed RQ 10 of the thesis. The changes in CF care related to the modulator treatments such as Kaftrio was discussed by the majority of participants in the current study. Modulator treatments are expected to have a significant impact on life expectancy and the health of patients living with CF (Aspinall et al.,2022). However findings in the current study suggest that the modulator treatments have raised some challenges in CF care, for example participants in this study reported that often motivation to adhere to other treatments can be limited. The second relating to changes in symptoms, findings of the current study suggest that patients living with CF are now presenting with new symptoms or returning symptoms after a period of being more ‘well’. Modulator drugs were rolled out for use in the UK in August 2020 (NHS, 2020). Therefore there is limited long-term evidence that suggest how patients may feel after a number of years taking the treatment.

These findings replicate the work of Tong Song et al. (2022) who suggested that as patients feel an improvement in symptoms their adherence to other treatments decreases, even though current advice is that modulator treatments should be used in addition to inhaled treatments. Tong Song et al. (2022) found that there was a significant decrease in adherence to dornase alfa and hypertonic saline when comparing pre and post modulator treatment, there was not however a significant decrease in adherence to antibiotics. Tong Song et al. (2022) attributed some of these changes to a

decrease in reported cough and mucus production following modulator treatments. Again this closely aligns with the current findings and the reduced perceived need to take nebulisers due to changes in symptoms which was reported by some HCPs.

In relation to theme 2 the current study found that there was an emphasis on having honest and open conversations with patients, something which for the experienced HCP's has improved and changed over time from a paternal approach to something more collaborative such as Personal Centred Care. The importance of practicing Person Centred Care has been emphasised in the work of Asimakopoulou and Scambler (2013) who advocate for patients being provided with enough information to make informed decisions and practice autonomy within their own care. These findings support studies focusing on adherence such as the work of Calthorpe et al. (2020) who found 85% of patients living with CF who were interviewed were able to openly discuss adherence with their team. There are a number of other studies focusing on other conditions which have also demonstrated the importance of work collaboratively to improve medication adherence such as: in those living with asthma or food allergies (Koplin et al., 2024) and those living with dementia (Laver et al., 2020).

However, these findings contrast with the recent work of Dawson et al. (2023) who conducted a qualitative study with patients living with CF. Dawson et al. (2023) concluded that a cultural change in the way adherence is discussed in CF care is required as patients felt it was in fact a paternal approach which encouraged them to not be honest in consultations. This raises a question, that there could be a difference in the way HCPs are interpreting consultations compared to patients living with CF. However that being said Calthorpe et al. (2020) recruited a mix of patients, carers and HCP's. Therefore findings in this area are mixed. In relation to this thesis studies 2 and 3 recruited patients living with CF, participants were not specifically asked about consultations, however there was a clear willingness to share adherence data with healthcare professionals.

The way in which HCP's select language when discussing adherence was a sub-theme within theme 2. HCP's referred to using more open ended questions and also framing questions in a more positive way. Gain versus loss focus framing has previously been applied to medication adherence (Zhao et al., 2012) and confirmed that gain frame messages are more likely to increase adherence, this could be applied to the findings of the current study in that HCP's will carefully frame messages to encourage more open discussion. Furthermore, Dawson (2023) reported that language is also important from the perspective of the patient. A meta-analysis which focused on communication and adherence found that communication was significantly correlated with adherence and there was an increased risk of 19% of low adherence, if communication is poor (Zolnierek and DiMatteo., 2010).

In regards to theme 4 the subtheme 'living with CF and a busy lifestyle' is related to previous findings which have highlighted the burden associated with living with CF. George et al. (2010) referred to the idea of 'social demands and work demands' which emphasises the need to be committed to treatment and care for the condition but also the desire to engage with social activities and also fulfil professional responsibilities.

As CF is typically diagnosed at birth and half of people born in 2024 with the condition are likely to live until they are at least 64 (CF Trust, 2023), meaning a large number of CF patients are young. HCP's in the study specifically referred to those who are living with CF as an adolescent, emphasising with how hard it can during these years when many desire to live a 'normal life'. This replicates the work of Sawicki et al. (2015) who reported that the majority of adolescent patients and their parents felt that their CF team understood what it was like to be an adolescent living with CF. However it is important to note that in the current study HCP's suggested that for these patients symptom tracking could be a reminder of the condition they are living with.

Themes 5 (Symptom tracking: it has a role for some patients?) and 7 (The practicalities of using symptom tracking data in clinic) were helpful when addressing RQ11. All but one the HCP's felt that overall symptom tracking data could be used in clinical appointments to promote useful discussion. These findings support that of Skyrme et al. (2024) who found that clinicians (and patients) reported benefits of using symptom tracking data in clinic with patients living with Rheumatoid Arthritis.

Prior experience of using data in the form of lung function data and adherence data from the CFHH was discussed by some of the HCP's in a way which would help them to feel more confident about discussing symptom data. Furthermore, participants were open to trying new things in clinic if they were likely to help and support their patients. However, it is suggested that further support would be required from admin teams to ensure that data was prepared and ready to be discussed with patients. Lack of support from other team members, although not specifically admin teams was a barrier found in the work of Girling et al. (2024) in relation to the CFHH, however this problem was addressed after a trial period. Other than this there was no barriers to symptom tracking which relating to having the time or opportunity, this contrasts with previous findings (Girling et al., 2024) who found that some HCP's reported they were too short of time to use CFHH data in clinical appointments.

Themes 3 (symptom tracking an additional burden?) and 6 (Contextual issues: The closure of CFHH) addressed the final research question (RQ 12). The suggestion that symptom tracking could provide patients with CF with an additional burden to contend with was highlighted by patients living with CF in study 3 of this thesis. Therefore it was suggested by a number of HCP's that using symptom tracking could be useful but perhaps as a short term measure for example, if a patient is not responding well to treatment or is struggling to see the importance of adherence. The concern relating to patients struggling to track data was also raised in the study by Skyrme et al. (2024) which recruited HCPs who care for

people with rheumatoid arthritis. In relation to CF care Rowbotham et al. (2023) published the James Lind Alliance priorities for patients living with CF, one of which included 'what are the effective ways of simplifying the treatment burden of people with CF?'. The priorities are informed by a survey completed by 1608 people who are in one of the following groups: patients living with CF, patients with CF who do not have access to modulator treatments, friends and family of people living with CF and also health professionals and researchers. This demonstrates the impact of treatment burden on these patients.

The closure of CFHH was commonly discussed during the interviews, within the current study participants felt unsure about how they would discuss adherence going forward without the tool to aid discussion with participants. However some of the participants referred to the extensive training which they had undertaken and explained how there was parts of this such as language and techniques which could be used going forward even without the data. Despite this there is evidence which supports the use of data, for example Lumley et al. (2022) reported that for patients using data in clinic can be proof of adherence and symptoms.

Interestingly what is clear from this is that a number of the findings from this study are similar to those findings from studies which recruited patients living with CF suggesting there is some alignment between the views of the two groups. For example, in study 2 of this thesis people living with CF reported that symptom tracking was acceptable and feasible, however in study 3 concerns were raised such as symptom tracking being a reminder of their condition. These findings were echoed in the current study.

Study strengths and limitations

The study was a unique opportunity to discuss the finding of the thesis with healthcare professionals to explore how this could be used in practice. This provides the findings of this thesis with more depth and also an alternative perspective.

All participants were working at sites where CFHH had been using adherence data in clinics (prior to the closure). Therefore it could be that participants were more likely to have an open-mind about symptom tracking due to their experience of using adherence data in clinical appointments. However, there are other programmes now being used across the UK e.g. Project Fizzyo which focuses on adherence to physiotherapy in children living with CF (Raywood et al.,2020). Therefore it is likely that the majority of trusts are involved in using some kind of electronic data.

Furthermore, in terms of recruitment, participants were asked to respond to an email if they were interested in taking part. Once participants had taken part they were asked to share information about the study with their colleagues. It is important to be aware of the limitations of this sampling approach, as the sample self-selected and volunteered to take part in the interview it could be that they are more interested in the topic. Although according to Robinson (2014) snowball sampling can be an effective form of recruitment in qualitative research.

Study Implications

The current study has a number of useful practical applications in relation to using symptom tracking in the clinical setting. Symptom tracking for patients with CF is not likely to be something which works for everybody all of the time. It is important to be aware of the burden people living with CF face as highlighted by Rowbotham et al. (2023) in the James Lind Alliance priorities, and if symptom tracking could be an additional factor. However, previous work in the area suggests that using data can promote discussion which is useful for both the HCP and the patient (Lumley et al., 2022) and previous findings from this thesis have shown that patients are happy to share data with HCP's. Therefore it could be that it is more suitable to use symptom tracking on an ad-hoc basis to support patients, for example if they are taking a new treatment or need additional support with adherence.

Conclusion

To conclude, this qualitative study found that overall HCP's felt that symptom tracking could be a useful tool and incorporated within clinical appointments. There were some concerns relating to adding to the burden for the people living with CF, however adaptions such as using symptom tracking for a short period of time could be a solution to this issue.

Next steps and potential future research

This is the final study within the thesis and therefore the findings of this thesis will explored within the next chapter, the general discussion.

Chapter 8- Discussion

This thesis took a mixed-methods approach to addressing the principle aim ‘to explore the feasibility and usefulness of self-monitoring and using adherence and symptom feedback data with patients with Cystic Fibrosis.’ To summarise, the thesis describes four studies that demonstrate that symptom tracking is feasible and a potentially useful tool for patients and professionals. Traditional methods would not have been able to provide insight into the individual relationship and differences between participants. The novel N-of-1 methods adopted in the current work enabled a much more detailed and thorough investigation of these relationships which showed that this is no consistent pattern between adherence and symptoms across participants and therefore a personalised approach is required to managing adherence. Future research could explore whether and how symptom tracking could work alone as an individualised intervention to increase adherence to nebuliser treatments in adults with CF, or if it could be used more effectively alongside healthcare professional input in a collaborative approach. Currently, there is not enough evidence from this thesis to suggest an intervention should be developed. The aim of this chapter is to discuss the contribution to knowledge that these findings make, where these findings fit in relation to previous literature within the area, as well as reviewing the strengths, limitations and applications of the body of work.

Both healthcare professionals and patients living with Cystic Fibrosis reported that the symptom tracking tool was *useful* and *feasible* as explored in the thesis. The qualitative findings from the N-of-1 pilot study suggested that participants found the symptom tracking period of six weeks acceptable and feasible (e.g. Its quite an easy one this because all you have to do is wear that (Fitbit) and fill it in, so it doesn’t take that long’). This was important to establish given that patients living with CF already have a substantial treatment burden (Altbabee et al., 2024) and it was imperative not

to add to this. As a result of this participants recruited into the main N-of-1 study were asked to monitor symptoms for a period of four months. Is important to be aware that there was some missing data, when participants were asked to monitor symptoms over a period of time, the average daily completion rate across the pilot study was 87.6%, in the four month study 11/18 participants had between 1.2%-33% of missing data and two participants did not complete for over half of the study days which meant their data could not be analysed. This is unsurprising as missing data is common within Ecological Momentary Assessment designed research (Markowski et al., 2021) and the longer time frame made this more likely to occur. Nonetheless the proportion of missing data was within the parameters or less than the amount found within other studies, for example Sarafaraz et al. (2010) reported that only 37.2% of patients living with CF completed the symptom monitoring study which lasted for six months.

A strategy which could be used to limit missing data is appropriately using reminders perhaps via text or email, which could help to limit the burden on participants. Within the current work time contingent prompts were used, meaning that an email reminder was sent to participants at the same time each day, the most common approach in EMA work according to a view conducted by de Vires et al. (2021). Furthermore, although this was not possible in the current work, if participants are provided with the opportunity to look back retrospectively this can remind participants if they have already completed the survey for that day. This could provide participants with the opportunity to review and engage with their data, evidence has suggested that this can lead to better outcomes for patients (Wicks et al., 2010). This would perhaps work well if the symptom tracking tool was to be developed into a Smartphone App. The feasibility of symptom monitoring in practice was also discussed with HCP's in study four of the thesis.

Within the qualitative study with HCP's, a total of eight participants were interviewed, only one participant expressed concerns related

to the feasibility of symptom tracking. The concerns of the HCP were in relation to how useful the tool would be to a patient living with CF, not about HCP's using the tool in practice (e.g. 'I think having the patient fill in lots of symptoms scores. Is probably not terribly useful'….). However others felt it would be a useful experience and despite likely needing some admin support and preparation, it could be something which could be implemented within the clinical setting.

Symptom tracking is a personal experience and some participants found this to be more useful than others. For a small number of people living with CF recruited into studies in this thesis, being made aware of symptoms on a daily basis had some negative implications. with reports that symptom tracking could be an unwelcome reminder of their condition. This was also a concern of the HCP's in the qualitative study. This has been reported in previous symptom tracking studies in patients living with chronic conditions (Ancker et al., 2015; Jones et al., 2021), and should be carefully considered in future symptom tracking studies. However these negative effects need to be balanced against the potentially positive effects. Some participants reported that they found the data useful in consultations with HCP's, almost proof or evidence of the way they have been feeling, which mirrors the recently published paper by Lumley et al. (2022). The recently coined term 'medical gaslighting' can be used to described the phenomena, Ng et al. (2024) use the following definition 'an act that invalidates a patients genuine clinical concern without proper medical evaluation, because of physical ignorance, implicit bias or medical paternalism' (Ng et al. 2024 p.922). Medical gaslighting is thought to be associated with chronic conditions and can lead to symptoms being dismissed due to being psychological rather than physical (Ng et al., 2024). This supports the findings of the current body of work which highlights that data can be used in clinical appointments to aid discussion and also provide both patients and clinicians with a tool to help focus consultations.

It is likely that if symptom tracking is to be used again or developed within this population it must be individualised appropriately for each patient to ensure they find it useful for their condition, for example asking participants which symptoms they would like to monitor, at which time and for how long. Allowing this kind of flexibility is likely to reduce the burden of tracking and facilitate more complete data. However this does not address concerns about tracking reminding people about their condition. Finding a careful balance between enabling effective self-management of long-term conditions and enabling people to get on with their lives unimpeded by concerns about their conditions must be prioritised.

Although symptoms were measured within the current body of work what still remains unclear is how exactly participants were rating their symptoms and of course it is likely that each participant would do this differently. This was explored within the qualitative chapter with people living with CF, specially within theme 1 (the feasibility of symptom tracking), where participants spoke of finding a 'benchmark'. For one participant this involved starting at 5 on the first day and rating following days accordingly based upon this. The issue here, which is likely to be relevant for other long-term health conditions is that participants are familiar with having a certain experience of symptoms, which is variable between people, so their ratings are likely to be in relation to this. This contrasts with symptom ratings in healthy patients where we might assume that they are rating from a benchmark of no symptoms. Therefore, perhaps future work could investigate this specific topic further and look at how exactly participants are rating their symptoms and explore whether they using the 'benchmark' to represent or even calibrate what they experience on an average day or whether their ratings are based on the best they could possibly feel whilst living with the condition. The subjective nature of symptoms could potentially mean that there are measurement issues with the standardisation of symptom tracking as participants could interpret the numbers differently as previously stated. Previous literature

which explored perspectives of symptom experiences and symptom reported in patients with Haemodialysis (Flythe et al., 2018) found that patients can under report symptoms, for reasons such as: wanting to normalise living with symptoms of chronic conditions and also reporting symptoms to the full extent could be an acknowledgement of decline or deterioration. However, this can be a problem with symptom tracking and subjective measures in general, qualitative studies like those used within this thesis could be used to help participants expand and provide more detail to the answers they selected, although retrospectively this can prove difficult.

Avoidance was also discussed by some participants in the qualitative chapter (theme 2: The impact of symptom tracking) (e.g. 'I like living in denial so I like to forget about CF until my appointment and things… I just put it to the back of my mind and get on with my life kind of thing, I don't like to think about it everyday if you like'). This was also discussed within theme 4 (subtheme 'An avoidant approach to coping'), in chapter 7 by the HCP's (e.g. 'understandably and much to the surprise of healthcare professionals, so you have patients want to forget about their CF, between clinic appointments. This amazes people..'). However, one of the HCPs suggested that sometimes reminding patients of their condition can be important (e.g. ' I mean, sometimes we do, we sometimes want them to remember that they've got CF'). Within CF research a recent paper recognised avoidant thinking as a coping strategy and found that those at risk of developing anxiety or depression are more likely to adopt this strategy (Ceyhan et al., 2024).

The concept of avoidance has been studied for a number of years in psychology, according to Maslow (1963) humans can reduce anxiety by either seeking knowledge or avoiding knowledge. Evidence from the health psychology literature suggests that some people would rather avoid information relating to their health-care which can provoke anxiety (Sweeny and Miller, 2012). This supports

the idea of monitors and blunters (Miller, 1987) which are effectively different coping styles which are adopted in response to threats to health. Miller (1987) theorises that monitors seek information to reduce stress, whereas blunters prefer to seek less information. The findings of Chatoo and Lee (2022) conducted a review of coping strategies and medication adherence, it was found that 50% of studies they evaluated for problem avoidance coping strategy reported a negative associated with medication adherence. Indicating there could be a link between adherence and coping strategies.

Specific interventions and forms of therapy have been developed to focus on decreasing avoidance and help patients better understand their emotions (Hayes et al., 2013). Acceptance Commitment Therapy (ACT), an extension of Cognitive Behaviour Therapy (CBT) (Forman et al., 2007) and is something that could be used within future work with the CF population in order to address avoidance and encourage higher levels of adherence. O'Hayer et al. (2021) tested the feasibility of using ACT in patients with CF to improve anxiety and depressive symptoms, concluding that it was feasible and potentially effective. According to Graham et al. (2022) more work is required to test the empirical evidence of using ACT to increase medication adherence, however findings relating to adherence to treatments for psychiatric treatment concluded that ACT delivered as part of an integrative treatment could be beneficial, especially in those who are low level adherers. Furthermore, a study which looked at adherence in multidrug-resistant Tuberculosis patients found a significant improvement in treatment adherence following ACT (As'hab et al. 2022). Suggesting the potential use of this therapy in CF and other conditions.

In terms of the approaches taken within the current thesis, N-of-1 methods were adopted to analysis quantitative data collected in the pilot study and the four month symptom monitoring study. Observational N-of-1 methods were selected as they focus on

monitoring a relationship between two variables over time (such as symptoms and adherence) (McDonald et al, 2017b). It is important to emphasise that the goal of this piece of work is not to encourage comparison or even analyse aggregated results, instead it is to allow the participants to perhaps manage or even understand their own symptoms better and also what promotes or creates a barrier to their own adherence levels. Within the context of N-of-1 the study aims to look at the differences within an individual's data set, rather than differences between data sets (or people) which is more common within the existing literature body when attempting to understand adherence in CF (Bradley et al., 2024, Quittner et al., 2019). Therefore, within the current body of work it would be inappropriate to adopt an RCT design when the findings are so unique that there is no general pattern amongst participants. This emphasises the suitability of N-of-1 methods in this area of psychology, due to their individualised approach (McDonald et al, 2017b) which compliments the current findings and celebrates the uniqueness of the findings for each participant The findings of the four month N-of-1 study will be discussed below.

The quantitative findings provide support four different relationships which can exist between treatment adherence and symptoms for different individuals. For clarity they will be referred to here as they were within chapter 5, relationship A, B, C and D. Relationship A: Higher adherence predicted increased symptoms (occurred 11 times) (positive relationship) Relationship B:Higher adherence predicted decreased symptoms (occurred 3 times) (negative relationship). Relationship C: Higher symptoms predicted lower levels of adherence (negative relationship) Relationship D: Higher symptoms predicted higher levels of adherence (positive relationship). Relationship C and D both occurred mostly commonly (13 times in total). This complexity between the relationship between symptoms of CF and adherence to nebuliser treatments will be explored.

Relationship A occurred a total of 11 times across four different participants. As this relationship would suggest that adherence can predict an increase in the level of the symptom experienced, this would be linked to possible side-effects from treatments. For example particular nebulisers such as hypertonic saline can break down mucus causing increased coughing (Elkins, 2011). This can be linked to the qualitative findings of the pilot study, in which participants referred to side-effects of treatment causing symptoms such as a dry cough (e.g. ‘the medication you are on causing side effects or whatever, because like I say I were fine then I were having that like dry cough so to me I were in a worse position symptoms wise (as a result of taking medication)’.

Relationship B occurred a total of 3 times across four different participants. Based upon drug trial studies (Wark et al.,2018; Ramsey et al., 2011), this would be an expected outcome for the relationship, for example a patient takes their nebuliser as prescribed and their symptoms improve. Interestingly this relationship occurred the least times in the current study. One of the participants in chapter 6 referred to the benefits of adhering to treatment in terms of keeping well in both the long term and short term (e.g. ‘So they work- they do work and long term benefits to having them is a lot- is more than just the short term benefit so they will work slowly over time I think is the best way of looking at it’).

Relationship C (higher symptoms predicted lower levels of adherence) occurred a total of 13 times across seven different participants. Previous literature has suggested that experiencing symptoms such as tiredness and fatigue can be a barrier to adherence (Eaton et al., 2020). Tiredness was a symptom identified within this study by three different participants, however other symptoms include: wheeze, pain, difficulty breathing, mucus and nominated symptom (fatigue). Arden et al. (2019) reported that tiredness can make adherence more difficult for some patients living with CF. Within the current study this type of relationship was most commonly identified for pain (4 times). Therefore these findings

could suggest that when participants are feeling less well they are less likely to adhere to their nebuliser treatments. This was also referred to in the pilot study, in relation to feeling tired and lacking in energy to complete the nebuliser treatment (e.g. ‘Yeah my adherence has been crap. Basically what happened is I was actually doing really well with it when I first got out of hospital and then I caught a cold and it just went… I physically didn’t have the energy to get up and do it ermm then its not sort of picked up since’).

Relationship D (higher symptoms predicted higher levels of adherence) supports the Necessity Concerns Framework (NCF) (Horne et al., 1999) suggesting that perhaps when patients are feeling more unwell, they view their treatment as being more of a necessity and will perhaps adhere more in the hope of symptoms improving. These findings also fit with the reflective motivation component of the COM-B (Michie et al, 2011) as the improvement in symptoms can cause the patients to understand the importance/necessity of taking the medicine as prescribed. However, it is important to highlight that these relationships differ from person to person and even within individuals there are differences depending on the symptom and how this impacts adherence to nebuliser treatments. Highlighting the need for individualised interventions. Across all participants this relationship was commonly identified for difficulty breathing (4 times). In the final study of the thesis one of the HCP’s suggested that symptoms experienced by participants prior to the modulator treatments would encourage them to take their treatments as prescribed (e.g. ‘A guide for them on when to do their nebulisers or to do their nebulisers because they felt their chest's bubbling or producing sputum and they could see the impact. A direct impact on doing their nebulisers there you know, either their sputum was less, they were able to move it more easily, they could breathe easier.’).

The findings from this study reveal that there is no consistent relationship between treatment adherence and CF symptoms and

therefore behaviour change techniques such as self monitoring and feedback may not be suitable for all patients (when the benefits of treatment taking cannott be clearly identified within the feedback data). However, it could be something which is useful for patients living with other conditions, perhaps those where treatments are much faster reacting. This emphasises the importance of developing interventions at an individual level so they have the potential to support adherence for each person. Something also highlighted in the work of Langendoen-Gort et al. (2022) who suggested that a ‘one size fits all’ approach can lead to inconsistent outcomes and therefore interventions should be tailored to the need of the audience.

However, within the healthcare setting this could raise challenges due to limited time and resources available within the NHS. The final study of the thesis discussed the realities of using symptom tracking data with CF patients in clinical appointments. HCP’s were mainly positive about using data and many spoke of how they would implement anything they could to help patients. Although, it was suggested that support of an admin team would be required to ensure that the materials are prepared ready for the consultation. This was something reported in the work of Girling et al. (2024) who found that some HCP’s were too short of time to use the CFHealthHub in clinical appointments. Which suggests that using symptom tracking in the real world could require additional resources from an already burdened NHS.

8.1 Applications in practice

Findings from this thesis suggest that symptom monitoring could be a useful tool for some patients who are living with CF according to patients themselves and also their HCP’s. However, there is not sufficient evidence to suggest that creating an intervention to present the relationship between symptoms and adherence would be useful in increasing adherence to nebuliser treatments in patients with CF. It could be that this finding is specific to this patient group and specifically nebulised treatments or that generally the

relationship is too complex to be used in this way. Although using the data to facilitate open and honest discussion during consultations could be an appropriate use self monitoring and feedback data. Previous work has found that monitoring symptoms using Patient Reported Outcome Measures (PROMs) can be useful in improving outcomes for patients (Lehman et al., 2023) , however there is a paucity of research which looks at PROMs and adherence data, like in the current work. If this type of data is to be used, it is of key importance that patients are able to understand their own data and the relationships between symptoms and adherence, the findings of this thesis suggest that not all patients are confident enough to understand and interpret this information.

What has become apparent as a result of the work in thesis is that the ability to self-monitor could provide patients with the opportunity to manage their condition away from the hospital when symptoms are steady. It could also be that HCP's could monitor patients symptoms without seeing patients in person, which could help to reduce the number of face to face appointments required. These findings support that of the CFHealthHub trial (Wildman et al., 2022). This trial improved weekly adherence and FEV1 scores across one year (Wildman et al., 2022). Within the trial patients and clinicians monitored adherence to nebuliser treatments, interventionist were trained specifically to help patients change behaviour and improve adherence (Wildman et al., 2021). This was investigated further in the work of Drabble et al. (2020) who again highlighted the importance of building relationships and rapport with interventionists, patients spoke about how having somebody to talk to who cared help them improve their adherence. This highlights the importance of working collaboratively with HCP's and using data to support adherence improvements. This evidence presented in the thesis demonstrates that this is something which is valued by both patients living with CF and HCP's.

The findings from this PhD suggest that a symptom monitoring tool, like the one used within this body of work, could be used by patients

who consider this to be beneficial and also shared with healthcare professionals (with the patients permission), providing an opportunity to review the data during and in between clinical appointments. Given the current pressures on the National Healthcare System (NHS) within the UK this could be useful and has the potential to save money and improve outcomes in the future. However due to the rapidly changing funding cycles within the NHS, the CFhealthHub is currently not receiving funding, although if it was to re-start the learning from this thesis could be applied.

Currently in the UK, there is a trial being run by the University of Nottingham and Nottingham University Hospitals named CARDS-CF, the trial aims to monitor 'tummy symptoms' such as bloating, pain and sickness in people with CF who are over the age of 12 (Nottingham University Hospitals, 2021). However the focus of this work is around creating an appropriate Patient Reported Outcome Measure (PROM) and not around understanding the relationship between symptoms and adherence unlike the current body of work. As this trial is still running no findings have been published. Obviously this symptom monitoring tool is focused around gastrointestinal, unlike the work of this thesis which monitored respiratory symptoms.

It is important to consider that symptom tracking could be de-motivating for participants and potentially impact negatively on levels of adherence, especially when the relationships found between symptoms and adherence are not particularly clear-cut as concluded within this thesis. In the current work it was not possible to provide all participants with clear information such as 'if your adhere for X number of days your cough will decrease' as initially anticipated. This could heighten any doubts in regards to the treatment and the necessity to concern, something which several papers cite the importance of the role of perceived treatment benefits/beliefs (Arden et al., 2019; Bucks et al., 2009 and Hogan et al., 2015) on treatment adherence.

For some patients monitoring symptoms may have negative consequences and therefore discussions about the usefulness (and any unintended consequences) of monitoring should be included in consultations when discussing the approach. For example within the study with HCP's it was acknowledged that symptom tracking could be a reminder of CF 'Sometimes a lot of our patients, they don't want the constant reminder of something. And I think if there's a constant reminder of, OK, I've, you know, I'm coughing or I'm not coughing, it's sort of detaches them from just their general everyday life that they're just trying to get on with'. Within the wider body of literature the findings which consider the negative implications of symptom tracking such as links to health anxiety are limited, MacKrill et al. (2020) looked at the effect of symptom tracking apps and concluded that the link between symptom tracking apps and increased health anxiety is unknown, however they could be linked to more awareness

This body of work found that symptom tracking is a unique experience that will be different for all users, the findings of this thesis suggest that some patients find benefit in being able to track their symptoms and having the autonomy to select symptoms which they perhaps experience more frequently or would like to understand better. The idea of making symptom tracking tailored to each person in terms of symptoms and also the length of time the patient wishes to track symptoms for, the importance of tailoring adherence interventions was highlighted in the work of Langendoen-Gort et al. (2022).

8.2 General limitations/strengths and future research

A Patient Participant Involvement (PPI) group was consulted two times throughout the duration of the PhD project. PPI work can improve research outcomes and aid the identification of priorities project design (Gray-Burrows et al., 2018) and also the acceptability and relevance with the patient group (Hoddinott et al., 2018). Within the current thesis this experience was very valuable in terms of ensuring that the study was as suitable and worthwhile to patients

as it could be, for example ensuring that the questions asked and symptoms selected were relevant and appropriate language was used. Furthermore ensuring that the ideas were acceptable and concerns relating to burden were discussed.

However, a potential limitation of the current body of work is that the PPI group were not used throughout the whole process. PPI work can occur throughout the design, implementation and dissemination process. Utilising best practice guidelines such as the GRIPP 2 (Staniszewska et al., 2011) criteria and the GRIPP 2- Long Form (Staniszewska et al., 2017) which aim to improve the quality, transparency and consistency of PPI work could have improved the current work. The GRIPP 2- Long Form (Staniszewska et al., 2017) also highlights the importance of disseminating findings. PPI work is something which would be recommended in future symptom tracking work (NIHR, 2024). Future work could ensure that PPI work is used throughout the research and dissemination process, something which does not typically happen in research and could make the process more meaningful for patient groups living with long term conditions.

Another possible limitation of the current work is related to sampling, all CF patients were recruited from a population of NHS patients who were actively using the CFHealthHub. Patients who were not engaging with the CFHealthHub could have had different treatment experiences from those using it and therefore could potentially hold different views about the benefits of self-monitoring and feedback etc. Although pragmatically and ethically speaking this group of patients had provided consent to be contacted about future research which is why they were approached. However, a purposive sample of people with CF were recruited to the study (e.g. both lower and higher adherers) to ensure there was variability within the sample and to be more representative of the CF population. Those who were in lower adherers group spoke within the qualitative study that this opportunity gave them motivation to take their treatments as prescribed. Furthermore, both patients

living with CF and HCP's were recruited from a number of different CF centres to encourage a more diverse sample of participants. In addition to this it should be acknowledged that participant recruitment and response rates were not recorded for the main N-of-1 study. This is due to the complexities of recruiting across three sites, in addition due to ethical reasons HCP's lead recruitment activities which meant unfortunately this data was not recorded. This information would help to provide more clarity about how many people were approached and how many agreed to take part in the study.

Furthermore, as previously referred to it is important to consider that symptoms are interpreted uniquely and it is difficult to calibrate this. Previous literature has suggested that patients living with long-term conditions can under report symptoms (Flythe et al., 2018). However once again the N-of-1 methods help to counteract this as the aim is not to aggregate scores and compare across participants instead to understand the unique relationship for the one patient. This means that the person objective interpretation of symptoms is not a problem. Furthermore, the current thesis adopted a mixed-methods approach which meant there was an opportunity to discuss patients experiences of symptoms during in-depth interviews.

As previously disuccsed in the early development of this thesis it was anticipated that within or post PhD programme there would be scope to develop an intervention in order to investigate whether interventions that utilise *feedback and monitoring* behaviour change techniques/strategies (BCTs) could be used to increase treatment adherence (Michie et al., 2013). However, the findings of this research revealed that the relationship between adherence and symptoms was unique across individuals and that adherence does not consistently predict improvement in CF symptoms. Therefore this would limit the benefits of showing patients feedback data, if the aim was to demonstrate clear benefits of treatment adherence on

symptoms. The findings from the study however capture the uniqueness of patients and how people respond differently to treatments and also suggest that utilising *feedback and monitoring* behaviour change techniques/strategies (BCTs) (Michie et al., 2013) could facilitate a collaborative approach between patients and HCP's when managing adherence to nebulised treatments in patients with CF.

The findings of this thesis are specific to CF and it is likely findings would be different in other long-term or chronic conditions, where the relationship between symptoms and adherence is different too. However, there is limited evidence available. The findings from this thesis emphasise the importance of a collaborative and patient-centred approach to healthcare, working together to share data and create plans for the patient to suit their needed specifically. This is something where BCT tools could be fostered not only to encourage behaviour change but to promote this relationship. Looking ahead, if this was to be further developed, patients should be given the opportunity to opt in or out to sharing their data with HCP's. For those who opt in, data could be used during consultations to inform clinicians of recent experiences in relation to symptoms and to aid discussion. However, prior to this work which looks at how this would/could be used within clinical consultations would be useful.

8.3 Reflexive Piece

The following section will reflect on the PhD process and specifically what has changed during the process, this part of the discussion will be written in first person:

My professional role and identity

As previously outlined within the method chapter positionality statement prior to the PhD I had no experience of working with people living with CF, neither did I have personal experiences of this condition. This meant that when I started the PhD I had lots to learn from my supervisors and advisors before really getting started with the research and working with patients myself. I worked as a

‘demonstrator’ for three years which meant I earnt a stipend whilst working on the PhD and helping with teaching.

Once my demonstratorship at Sheffield Hallam finished we were at the start of the pandemic and I was in a position where I needed a steady income and I also wanted to build my experience whilst working on my PhD. I spent a year during the pandemic working in a Public Health role, I worked on a large scale intervention which aimed to improve levels of Physical Activity in deprived communities of Lancashire.

I value this experience of working outside academia, I learnt so much about partnerships, working in communities, funding bids and how to approach things pragmatically when working in the real world. A large part of my role was also translating complex research and interventions to members of the public, this is a skill which I have applied to collecting qualitative data during my thesis.

Whilst working full-time I was completing the data collection for the qualitative study with patients living with Cystic Fibrosis. I found this experience incredibly moving- collecting this data during the pandemic which was such a scary time for everyone but especially those living with long-term conditions. Ensuring participants were not overburdened was the main priority, there was of course some participants who did not respond to the invite but others who were incredibly keen to arrange their interview. I felt some of the participants enjoyed having the opportunity to speak to somebody different during this lonely period of time. I felt this made a difference to the way I conducted the interviews, perhaps relaxing myself and I felt as a result of this the data was so interesting and helpful. However as a researcher it was a challenging time to be in the middle of PhD data collection the guidance from the university was constantly being circulated and I was collecting data on video call for the first time.

Following this I started a Psychology lectureship at Sheffield Hallam University. I found it challenging going back to Sheffield Hallam in

this role, before the pandemic I was heavily involved in the PhD community and so much had changed once I returned. I experienced Imposter Syndrome and felt like I was both a student and member of staff at the same time which was tricky.

Throughout the process of the PhD- the good and bad, I have developed so much in confidence. I am now a Senior Lecturer in Psychology. Despite the challenges I enjoy working in academia and I image this is something I will do for a long time. I have developed new modules, lead modules, supervised a number of projects both Undergraduate and Postgraduate and proudly been nominated for an 'Inspirational Teaching Award' every academic year. I share my PhD journey with students and I am passionate about teaching them about real life research and how they can use their knowledge in the real world. I have implemented this in a new module 'Applying Psychology' where students develop an intervention for their assessment and use the Behaviour Change Wheel (Michie et al., 2014) to guide them through the process. Whilist reflecting upon this it is clear how my positionality has impact my work within my academic career and my PhD research also.

Working full time whist completing the PhD has certainly not been easy, it has been a lot to manage personally both for me and my close family who have supported me. Personally I found it difficult to fully embrace the experience of being a 'PhD researcher' once working full time as it is so difficult to split time across different responsibilities. I often wished I could go back to being a full time PhD student.

Methodologically

Following the completion of the six week symptom tracking period it was clear that the development of an intervention was not the way to progress with the project, at the time this was difficult to process. I was less experienced and felt that everything with the PhD would pan out according to a Gantt chart and timelines which were set in

the first few months! However this was a valuable learning experience and the first to teach me that research often does not work the way we expect it to. Therefore, being flexible and adaptive is a necessity.

Using the mixed-methods approach to address the research questions, came with challenges and at times was a lot to manage. Collecting data each day for four months for a number of participants was a lot. I still remember on Christmas Day ensuring checking things had been sent and also when on holiday in the Isle of Arran panicking that I had no signal and desperately trying to find WiFi to check things. At this point in time I lived and breathed everything about the PhD. Dealing with large data sets was something I personally found difficult, however a useful skill which has helped me feel more confident with collecting data of this nature. I always felt that the qualitative data collection came more naturally to me. Although I genuinely feel that the use of mixed-methods data has worked well during the project and I enjoy using both qualitative and quantitative methods in my work. The N-of-1 data allows the exploration of the relationship between symptoms and adherence, but the qualitative data allows the exploration of this with patients living with CF and their healthcare professionals.

Although I delayed each email so it was sent at the correct time each day I still felt the need to check each day that emails had been sent appropriately. If I was to use this form of data collection again I would look into a more competent automated system which could help relieve some of the burden.

Not only was the data collection period intense for me as the researcher but I was reliant on HCP’s to help me recruit participants into the study. Whilst managing such busy roles I was so thankful for them going above and beyond to support my study. As I worked with multiple sites which were based across the country their help meant that I could work with participants remotely rather than spending time and money travelling around the country. However relying on others was sometimes a challenge and if I was

responsible for recruitment I would have been able to capture more detail (for example we were not able to capture recruitment rates for participants in the main study).

Reflecting on the process of major corrections

Working through my major corrections has been challenging and would not be possible without the support of my supervisors, Maddy and Jenny and my close family. However, I can personally see the improvements in my work and as researcher I have learnt a lot during the past 16 months.

I am really thankful for the opportunity I had to share the findings with Healthcare Professionals and discuss my findings with them and think about how the findings could fit in real practice. This has added so much to the story of my thesis.

During this time I have personally developed resilience, as previously discussed I have tried to be open with students about knock-backs and how it is important to accept things might not work out as planned, at any point during your career. I have had times when I doubted myself and ability to do this but I feel that this work is important and deserves to be out there. Thinking of all the patients I have spoke to during this time has kept me going.

What would I do differently?

If I could start this journey again, I would now know that my journey is not likely to be a perfect journey and I could come across challenges and disruptions. I think accounting for these disruptions would be helpful- things like NHS ethics are time consuming and cannot be changed. Obviously nobody could have anticipated that I would be working on this through a pandemic!

I would also like to factor in time to present my findings back to the PPI group, to discuss exactly what the patients think and what they would like me to do with this work going forward. I enjoyed using the Data-Prompted interviews and felt this was an opportunity to share the data with participants. This was their data, which they had

collected each day for a long period of time and I felt they were owed that opportunity. I was determined that the process would not be transactional. Next time I would like to do something like this on a larger scale.

The thread through all of this; working in industry, lecturing and researching is that I have a passion for working with people and trying to help others in my professional role.

What next?

Professionally, I have been lucky enough to secure additional research hours 'Significant Potential for Research' this means over the next three years I will have time dedicated to working on research. I will spend some of these hours working to publish two papers from the thesis. I feel that disseminating this work will be useful for both people living with Cystic Fibrosis and Healthcare Professionals. I have also been invited to work on a PhD programme to shadow experienced supervisors and get some experience of the process from the other side, I feel I have plenty of experience for this and look forward to the opportunity.

However, this will have to wait a little while as I will be taking some time off work to enter a new chapter Motherhood! I think some of the lessons learnt on this journey will even be useful there!

8.4 Concluding remarks

This thesis offers a unique contribution to the field of Health Psychology, firstly this body of work presents symptom tracking and adherence data to both HCP's and patients living with CF in order to understand if symptom tracking is acceptable and feasible in the real world. Secondly, this thesis has utilised novel N-of-1 methods which have enabled greater understanding around individual relationships between symptoms and adherence. This mixed methods design has helped build greater understanding around the

relationship between symptoms and adherence in both patients living with CF and HCP's who care for them.

The outcomes from this thesis have contributed novel research findings to the body of evidence in health psychology which investigates medication adherence; in particularly medication adherence in patients living with Cystic Fibrosis. Medication adherence is a complex behaviour and the relationship between adherence and symptoms of CF is extremely complex. This work helps deepen understanding of this relationship and also explore the practical applications of using symptom tracking. The findings suggest that symptom tracking and feedback data could help some patients CF who value this type of activity/feature, to understand, manage and reflect on their adherence and get a better understanding of their symptom experiences too. Finally this piece of work suggests that HCP's also find symptom monitoring to be feasible and something which could be embedded as part of their practice.

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Appendices

Appendix A: PPI topic guides

PPI meeting- project summary

Hi, I'm Rosie Martin, a Psychology PhD student at Sheffield Hallam University (SHU). I'm linked directly to the ACtiE project, as I am supervised by Maddy Arden, Martin Wildman and also Jenny Porritt, Jenny is based at SHU.

The aim of my project is to investigate the role of self-monitoring Patient Reported Outcome Measures (you will see these referred to as **PRO's** or **PROM's**) for example questions you may answer at the clinic such as 'have been coughing during the day?' We want to map these measures onto patients adherence to their nebuliser.

However as you are well aware this is a long process and involves lots of different procedures so to start with I would just like to chat to the PPI group. Which will help guide the type of questions, which are included in the study, and also I would be interested to find out if the group feel it is feasible for patients to answer questions every day for up to 2 months.

Here are some areas I would like to discuss in a little more detail:

- What kind of symptoms are experienced before an exacerbation?
- Does this to predict an exacerbation in the following days/weeks?
- Do you change anything during this time? Or is there anything you could change to prevent or delay the exacerbation?
- How do you feel after your exacerbation is treated?

Acceptability of keeping a daily diary

- How does the group feel about answering questions on a daily basis?
- How would you feel about keeping a daily diary*
- How does the group feel about wearing a watch or receiving an email reminder? This would prompt the participants to answer the PROM's.
- Would this be adequate or is a text message reminder preferred?

Participation

- This is would be to get the initial symptoms together which will be tracking the next study.
- Would this be something the PPI group would be interested in?

Patient Reported Outcome Measures

- **CFQ-R-** How do the group feel about this scale? (see attachment)
- **CFQoL-** How does the group feel about this scale (see attachment)
- Which scales and also answer system is referred?

Appendix B: Participant facing documents study 1 (chapter 4)

Participant Information Sheet

Study title: Investigating the perception and comprehension of graphs displaying health-related data

Invitation: As a doctoral researcher at Sheffield Hallam University I would like to invite you to take part in our research study. Before you decide we would like you to understand why the research is being carried out and what it would involve if you were to take part.

What is the purpose of the study?

The purpose of this research is to investigate how best to present graphs which contain healthcare data to people in a way which they understand.

Do I have to take part?

No. It is up to you whether or not you decide to take part in this study. If you do decide to take part you will be presented with this online information sheet and asked to read an online consent form. If you choose not to take part you do not need to give a reason. At the end of the questionnaire participants can opt to be entered into a prize draw with a chance to win a £20 Amazon voucher.

What would taking part involve?

If you agree to participate in the study, you will be asked to complete this online questionnaire. As part of the questionnaire you will be presented with a variety of graphs and asked questions about these. Participating in the study should take approximately 20 minutes of your time.

Am I eligible?

If you are over 18 and living in the UK you are eligible to take part.

What are the possible disadvantages and risks of taking part?

There are no known risks associated with the study.

Will my taking part in the study be kept confidential?

Yes. If you would like to take part in the prize draw you will be asked to provide your email address. This is optional. This personal data will be kept confidential and stored separately to the data you provide in response to the questionnaire. The study has Research Ethics Committee (REC) approval (R12789084). Research data will be completely anonymised and may be published in an academic journal and PhD thesis. This data could be stored for up to 5 years in line with journal requirements.

What will happen if I don't want to carry on with the study?

You can withdraw from the study at anytime whilst you are in the process of completing the study online. However once answers have been submitted they can not be withdrawn.

What if there is a problem?

Any complaints about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. Detailed information on who to contact are given at the end of this information sheet.

What will happen to the results of the research study?

The findings from this study will be reported in the thesis of the PhD programme. It is also likely that findings will be

used in published research articles and presented at conferences. All results will be anonymous.

Who is organising and funding the research?

The research is funded by Sheffield Hallam University as part of an educational programme.

Who has reviewed the study?

The study has been reviewed by the ethics committee at Sheffield Hallam University (study code R12789084).

Legal basis for the research study

The University undertakes research as part of its function for the community under its legal status. Data protection allows us to use personal data for research with appropriate safeguards in place under the legal basis of public tasks that are in the public interest. A full statement of your rights can be found at https://www.shu.ac.uk/about-this-website/privacy-policy/privacy-notices/privacy-notice-for-research . However, all University research is reviewed to ensure that participants are treated appropriately and their rights respected. This study was approved by Sheffield Hallam Research Ethics Committee. Further information at https://www.shu.ac.uk/research/ethics-integrity-and-practice

Thank you for taking the time to read this information sheet and for considering taking part in this study.

If you want further general or specific information about the research please contact:

Rosie Martin
Doctoral Researcher
Sheffield Hallam University
Department of Development and Society

Collegiate Crescent
S10 2BA

Email address: rosie.martin@shu.ac.uk

Supervisors contact details: m.arden@shu.ac.uk and j.porritt@shu.ac.uk

You should contact the Data Protection Officer if:

you have a query about how your data is used by the University you would like to report a data security breach (e.g. if you think your personal data has been lost or disclosed inappropriately) you would like to complain about how the University has used your personal data DPO@shu.ac.uk

You should contact the Head of Research Ethics (Professor Ann Macaskill) if you have concerns with how the research was undertaken or how you were treated

a.macaskill@shu.ac.uk
Postal address: Sheffield Hallam University, Howard Street, Sheffield S1 1WBT Telephone: 0114 225 5555

ONLINE PARTICIPANT CONSENT FORM

TITLE OF RESEARCH STUDY: Investigating the perception and comprehension of graphs displaying health-related data

Please read the following statements:

1. I have read and understood the Information Sheet for this study.
2. I am aware that I can contact the researcher if I have any questions related to the study.

3. I understand that I am free to withdraw from the study by closing my internet browser.

4. I understand that once I have submitted my answers my data cannot be withdrawn.

5. I agree to provide information to the researchers under the conditions of confidentiality set out in the Information Sheet.

6. I am 18 years of age or older and live in the UK

7. I wish to participate in the study under the conditions set out in the Information Sheet.

8. I consent to the information collected for the purposes of this research study, once anonymised (so that I cannot be identified), to be used for any other research purposes.

I provide consent to participate in this study

Researcher contact details: rosie.martin@shu.ac.uk

Supervisors contact details: m.arden@shu.ac.uk and j.porritt@shu.ac.uk

Study debrief

Study title: Investigating the perception and comprehension of graphs displaying health-related data

Thank you for your time. The purpose of the study was to investigate participants' understanding and preferences of graphs displaying health-related data.

If you have entered the prize draw your email address will be stored safely and separately from any study-related data. If you are the winner you will receive the voucher via email by (date to be added).

Thank you again for taking the time to complete the study. If you have any further questions about the study please contact Rosie Martin on the following email rosie.martin@shu.ac.uk.

Supervisors contact details: m.arden@shu.ac.uk and j.porritt@shu.ac.uk

If you wish to be entered in to a prize draw to win a £20.00 gift voucher, please provide an email address below.

Please note your answers will not be stored with your email address.

Appendix C: Study 2 protocol (chapter 5)

Note- highlighted section are changes made from pilot study to main study

Sheffield Hallam University

Sheffield Teaching Hospitals NHS
NHS Foundation Trust

An N-of-1study to investigate the relationship between self-monitoring symptoms using daily diaries, and adherence to nebuliser treatments in adults with Cystic Fibrosis

Details of applicants

PhD student Rosie Martin, who is based at Sheffield Hallam University, is completing this study as part of the PhD. Rosie's director of studies is Professor Maddy Arden, a Professor of Health Psychology with particular expertise in health behaviour change. Maddy is based at Sheffield Hallam University. Dr Jenny Porritt is the second supervisor and is also based at Sheffield Hallam University, Jenny is a Health and Care Professions Council (HCPC) registered Health Psychologist. The third supervisor is Dr Martin Wildman, Martin is a consultant in Respiratory Medicine and Adult Cystic Fibrosis at Sheffield Teaching Hospitals. He is joint PI on the NIHR Applied Research Programme Grant: ACtiF and is leading the CFHealthHub Programme.

For details contact Rosie Martin, rosie.martin@shu.ac.uk.

Dept. of Psychology, Sociology and Politics

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1.2: Title of the project

An N-of-1 study to investigate the relationship self-monitoring symptoms using daily diaries, and adherence to nebuliser treatments in adults with Cystic Fibrosis (CF)

Section 2: Research questions

- Which symptoms of Cystic Fibrosis affect patients on a daily basis?
- How feasible is tracking CF symptoms on a daily basis?
- How does adherence map onto CF symptoms experienced by patients over a period of time?
- How can symptoms and adherence be best presented to patients so that they can understand the relationship between symptoms and adherence?
- What is the temporal relationship between symptoms and adherence?

Section 3: Abstract

Background

This PhD is linked directly with the 'Development and evaluation of an intervention to support adherence in adults with Cystic Fibrosis (ACtiF)'. This programme, funded by NIHR and NHS England has developed the CFHealthHub platform.

Previous research has shown that medication adherence is low in those with Cystic Fibrosis (CF), particularly adherence to nebulisers. However symptoms and adherence have not been mapped together. It is important that patients and professionals knowledge of the relationship between adherence and symptom experience/relief is increased if the importance of adherence is to be fully understood.

Aims

The study aims to establish a method which will accurately and sensitively measure patient reported outcomes (PRO), in a format which is acceptable to patients with CF. Once the data has been collected

objective adherence and PRO data must be presented to patients in a way which they understand. The final aim is to assess, the effect of self-monitoring PROS on: nebuliser adherence, beliefs about the effectiveness of the treatment and motivation to adhere, whilst assessing acceptability and feasibility.

Methods

The study will use a mixed methods approach. Participants will be asked to keep daily diaries, which will track their symptoms, quantitatively. Semi-structured interviews will also be used to assess the acceptability of the diary methodology, and transcripts will be analysed using thematic analysis. Similar methods will be used for the second part of the study in which adherence will be monitored and presented alongside symptoms to participants. Questionnaires will be used to explore any changes in beliefs about adherence. Additionally, physical activity will be measured using a Fitbit.

Section 4: Aims of the studies

i. To establish a method to accurately and sensitively measure daily patient reported outcome measures (PRO's) in a way that is acceptable TO people with CF.

ii. To design a way in which the PRO data and objective adherence data can be shown to people with CF in a way that they understand.

iii. To assess, the effect of self-monitoring PROS on: nebuliser adherence, beliefs about the effectiveness of the treatment and motivation to adhere.

iv. Acceptability/ feasibility will also be assessed.

Section 5: Background

Cystic Fibrosis (CF) is a life-limiting, genetic condition. The disease affects around over 10,000 people in the UK (CF registry, 2015). The disease causes abnormally thick and viscous mucus to develop (Davis et al, 2005), which can lead to a range of symptoms including respiratory problems such as coughing and shortness of breath (Sawicki et al, 2008). CF is also associated with other symptoms affecting other areas and aspects of the body such as the pancreas, digestive track and can cause malnutrition (Spoonhowever and Davis, 2016).

Thirty years ago it was rare for a patient with CF to reach adulthood (Knudsen et al, 2016). The CF registry more recently suggests the age 41 is the median predicted survival age in the UK (CF registry, 2015). One of the reasons for the increase in life expectancy is due to the recent advances in medicine. Ivacftor, a CFTR potentiator, is an example of this, the drug targets the protein of CF and increases chloride movement, which helps treat the condition (Whiting at al, 2014).

Other examples include the use of nebulisers to convert solutions of medications into a fine mist, which can be penetrated deep into the lungs. Such as Dornase Alpha which has been found to reduce exacerbations and maintain lung functions in younger patients with CF, in a two year randomised-control trial (Quan et al, 2001).

Treatment programmes typically include inhaled medication, intravenous treatments, oral tablets and physiotherapy sessions. According to Goss and Quitner (2007) the success in improving life expectancy in the US was due to both therapies which help improve symptoms and function, and interventions which helped patients manage the condition.

Previous literature (Quinttner et al, 2014; Bregenballe et al, 2011) has consistently reported, as is common in other long-term conditions, that medication adherence in patients with CF is poor. McGrady and Hommel (2013) found that when adherence was self-reported by children and adults with CF it ranged from 38% for chest physiotherapy and 50% for nutritional supplements and respiratory medications. Medication adherence is important both for the patient and also to the healthcare systems, as this could cut or increase costs significantly. As high and moderate adherence levels help to reduce hospitalisations and acute care use (Quittner et al, 2014).

The role of medication feedback on adherence

Factors such as age, gender and treatment burden have previously been used to explain this poor adherence in those with CF (Bregnballe et al, 2011). Findings suggest one possible barrier could be due to the fact that medication does not give patients an instant relief from symptoms when taking their nebuliser (Arden et al, 2016; Sawicki, 2015).

Sawicki et al (2014) found that a lack of perceived consequences from non-adherence, for example thinking that therapies make no difference in

symptoms of CF and not noticing an immediate impact from skipping treatment can result in patients not adhering for a pro-longed period of time. Which can impact negatively on the condition.

Furthermore, Bucks et al (2009) used the self-regulatory model (Leventhal et al 1980) to explore relationships between illness perceptions, treatment beliefs, emotional representations and adherence in adolescents with CF. It was hypothesised that strong beliefs about necessity for treatment and fewer concerns regarding treatment would be predictive of better self-care. Indeed it was concluded that treatment beliefs were significant predictors of good adherence.

Illness perceptions are one of many factors which can be measured using patient reported outcome measures.

Patient reported outcomes (PRO's)

A PRO is a measurement that can help patients to engage in their treatment plan and also in making decisions regarding their treatment (Aaronson et al., 2011). PRO's can be designed to measure general quality of life or target those with a specific disease, for example the Brief Pain Inventory (Cleeland, 1991).

The NHS PROMs programme was implemented in 2009, patients were asked to record their measures before and after elective surgeries, for specific operations were chosen: hip and knee replacements, hernia repair and varicose veins surgery (Barham and Devlin, 2011). Between April 2014 and March 2015 around 267,046 measurements were collected across hospitals in the UK for the same elective procedures (NHS, 2016). All patients were asked to complete the EQ-VAS, which records self-rated health on a vertical 20cm scale. Along with the EQ-5D Index, which consists of 5 dimensions: mobility, self care, usual activities, pain/discomfort, anxiety/depression, the scale has been favoured by the National Institute for Health and Clinical Excellence (Barham and Devlin, 2011).

A specific measure was also included in all patients excluding those who had a groin hernia repair (NHS, 2016). The NHS PROMs programme helped determine improvement prior and post surgery, an average health gain was also produced which enabled a clear comparison amongst patients.

The main disease specific patient reported outcome measures for CF include The Cystic Fibrosis Questionnaire-Revised (CFQ-R) (Quittner, 2005) and the Cystic Fibrosis Quality of Life measure (CFQoL) (Gee et al, 2000).

According to Goss and Quittner (2007) future research in the area of CF will include a range of PRO outcome measures. Using such outcome measures can be used in clinical practice to improve the quality of care and help guide specific individual interventions.

The CFQ-R (Quittner, 2005) has been viewed the gold standard according to Knudsen et al (2016) due to the amount of reliability and validity testing the measure has received. The questionnaire has also demonstrated robust psychometric properties, which was tested in a sample of over 7,000 American patients (Quittner et al,2011).

There are nine specific domains of the CFQ-R including: physical functioning, vitality, treatment burden, respiratory symptoms, role functioning, emotional functioning and social functioning. There are a number of formats to the questionnaire child, adult/ adolescent and child completed by an adult (Quittner, 2005).

Specific domains are often adopted in research which tends to be dependent on what the researching is measuring. The respiratory domain of the CFQ-R has been used in drug trials, particularly inhaled drugs. For example, Ramsey et al (2011) describe a clinical trial for AZLI: an inhalation solution in which the respiratory symptom domain of the CFQ-R was used to help determine improvement. At week 48 the control group scored 62 on the measure and the Ivacaftor group scored 74. The highest possible score is 100, this demonstrates a low effect from the symptoms. Participants in the Ivacaftor group also gained on average 2.7kg more in weight than the placebo group and had a lower proportion of participants who experienced serious adverse effects. The use of the respiratory domain specifically demonstrates how change in participants can be observed using the CFQ-R.

The respiratory domain will be used in the current project to help guide questionnaire development. The treatment burden domain will also be used as one of the outcome measures. To help assess how feasible a diary methodology is when working with a population who spend a large amount of time taking their treatment each day.

The current study will use PROs in the format of a daily diary, as patients will be asked about their symptoms in a questionnaire, which they will be asked to answer each day. Which will enable small changes in symptoms to be sensitively observed.

Using PRO's to measure adherence

There is a range of different approaches to measure adherence. Firstly, objective measures such as examining pharmacy refill records, pill counting or using pill bottles which monitor how often they are opened. Secondly, biochemical measurements can be used. This includes adding nontoxic makers to medication which can be measured in blood or urine (Brown et al, 2010). Subjective measures, such as outcome measures, can also be used to measure adherence. Such as the Medication Adherence Questionnaire (MAQ) (Morisky et al, 2008), the MAQ is often more preferable as it less time-consuming than other options such as the Brief Medication Adherence scale (Svarstad et al, 1999).

Daily Diary Methodology

Diary studies have developed over recent years, adopting technological advances into the methodology. The use of daily diaries is becoming increasing popular, specifically in areas within psychology, health psychology being one of them (Skaff et al, 2009). There are many advantages associated with this type of measurement; participants have the ability to enter data at any time, as they are experiencing it, which enables the capture of real life experiences. This also reduces retrospective memory bias (Lida et al, 2012).

However there is also a range of drawbacks associated with the method for example often financial incentives are needed to ensure participants will keep a diary for a prolonged period of time. Additionally, research (Sawicki and Goss, 2015) has demonstrated that patients with CF invest a large amount of time into their treatment regimen, which can be seen as a burden and impact on the wellbeing and also health related quality of life of the patient. Because of this, this population could be less likely to complete a daily diary. However some studies have found good adherence to daily diaries and the modality seems to be important.

For example, a recent study with gay men who were HIV positive, highlighted the acceptance of using mobile phones or web-enabled devices to keep daily diaries (Cherenack et al, 2016). Two different modalities were adopted- internet on any web-enabled device and voice reporting which was accessible via telephone. Participants were randomised and asked to keep one type of daily diary for 33 days and then the second type for a further 33 days, therefore all participants experienced both types. Internet diaries were preferred (77.5%) compared to voice diaries (67.7%). The study also reported a good retention rate of 93.4%. This emphasises the important of using internet diaries and demonstrates that although daily diaries can be intense it I possible to achieve a good retention rate when using the methodology in health psychology.

El Miedany et al (2016) recruited 211 patients with early rheumatoid arthritis into a double-blind randomised-control study for 12 months. A group using electronic patient reported outcome measures (ePROM) were compared to a group of patients who used a standard paper format. It was concluded that patients adherence to anti-rheumatic therapy was significantly higher in the ePROMs group. Using ePROMs was found to help patients monitor their condition and disease activity, which aided the treatment adherence.

The CF Health Hub programme of research

This PhD project is linked directly with the 'Development and Evaluation of an Intervention to Support Adherence in Adults with Cystic Fibrosis (ACtiF)'. Which has developed the CFHealthHub platform to help improve initiative and interventions in this population. Patients are provided with chipped nebulisers and the data from this is transferred onto their account on CFHealthHub. Patients are also provided with resources and tools to aid their adherence. Some of which are provided by CF patients and others by healthcare professionals, to meet their needs specifically. The ACtiF project and therefore the CF Health Hub are led by NIHR Programme grant which is led by Dr Martin Wildman. Associated to this programme of research is the development of a longitudinal trials within cohorts platform, or 'Data Observatory'. The Data Observatory participants have been given the opportunity to consent for their CFHealthHub data to be included in future research studies this will

provide the mechanism for collecting adherence data for this project however explicit consent will be sought from participants for inclusion in the proposed study.

Section 6: Plan of investigation

6.1 Methodology

The study will consist of 24 patients recruited through the Sheffield, Nottingham and Southampton adult CF centres. All participants will be CFHealthHub Data Observatory participants using the CFHealthHub (CFHH) and chipped nebulisers which measures objective adherence as part of their current treatment plan. Consent for this data collection will have previously been given as part of the REC approval for the CFHealthHub data observatory (REC reference 17/LO/0032).

Participants will be purposively sampled to include those with different: levels of adherence and lung function and exacerbation levels, to ensure participants with different characteristics and potentially different symptom experiences and profiles are recruited into the study

Participants will be asked to record between seven and ten CF-PROM's everyday a total of four months using an online survey programme called Qualtrics©. A reminder, containing a link to questionnaire, will be sent to individuals each day. The reminder will be sent by text message or email, to complete the questionnaire. The questionnaire will be presented in a visual analogue scale, participants will be asked to score their symptoms from 0-10 using a 'slider'. Participants will also be asked if they would like to nominate on additional chosen symptom for the duration of the study, they will be asked to rate that symptom each day.

All participants will be asked to participate in an interview. Participants will be given the option of an interview over the phone, Skype or face-to-face. At the end of the four month period.

The interview will focus on the perceived acceptability and burden of recording symptoms and the Qualtrics© questionnaire format. During the interview participants will be shown their recorded symptoms on a line graph and bar chart (sent beforehand via email or postal service if the interview is over the telephone). Participants will be asked about their interpretation of the data, which type of presentation they prefer, and their

reasoning behind this. The semi-structured interviews will be analysed using a thematic analysis or content analysis

Symptom data will be analysed to assess which symptoms show variability, and how these symptoms relate to measures of objective adherence over the four month period of symptom measurement.

If participants do not record their symptoms for three days they will receive a telephone call from the researcher, to check everything is well and reminders are being received. Participants will also be sent a reminder to record their daily diary each day, by email or to their mobile phone.

Adherence data from CFHH will also be used, and mapped onto the symptoms tracked by patients using the daily diary. This data will be transferred in an encrypted, password-protected email from a member of the CF team at the associated hospital or from The School of Health and Related Research (SHARR), based within the University of Sheffield which is where the CFHH is managed

At the interview participants will be presented with a more complex chart, showing nebuliser adherence mapped onto CF-PROMS (symptoms) and asked to explore the identification of patterns in CF-PROMs.

Questionnaire items will be used to assess the extent to which people understand the link between symptoms and adherence, and how and if this affects their beliefs about treatment effectiveness. Measures will be taken in prior to participation and post participation. Personal data will be taken from participant's hospital records. Table 1 details all information, which will be collected in both studies.

Table 1. Data that will be collected and the source

Data Type	**Point of data collection**	**Source of data**
Body Mass Index (BMI)	Prior, post participation and at interview points	Associated CF centre

	For the duration of the study and one year before	
Medication	Prescription history during the study and for one year before	Associated CF centre
Exacerbation information	Prior, post participation and at interview points One year prior and for the duration of the study	Associated CF centre
Nebuliser adherence	For the duration of the study and for one year before	Associated CF centre
Forced Expiatory Volume in 1 second (FEV1)	For the duration of the study and for one year before	Associated CF centre
Outcome measures	Baseline and follow-up	Participant

Participants will be given a Fitbit to wear throughout the study, this is something they must return at the end. Daily activity (step count) will be recorded to identify any patterns in symptoms and activity.

6.2 Participants

Participants for the current study will be recruited through Sheffield Teaching Hospitals (STH), Nottingham University Hospitals (NUH) and University Hospital Southampton (UHS). See table 3.

Site Name
Sheffield Teaching Hospitals (STH)
Nottingham University Hospitals
University Hospital Southampton

Inclusion criteria:

1. CF patients aged 16 years (this is the age when participants move from child to adult in Sheffield) who are currently receiving treatment through the adults CF Unit at STH,NUH or UHS.

2.Participants must use the I-neb or E-track nebuliser.

3. Participants must be English-speaking.

4.Participants will also need to own a smartphone.

5. CFHealthHub Data Observatory participant.6.Participants will be sampled based on their exacerbation history, those who have received intravenous antibiotic treatment for an infection two or more times in the previous year will be invited to take part.

Exclusion criteria:

1. Those with CF who are under the age of 16.

2. Patients who are not using I-neb or E-track nebuliser as a part of their daily treatment

3. Those who are not receiving treatment through STH, NUH or UHS.

   Patients who are in the palliative phase of treatment, pregnant or on the transplant list, at the start of the study, will also be excluded from taking part in the study.
4. Those who took part in the original six week symptom tracking period will not be asked to take part.

6.3 Sample size

Due to the chosen methodology (N-of-1) a relatively small sample size is required, however due to the strong likelihood of attrition a larger sample will be recruited. Previous N-of-1 studies have recruited at least seven participants (McDonald et al., 2017). Therefore an additional 24 participants (will be recruited, as it is anticipated the attrition rate will be around 50%. In combination with the six participants already recruited it is estimated that the final sample size will be 18.

The sample will be purposeful taking into account recent exacerbations and symptoms to ensure maximum variability in the symptoms tracked.

6.4 Recruitment and Informed Consent

A member of the clinical team will identify appropriate patients who fit into one of the sub-groups and also meet the eligibility criteria. The patients who will be approached will be those who have already agreed to participate in the CF Health Hub Data Observatory study (REC reference 17/LO/0032), and as part of that participation have indicated that they are willing to be contacted about future research studies.

An invitation letter and information sheet will be sent in the post to these patients from a member of the clinical team. The invitation letter will explain to patients that a member of the clinical team will contact them to discuss the study either over the telephone or during their next scheduled clinic visit.. In the discussion with the clinical team member, patients will have the opportunity to ask any questions they have about the study. The clinical team member will then ask the patient if they are interested to participate in the study. If the patient agrees, the clinical team member will provide the patient's contact details (phone number or email) to researcher Rosie Martin. The researcher will then approach the patient either at the same clinic visit OR by telephone to arrange another study visit at the clinic. This is the process which has been used to date, however if recruitment is low the clinical team at each site will be provided with a large and varied number of set 'appointment' slots to fill.

The researcher will then contact the patient to arrange a study visit. At the beginning of the study visit, the researcher (Rosie Martin) review the study information with the patient and the information sheet and complete the informed consent form with the patient, should they agree to participate.

Alternatively a member of the clinical team or the site interventionist who have the appropriate training, can take consent at this time. Following this their contact details will be passed onto Rosie over the telephone who will then contact the participant to help set up the Fitbit (if required) and ask questions relating to the symptom survey (e.g. what time they would like to receive it, if they would like to nominate a symptom).

6.5 Interviews

Participants will be asked if they would prefer to be interviewed over the telephone or face-to-face. Efforts will be made to suit participant's circumstances. It is anticipated that each interview will last for around 30-40 minutes. Those who chose to be interviewed on the telephone will receive their personal charts by email or in the post prior to the interview. Participants who prefer to be interviewed at home will receive the charts on the day of the interview. The lone working policy from SHU will be adopted, to protect the safety of the researcher.

All interviews will be audio recorded on a Dictaphone and transcribed verbatim. Anonymised transcripts will be stored on a password-protected computer. Transcripts will only be accessible by the research team. If a participant raises a safeguarding issue during their interview or at point during their participant in the study, Dr Martin Wildman who as an advisor for doctoral research programme will be contacted. As an employee of Sheffield Teaching Hospitals (STH) Dr Wildman is contractually bound to follow the appropriate safeguarding procedures, once the issue has been reported. STH is part of the Adult Safeguarding Partnership in conjunction with Sheffield City Council, therefore the policies are in place should this event occur. Disclosures will also be reported to the ethics committee so they are also aware.

If participants prefer to be interviewed from home the university's lone-working policy will be adopted. This requires the researcher to complete a risk-assessment and have contact with a Sheffield Hallam employee before and after each interview.

An interview schedule will be used as a guide when interviewing participants.

6.7 Outcome measures

Outcome measures will be used in prior to participation and post participation. See table 4 for more detail.

Table 4. Description of outcome measures

Outcome measures	**Description**	**Format**	**When the measure will be given to participants ?**
Nebuliser adherence	Taken from CFHH	All adherence will be obtained	Throughout the study
eliefs about Medicine Questionnaire-specific (Nebuliser Adherence) (BMQ 21- item) (Horne, 1999) and items adapted from this measure.	A validated self-report tool, edited by the author to identify necessities and concerns for nebuliser treatment.	Questionnaire (Self-report)	Baseline and four month follow-up

Intention and self-efficacy to adherence	Five item Likert scales will be used to measure intention and self-efficacy to adhere.	Likert scale	Baseline and four month follow-up
Symptoms over time	Collected using a daily diary in a visual analogue scale format.	Daily diary	Each day (for a total of four months)
CFQ-R treatment burden domain	A domain taken from the CFQ-R	Questionnaire (self-report)	Baseline and follow-up
Daily activity	A watch like device which participants will be asked to wear each day through their participation.	Measurement from Fitbit device	Each day

6.8 Statistical analysis

Quantitative data will be collected through the use of daily diary methodology, time series analysis using SPSS will be used to analysis the data.

The data will also be used to create graphs and charts, which depict symptoms and also adherence.

6.9 Analysis

Semi-structured interviews will be used as the qualitative component of each study. Interviews will be analysed using experimental thematic analysis or content analysis, as the interview is focusing on the ease of reading graphs (Braun and Clarke, 2013). A thematic analysis involves the following stages:

- Reading through transcripts thoroughly and becoming familiarised with the data.
- Generating initial codes
- Searching for themes

- Reviewing themes
- Defining and naming themes

6.10 Data storage

The interview will be audio recorded and stored on a password protected computer drive using an identification number. This computer drive is only available to the research team. Transcriptions of the interviews will be anonymised and all anonymised transcripts will be stored for a minimum of 5 years (in line with any journal requirements for storage of data).

All audio recordings will be deleted after transcription. All data will be stored on a University password-protected account in a secure drive. Personal data will be stored separately, a conversion sheet which includes identification numbers will also be stored separately in this drive (the document will be password protected).

Interviews will be transcribed by the researcher or by a private transcription company used by Sheffield Hallam University; data will be transferred securely using a unique username and password to upload the data. According to the company website, each of the computers are installed with biometric access encrypted hard drives to safeguard sensitive data. Once the interviews have been transcribed the researcher (RM) will log on to download the transcriptions using unique account details, which will not be shared with anybody else. As a part of the security agreement once transcripts are completed by the company audio files are deleted. Anonymised transcripts will be stored securely on a Sheffield Hallam password-protected account.

6.11 Withdrawal

Participants will be given the opportunity to withdraw at anytime throughout the study, details of which will be provided in their information sheet. However once data collection has finished participants will no longer be able to withdraw. This will be made clear to them in the participant information sheet. If participants withdraw from the study before the study is complete they can choose to request that all data is if they make this request known to the researcher. If not then the data

collected up to the point of the withdrawal will be included in the study and analysis.

6.12 Instruments

The Beliefs about Medicine Questionnaire- specific (Nebuliser Adherence) (BMQ 21- item) (Horne, 1999) This measure has been adapted by Horne, to suit those who take a nebuliser.

The CFQ-R (Quittner, 2005) treatment burden domain will also be used in the current study. The domain consists of three questions, with four multi-choice answers.

6.13 Project plan

As the studies are part of a PhD thesis it is important that proposed time frames are met to ensure the research is conducted and written up within the appropriate amount of time.

Table 5. Project plan for study

Study 1	
Month	**Task**
January	NHS Research Ethics Committee review and HRA approval
Febuary	Clinical team will identify patients
March	Contact patients once they have provided consent
April	Begin recruitment
April, May, June,July	Monitor symptoms for three weeks

August	Interview participants

6.14 Resources

The project also requires a Qualtrics account (online survey tool), which is free to students at Sheffield Hallam University.

Interview transcription to be complete by a private company, this is funded by Sheffield Hallam University.

Section 7: Methods for disseminating research results

It is anticipated that the findings from the study will be published in respected health psychology and/or medical journals and presented at appropriate conferences, such as the Division of Health Psychology annual conference 2019.

Section 8: Strategy for taking the work forward in the research projects are productive

Section 9: References

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Appendix D: Participant information sheet and consent form pilot study (Chapter 5)

Sheffield Hallam University

Sheffield Teaching Hospitals NHS
NHS Foundation Trust

University Of Sheffield.

Participant information sheet

Study title: A pilot study to investigate the role of self-monitoring symptoms using daily diaries, to increase adherence to nebuliser treatments in adults with Cystic Fibrosis (CF).

I**nvitation:** We would like to invite you to take part in our research study. Before you decide we would like you to understand why the research is being carried out and what it would involve if you were to take part. **One of the team will go through the information sheet with you and answer any questions you have.** This should take about five to ten minutes. Talk to others about the study if you wish and ask us if there is anything that is not clear.

What is the purpose of the study?
The purpose of this research is to pilot the symptoms and patient-reported outcome measures which have been identified in the existing CF literature. We will also investigate the feasibility of using a daily diary in patients with CF. To do this you will be asked to answer questions regarding your symptoms on a daily basis, this will act as your 'daily diary' for the purpose of the study.

Why have I been invited?
You have previously given your informed consent to participate in the CF Health Hub Data Observatory study, and as part of that study you indicated that you would be willing to be contacted about future research studies for which you may be suitable. We are recruiting adults (aged 16 and over) who have CF, and attend Sheffield Teaching Hospitals, to take part in this study.

To take part you must be a participant in the CFHealthHub Data Observatory, as we will be using your adherence data to present alongside the symptoms that you will be asked to record on a daily basis for a total of 6 weeks.

Do I have to take part?
No. It is up to you whether or not you decide to take part in this study. If you do decide to take part you will be given this information sheet to keep and asked to sign a consent form. If you choose not to take part you do not need to give a reason and your care will not be affected in any way.

What would taking part involve?

You will be asked to track your symptoms of CF each day in a 'daily diary'. This is a short questionnaire which will take an average two minutes to answer. These questions can be answered wherever you like; at home, work or at a friends house. You will be sent the link to your mobile phone at an agreed time convenient to yourself. However it is important that you answer these questions at the same time each day.

You will be asked to keep a daily diary for three weeks, you will then be interviewed about how you found keeping a diary and then asked to track again for a further three weeks in total. This time your adherence will also be monitored. The study will finish with a final interview.

If you do not respond for three days or more you will receive a telephone call, to check you are still receiving the reminders and are happy to continue your participation.

Along with symptom tracking you will be asked to wear a Fitbit, which is a wireless activity monitor you wear around the wrist. This will help to monitor daily exercise by counting the number of steps you take each day. This device will need to be paired with your phone. The Fitbit will be lent to you for the duration of the study and you will be kindly asked to return it after your participation. If the Fitbit stops working or gets lost, wherever possible an attempt will be made to replace the device. However if this is not possible you will be asked if you would like to continue with all other aspects of the study except for this. If there is an issue with the device data generated until this point may be used.

What are the possible benefits of taking part?
Tracking daily symptoms can help you to become more aware of patterns in your condition. We will show you charts of symptoms and how that might link to your adherence data.

What are the possible disadvantages and risks of taking part?

The disadvantages of taking part in the current study mean that you will need to spend a small amount of time each day answering the questions provided. Participation is fairly time-consuming, as it requires daily participation.

Will my taking part in the study be kept confidential?
Yes, your data will be kept confidential. It will be governed by the Data Protection Act (1998) and has Research Ethics Committee (REC) approval (SHU Reference AM/RKT/435-MAR). Information will be completely anonymised if it is to be analysed or published outside the supervisory team.

Only the researcher and supervisory team will be able to see your personal information. The information that can identify you personally will never be given to anyone else or published. Only relevant sections of your medical notes will be looked at by the researcher this includes; lung function scores, Body Mass Index (BMI), prescription information, adherence data and genetic mutation.

If anything you raise during your participation is a safeguarding issue Dr Martin Wildman or Dr Rachael Curley will be informed of this. The appropriate steps will then be taken to ensure the issue is dealt with as stated in the hospital policy.

What will happen if I don't want to carry on with the study?
You can withdraw your consent at anytime in the future without giving a reason. If you withdraw your consent, any information collected with consent will remain and be used in the study. No further information will be collected and a record will be kept that you withdrew consent or were unable to continue to provide consent. Your care will not be affected in any way if you change your mind and withdraw from the study.

If you wish to withdraw please contact Rosie Martin using the contact details listed at the end of this information sheet. Alternatively if you wish to withdraw you can stop keeping your diary and you will be contacted within two days to ask if you would like to continue.

What if there is a problem?
Any complaints about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. Detailed information on who to contact are given at the end of this information sheet.

If there is a problem which is specific to your condition it is important you contact a member of the clinical team at STH.

What will happen to the results of the research study?
The findings from this study will be reported in the thesis of the PhD programme. It is also likely that findings will be used in published research articles and presented at conferences. All results will be anonymous.

Will my general practitioner (GP) be contacted?
Your GP will not be contacted as part of your participation in this study, similarly there will be no contact if you chose not to participate.

Who is organising and funding the research?
The research is funded by Sheffield Hallam University as part of an educational programme.

Who has reviewed the study?
All research in the NHS is reviewed by an independent group called a Research Ethics Committee, to protect the interests of patients and participants in research. This study has been reviewed and given favourable opinion by Research Ethics Committee and the Sheffield Teaching Hospitals NHS Foundation Trust R&D Department (Clinical Research Office). Sheffield Hallam Research and Ethics committee have also reviewed and passed the study.

Thank you for taking the time to read this information sheet and for considering taking part in this study.

Further information and contact details:

A member of the clinical team will contact you either by telephone or at your next clinic appointment to discuss the study with you and answer any questions you may have. After this discussion and if you agree, the clinical team will provide your contact details to the researcher Rosie Martin. The researcher will then contact you to arrange a study visit and to receive your informed consent to participate in the study.

If you want further general or specific information about the research please contact:

Rosie Martin
Doctoral Researcher
Sheffield Hallam University
Department of Development and Society
Collegiate Crescent
S10 2BA

Email address: rosie.martin@shu.ac.uk

If you have any complaints that you would like to be dealt with independently please contact:

Information removed

Centre Number:

Study Number:

Participant Identification Number for this trial:

CONSENT FORM

Title of Project: A pilot study to investigate the role of self-monitoring symptoms using daily diaries, to increase adherence to nebuliser treatments in adults with Cystic Fibrosis

Name of Researcher: Rosie Martin

.

1. I confirm that I have read the information sheet (Version X dated XX) for the
   above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.

3. I understand that all interviews whether face-to-face or over the telephone or Skype will be audio recorded.

4. I understand that anonymised quotes from interviews may be used in the PhD thesis and publications.

5. I agree to take part in the above study.

Name of Participant	Date	Signature
Name of Person taking consent	Date	Signature

For further details please contact:

Rosie Martin
Doctoral Researcher
Sheffield Hallam University
Department of Development and Society
Collegiate Crescent
S10 2BA

Email address: rosie.martin@shu.ac.uk

Professor Madelynne Arden
Professor of Health Psychology
Department of Psychology, Sociology & Politics
Sheffield Hallam University

Telephone number: 0114 225 5623
Email address: m.arden@shu.ac.uk

Appendix E: CFHealthHub Graph Examples

Removed due to copyright reasons

CFHealthHub (2023) *Reducing the burden of Cystic Fibrosis by creating habits of self-care* https://www.cfhealthhub.com/

Appendix F: Participant information sheet and consent form (main N-of-1 study and qualitative study) chapter 5 and 6

Sheffield Hallam University

Sheffield Teaching Hospitals NHS
NHS Foundation Trust

The University Of Sheffield.

Participant information sheet

Study title: An **N-of-1**study to investigate the **relationship between** self-monitoring symptoms using daily diaries, **and** adherence to nebuliser treatments in adults with Cystic Fibrosis

I**nvitation:** We would like to invite you to take part in our research study. Before you decide we would like you to understand why the research is being carried out and what it would involve if you were to take part. **One of the team will go through the information sheet with you and answer any questions you have.** This should take about five to ten minutes. Talk to others about the study if you wish and ask us if there is anything that is not clear.

What is the purpose of the study?
The purpose of this research is to monitor the symptoms and patient-reported outcome measures which have been identified in the existing CF literature. We are interested in investigating the relationship between symptoms and adherence. To do this you will be asked to answer questions regarding your symptoms on a daily basis, this will act as your 'daily diary' for the purpose of the study.

Why have I been invited?
You have previously given your informed consent to participate in the CF Health Hub Data Observatory study, and as part of that study you indicated that you would be willing to be contacted about future research studies for which you may be suitable. We are recruiting adults (aged 16 and over) who have CF, and attend Sheffield Teaching Hospitals to take part in this study.

To take part you must be a participant in the CFHealthHub Data Observatory, as we will be using your adherence data to present alongside the symptoms that you will be asked to record on a daily basis for a total of four months.

Do I have to take part?
No. It is up to you whether or not you decide to take part in this study. If you do decide to take part you will be given this information sheet to keep and asked to sign a consent form. If you choose not to take part you do not need to give a reason and your care will not be affected in any way.

What would taking part involve?

You will be asked to track your symptoms of CF each day using an electronic' daily diary'. This is a short questionnaire which will take an average two minutes to answer. These questions can be answered wherever you like; at home, work or at a friends house. You will be sent the link to your mobile phone at an agreed time convenient to yourself. However it is important that you answer these questions at the same time each day.

You will be asked to keep an electronic daily diary for four months, the study will finish with an interview.
If you do not respond for three days or more you will receive a telephone call, to check you are still receiving the reminders and are happy to continue your participation.

Along with symptom tracking you will be asked to wear a Fitbit, which is a wireless activity monitor you wear around the wrist. This will help to monitor daily exercise by counting the number of steps you take each day. This device will need to be paired with your phone. The Fitbit will be lent to you for the duration of the study and you will be kindly asked to return it after your participation. If the Fitbit stops working or gets lost, wherever possible an attempt will be made to replace the device. However if this is not possible you will be asked if you would like to continue with all other aspects of the study except for this. If there is an issue with the device data generated until this point may be used.

What are the possible benefits of taking part?
Tracking daily symptoms can help you to become more aware of patterns in your condition. We will show you charts of symptoms and how that might link to your adherence data.

What are the possible disadvantages and risks of taking part?

The disadvantages of taking part in the current study mean that you will need to spend a small amount of time each day answering the questions provided. Participation is fairly time-consuming, as it requires daily participation.

Will my taking part in the study be kept confidential?
Yes, all of your personal (identifiable) data will be kept confidential. It will be governed by the Data Protection Act (1998) and has Research Ethics Committee (REC) approval (SHU Reference AM/RKT/435-MAR). Only anonymised information (which does not contain any identifiable information) will be analysed or published outside the supervisory team.

Only the researcher and supervisory team will be able to see your personal information. The information that can identify you personally will never be given to anyone else or published. Only relevant sections of your medical notes will be looked at by the researcher this includes; lung function scores, Body Mass Index (BMI), prescription information, adherence data and genetic mutation.

If anything you raise during your participation is a safeguarding issue Dr Martin Wildman or Dr Rachel Curley will be informed of this. The appropriate steps will then be taken to ensure the issue is dealt with as stated in the hospital policy.

What will happen if I don't want to carry on with the study?
You can withdraw your consent at anytime in the future without giving a reason. If you withdraw your consent, any information collected with consent will remain and be used in the study. No further information will be collected and a record will be kept that you withdrew consent or were unable to continue to provide consent. Your care will not be affected in any way if you change your mind and withdraw from the study.

If you wish to withdraw please contact Rosie Martin using the contact details listed at the end of this information sheet. Alternatively if you wish to withdraw you can stop keeping your diary and you will be contacted within two days to ask if you would like to continue.

What if there is a problem?
Any complaints about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. Detailed information on who to contact are given at the end of this information sheet.

If there is a problem which is specific to your condition it is important you contact a member of the clinical team at UHS.

What will happen to the results of the research study?
Anonymised findings from this study will be reported in the thesis of the PhD programme. It is also likely that findings will be used in published research articles and presented at conferences. All results will be anonymous.

Will my general practitioner (GP) be contacted?
Your GP will not be contacted as part of your participation in this study, similarly there will be no contact if you chose not to participate.

Who is organising and funding the research?
The research is funded by Sheffield Hallam University as part of an educational programme.

Who has reviewed the study?
All research in the NHS is reviewed by an independent group called a Research Ethics Committee, to protect the interests of patients and participants in research. This study has been reviewed and given favourable opinion by Research Ethics Committee and the Sheffield Teaching Hospitals NHS Foundation Trust R&D Department (Clinical Research Office). Sheffield Hallam Research and Ethics committee have also reviewed and passed the study.

Legal basis for the research study

The University undertakes research as part of its function for the community under its legal status. Data protection allows us to use personal data for research with appropriate safeguards in place under the legal basis of **public tasks that are in the public interest.** A full statement of your rights can be found at https://www.shu.ac.uk/about-this-website/privacy-policy/privacy-notices/privacy-notice-for-research . However, all University research is reviewed to ensure that participants are treated appropriately and their rights respected. This study was approved by Sheffield Hallam Research Ethics Committee. Further information at https://www.shu.ac.uk/research/ethics-integrity-and-practice

Thank you for taking the time to read this information sheet and for considering taking part in this study.

Further information and contact details:

A member of the clinical team will contact you either by telephone or at your next clinic appointment to discuss the study with you and

answer any questions you may have. After this discussion and if you agree, the clinical team will provide your contact details to the researcher Rosie Martin. The researcher will then contact you to arrange a study visit and to receive your informed consent to participate in the study.

If you want further general or specific information about the research please contact:

Rosie Martin
Doctoral Researcher
Sheffield Hallam University
Department of Development and Society
Collegiate Crescent
S10 2BA

Email address: rosie.martin@shu.ac.uk

If you have any complaints that you would like to be dealt with independently please contact:

Information removed

You should contact the Data Protection Officer if:	**You should contact the Head of Research Ethics (Professor Ann Macaskill) if**
• you have a query about how your data is used by the University • you would like to report a data security breach (e.g. if you think your personal data has been lost or disclosed inappropriately) • you would like to complain about how the University has used your personal data DPO@shu.ac.uk	• you have concerns with how the research was undertaken or how you were treated a.macaskill@shu.ac.uk
Postal address: Sheffield Hallam University, Howard Street, Sheffield S1 1WBT Telephone: 0114 225 5555	

Centre Number:

Study Number:

Participant Identification

Number for this trial:

CONSENT FORM

Title of Project: An N-of-1study to investigate the relationship between self-monitoring symptoms using daily diaries, and adherence to nebuliser treatments in adults with Cystic Fibrosis

Name of Researcher: Rosie Martin

.

1. I confirm that I have read the information sheet (Version 5 dated 29.11.18) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.

3. I have seven days after completing/ withdrawing from the study to request my data is withdrawn. After this point my data may be used.

4. I understand that all interviews whether face-to-face or over the telephone or Skype will be audio recorded.

5. I understand that anonymised quotes from the electronic daily diary and anonymised interviews may be used in the PhD thesis and publications.

6. I agree to take part in the above study.

Name of Participant	Date	Signature
Name of Person taking consent	Date	Signature

For further details please contact:

Rosie Martin
Doctoral Researcher
Sheffield Hallam University
Department of Development and Society
Collegiate Crescent
S10 2BA

Email address: rosie.martin@shu.ac.uk

Professor Madelynne Arden
Professor of Health Psychology
Department of Psychology, Sociology & Politics

Sheffield Hallam University

Telephone number: 0114 225 5623
Email address: m.arden@shu.ac.uk

Appendix G: Analysis worksheet example of N-of-1 analysis from the main study (chapter 5)

Note: This is an example of analysis notes which were created for each participant to ensure a methodical and rigorous analysis was conducted. The stages outlined by McDonald et al (2020) were followed (with the addition of the pre-inferential step added as a bullet point below), for each symptom, recorded by each participant (if enough data was available and if the symptom had not been rated as a constant zero).

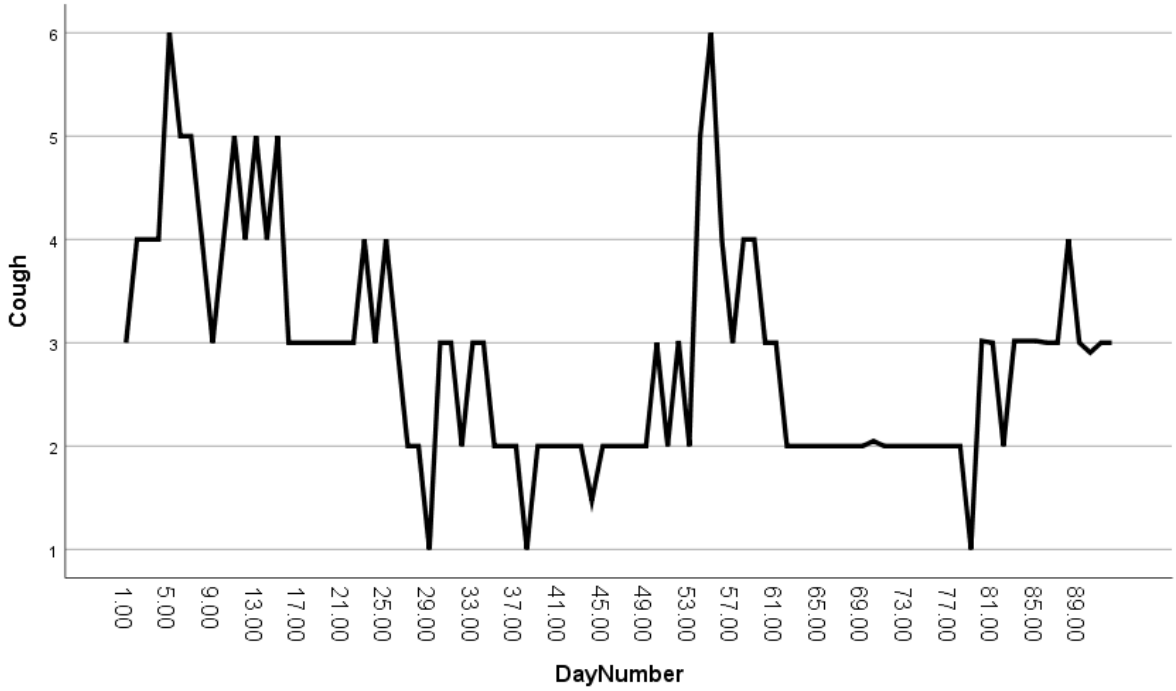
In the case of participant 9 pain and nominated symptom were excluded from the analysis because of missing data.

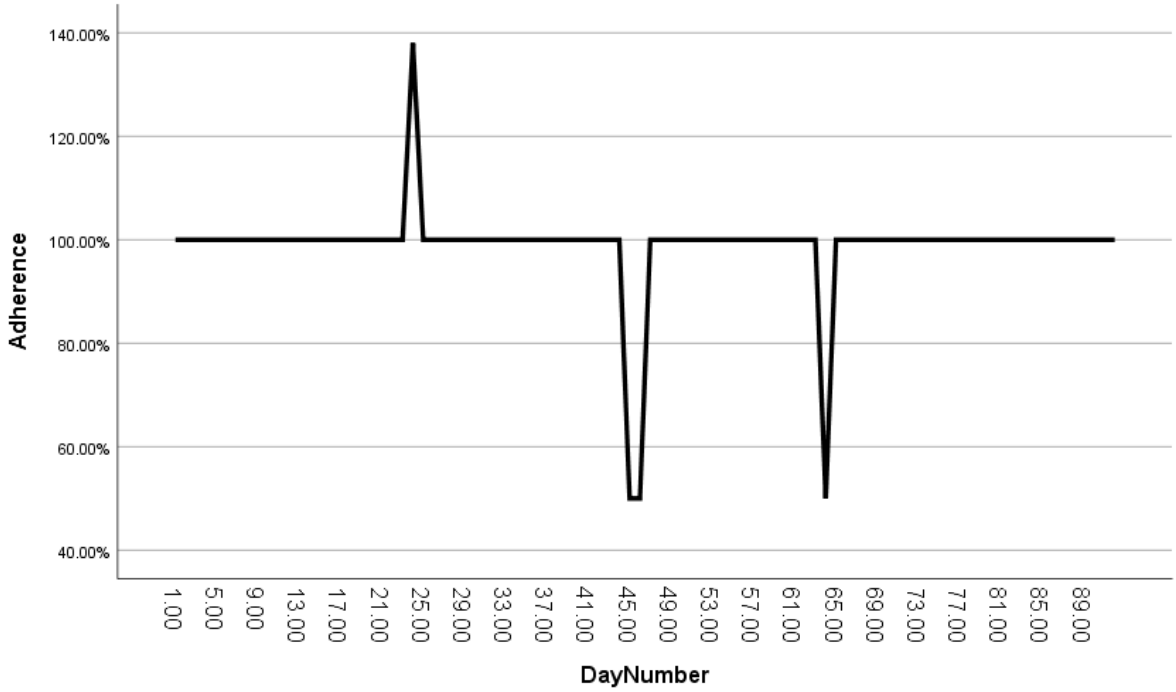
Steps 1 and 2 are undertaken for each data set as a whole, following this each symptom was analysed separately.

1. **Format the data set**
   Each variable is represented by a separate column in the data set, each participant has a separate data set.
2. **Identify and impute missing data**
   The amount of missing data for each variable was calculated and following this Little's Missing Completely at Random (Little, 1988) was conducted to check the patterns of missing data. For any missing data a missing value analysis was undertaken and missing data was completed using the Estimated Means option. If the data for a specific variable was missing by 40% or more the variable was excluded from the analysis.

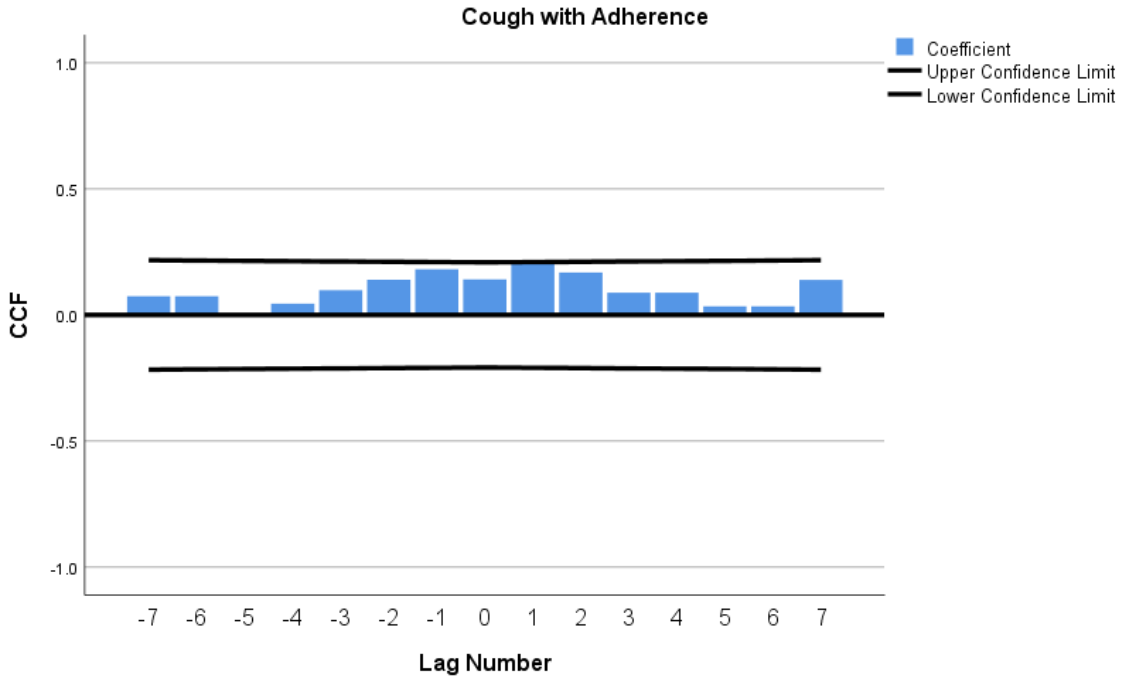
   Cough

3. **Plot the data**
   Sequence charts was produced for cough and adherence to allow for the visual inspection of the data across the study period. The sequence charts are not used for any form of the inferential analysis.





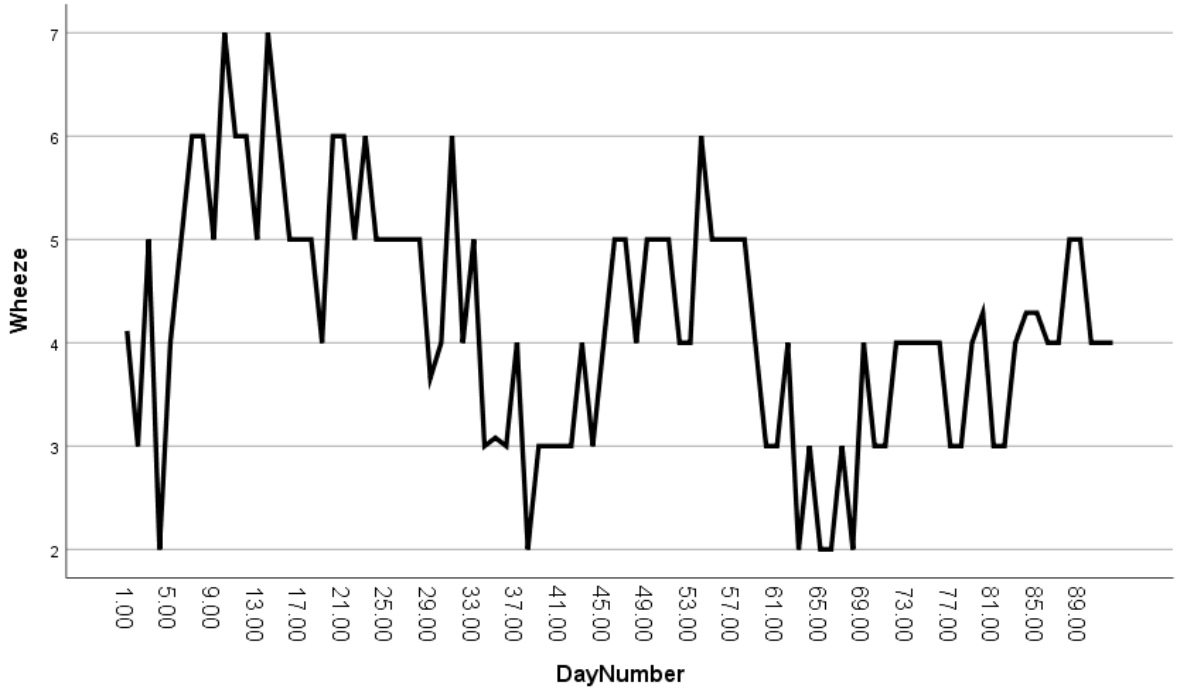
- **Pre-analysis exploration of temporal relationships between adherence and symptom variable.** This will be explored using cross-correlation charts. The outcome variable will be determined based on the results of the cross-correlation chart. This will determine which variable should be subject to autocorrelation analysis (if the data passes the confidence interval on more than one day the findings from the highest day are used). According to McDonald et al (2020) the outcome variable should have autocorrelation explored. If the cross-correlation chart shows no evidence of a relationship at the point no further analysis is undertaken.



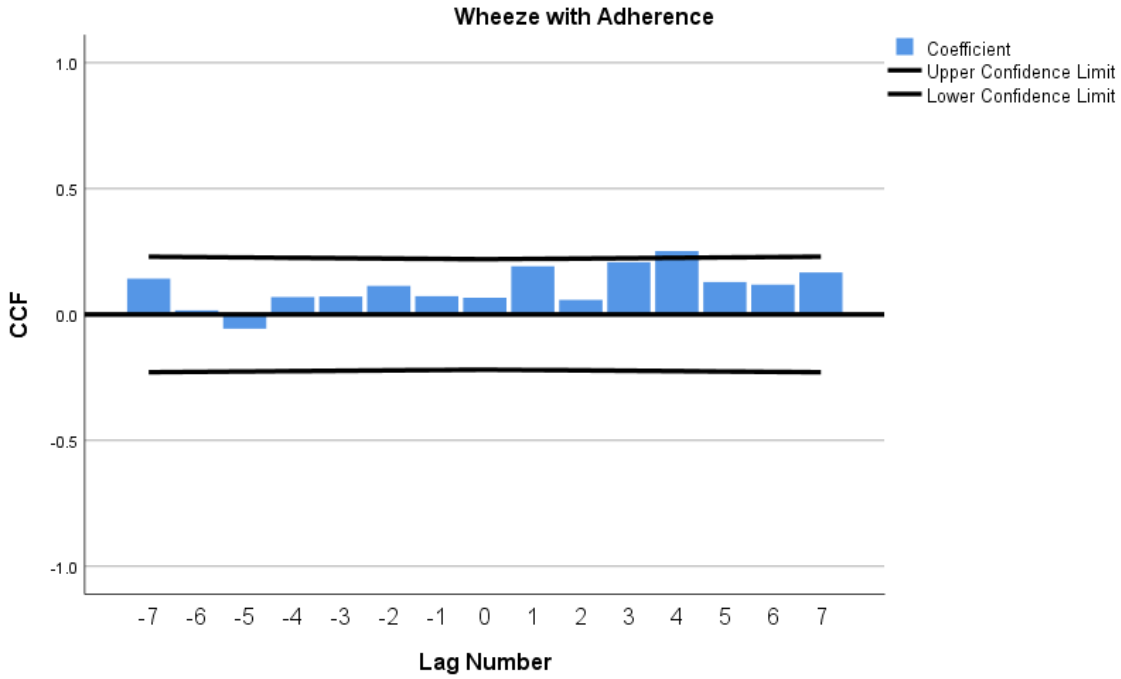
Therefore no further analysis was undertaken for cough and adherence for this participant as the confidence interval is not clearly passed.

Wheeze

3. **Plot the data**
   Sequence charts was produced for wheeze to allow for the visual inspection of the data across the study period. The sequence charts are not used for any form of the inferential analysis.



- **Pre-analysis exploration of temporal relationships between adherence and symptom variable.** This will be explored using cross-correlation charts. The outcome variable will be determined based on the results of the cross-correlation chart. This will determine which variable should be subject to autocorrelation analysis (if the data passes the confidence interval on more than one day the findings from the highest day are used). According to McDonald et al (2020) the outcome variable should have autocorrelation explored. If the cross-correlation chart shows no evidence of a relationship at the point no further analysis is undertaken.



This cross correlation chart shows there is possibly a positive relationship in which wheeze could lead to adherence in four days time.

Therefore:
Wheeze is the predictor variable
Adherence is the outcome variable

The hypothesis for this is:
Does wheeze on day 0 predict adherence four days later?

4.Assess the stationarity of the data on outcome variable

Adherence data was split into 2 and then 3 partitions to investigate the variance of the data within the outcome variable over the study period.

Descriptive Statistics

Partitionin2		N	Minimum	Maximum	Mean	Std. Deviation
half1	Adherence	46	50.00%	138.00%	98.6522%	11.88878%
	Valid N (listwise)	46				
half2	Adherence	46	50.00%	100.00%	98.9130%	7.37210%
	Valid N (listwise)	46				

Descriptive Statistics

Partitionin3		N	Minimum	Maximum	Mean	Std. Deviation
part1	Adherence	29	100.00%	138.00%	101.3103%	7.05642%
	Valid N (listwise)	29				
part2	Adherence	30	50.00%	100.00%	96.6667%	12.68541%
	Valid N (listwise)	30				
part3	Adherence	33	50.00%	100.00%	98.4848%	8.70388%
	Valid N (listwise)	33				

- Assess time trends on outcome variable

As the logistic regression is significant. According to McDonald et al (2020) this suggest that 'day number' should be included in the final regression model as there could be evidence of a significant trend over time.

Coefficients

	Unstandardized Coefficients		Standardized Coefficients		
	B	Std. Error	Beta	t	Sig.
DayNumber	1.000	.001	1.059	1968.776	.000
(Constant)	.010	.000		36.766	.000

The dependent variable is ln(1 / Adherence).

-Assess periodic patterns on outcome variable

Periodic patterns were investigated the measure the differences in adherence between weekdays and days at the weekend. As the confidence interval does contain a 0 this

means that there is no evidence of periodic patterns and therefore this variable will not be included in the final model.

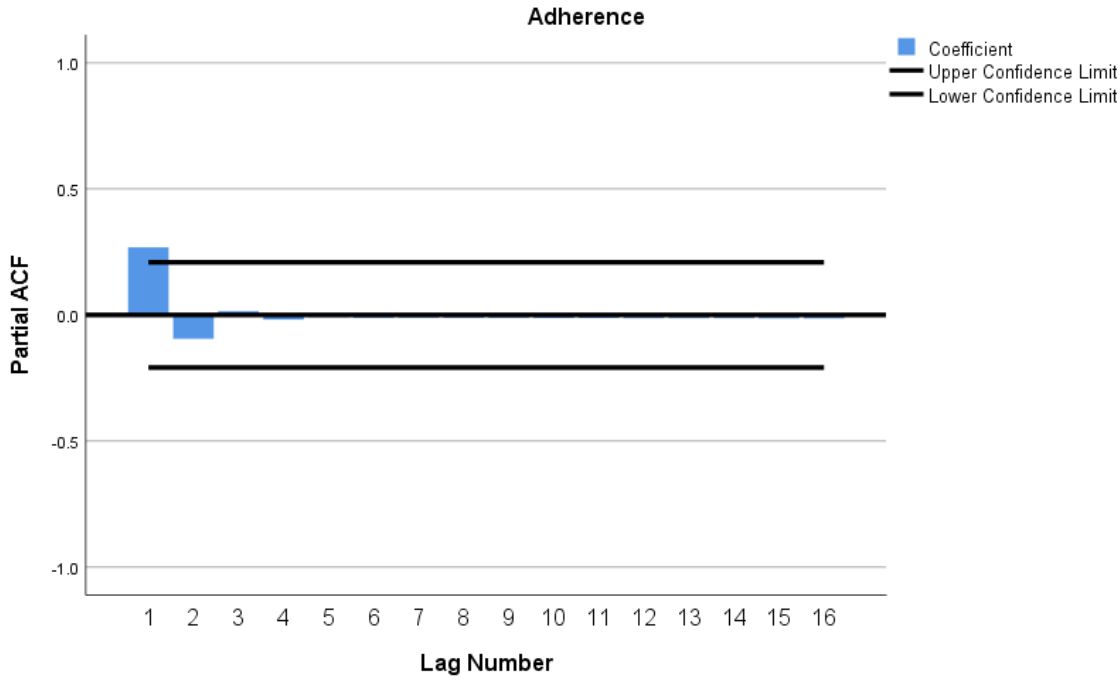
Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients			95.0% Confidence Interval for B	
		B	Std. Error	Beta	t	Sig.	Lower Bound	Upper Bound
1	(Constant)	97.431	3.110		31.328	.000	91.253	103.610
	Weekendorweekday	1.054	2.288	.048	.461	.646	-3.492	5.599

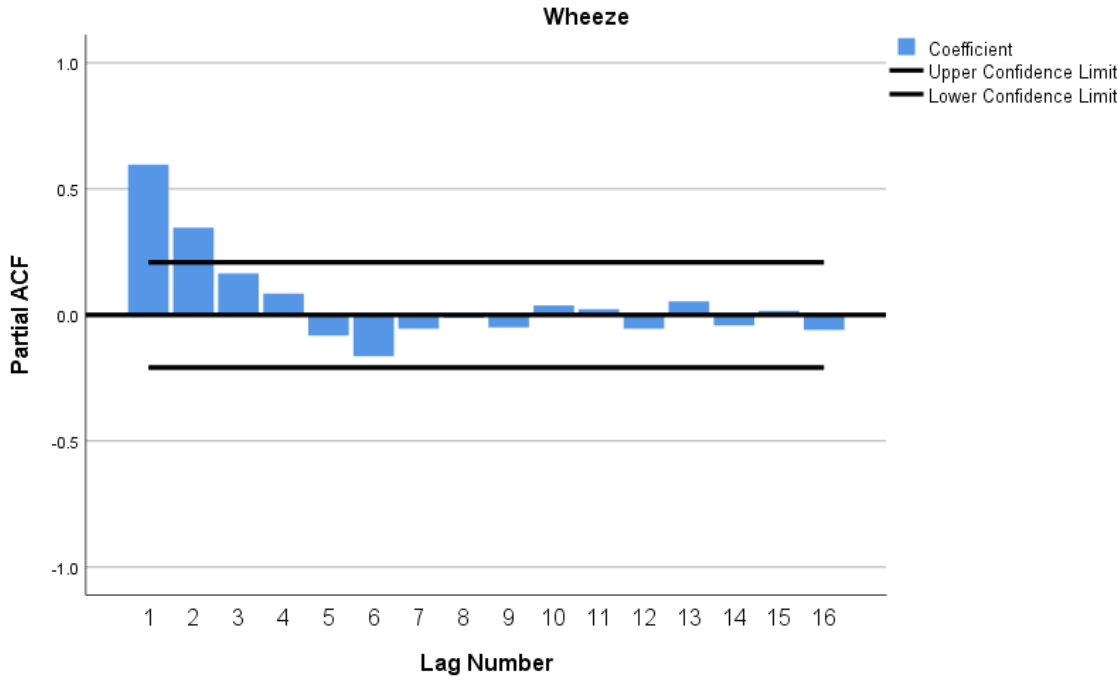
a. Dependent Variable: Adherence

5.Check for autocorrelation in the outcome variable.

The autocorrelation chart for adherence shows that there is evidence of autocorrelation at day 1. Therefore a new lagged variable will be created in the next step.



As an extra precaution autocorrelation was also checked in the predictor variable (wheeze), the chart shows that there is evidence of autocorrelation at day 1 and 2 and therefore results should be interpreted with caution.



6. Create lagged variables (within the outcome variable)

New lagged variable created for adherence which is lagged by one day.

Created Series

	Series Name	Case Number of Non-Missing Values		N of Valid Cases	Creating Function
		First	Last		
1	Adhere_1	2	92	91	LAGS(Adherence,1)

7. Confirm autocorrelation has been adequately specified

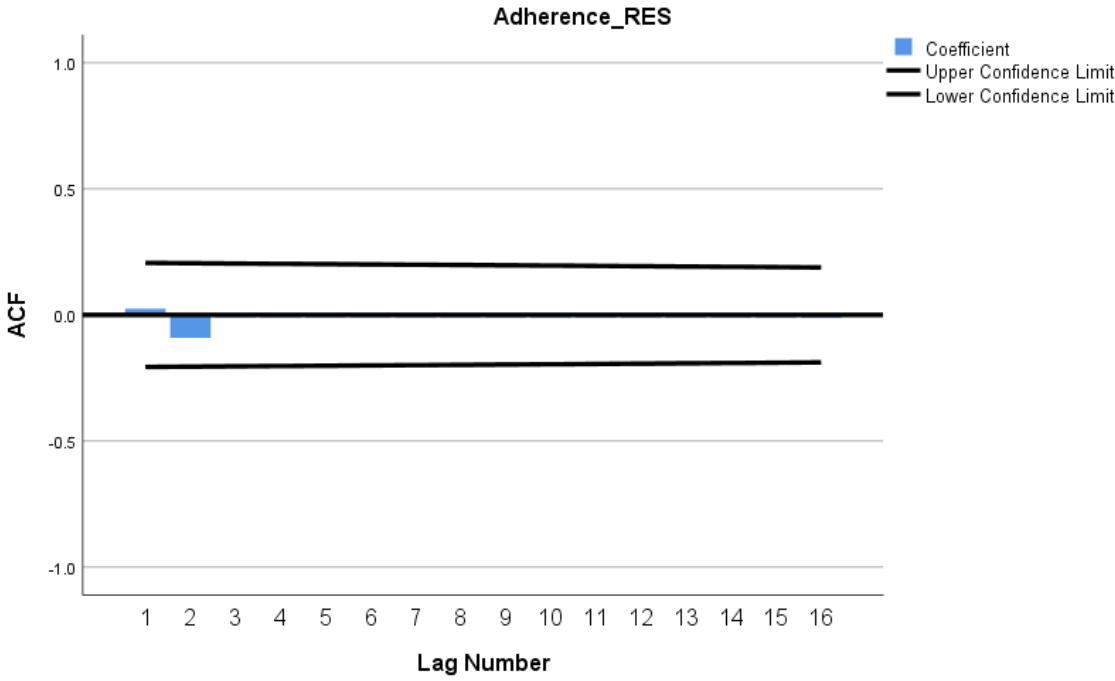
Following this a regression is completed, simply to create the new unstandardised residual variable.

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
		B	Std. Error	Beta			Lower Bound	Upper Bound
1	(Constant)	72.275	10.136		7.131	.000	52.136	92.415
	LAGS(Adherence,1)	.268	.102	.268	2.627	.010	.065	.471

a. Dependent Variable: Adherence

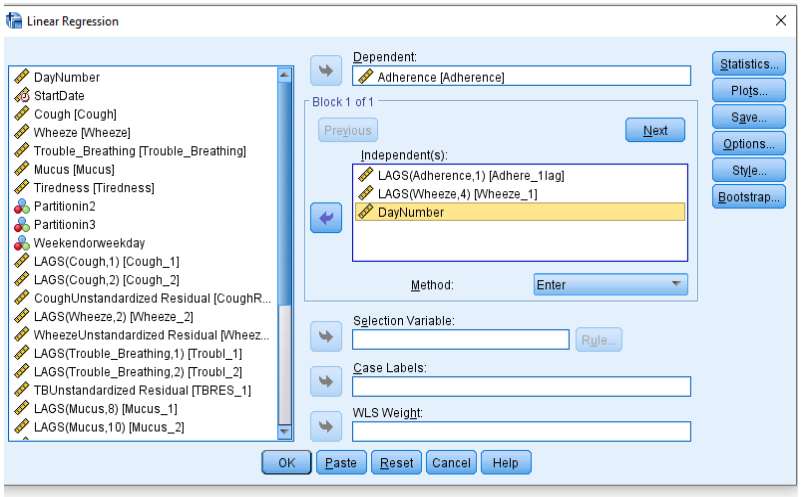
The autocorrelation plot with the new variable suggests that there is no evidence of autocorrelation within the unstandardised residual variable.



8. Conduct the dynamic regression.

Based on this analysis the following variables should be included in the final regression:

Outcome variable:
Adherence
Predictor variables:
Wheeze lagged by four days (as shown on the cross-correlation chart)
Adherence lagged by one day (as shown on the auto-correlation chart)
Day number (time-trends)



9. Interpret the regression output

Model Summary[b]

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	.334[a]	.112	.080	9.64750%

a. Predictors: (Constant), DayNumber, LAGS(Adherence,1), LAGS(Wheeze,4)

b. Dependent Variable: Adherence

ANOVA[a]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	983.220	3	327.740	3.521	.018[b]
	Residual	7818.234	84	93.074		
	Total	8801.455	87			

a. Dependent Variable: Adherence

b. Predictors: (Constant), DayNumber, LAGS(Adherence,1), LAGS(Wheeze,4)

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
		B	Std. Error	Beta			Lower Bound	Upper Bound
1	(Constant)	67.319	11.029		6.104	.000	45.386	89.252

	LAGS(Adherence,1)	.228	.105	.228	2.176	.032	.020	.437
	LAGS(Wheeze,4)	1.881	.993	.220	1.895	.062	-.093	3.855
	DayNumber	.019	.045	.049	.428	.670	-.070	.109

a. Dependent Variable: Adherence

The regression shows that adherence at day zero predicts adherence the next day.

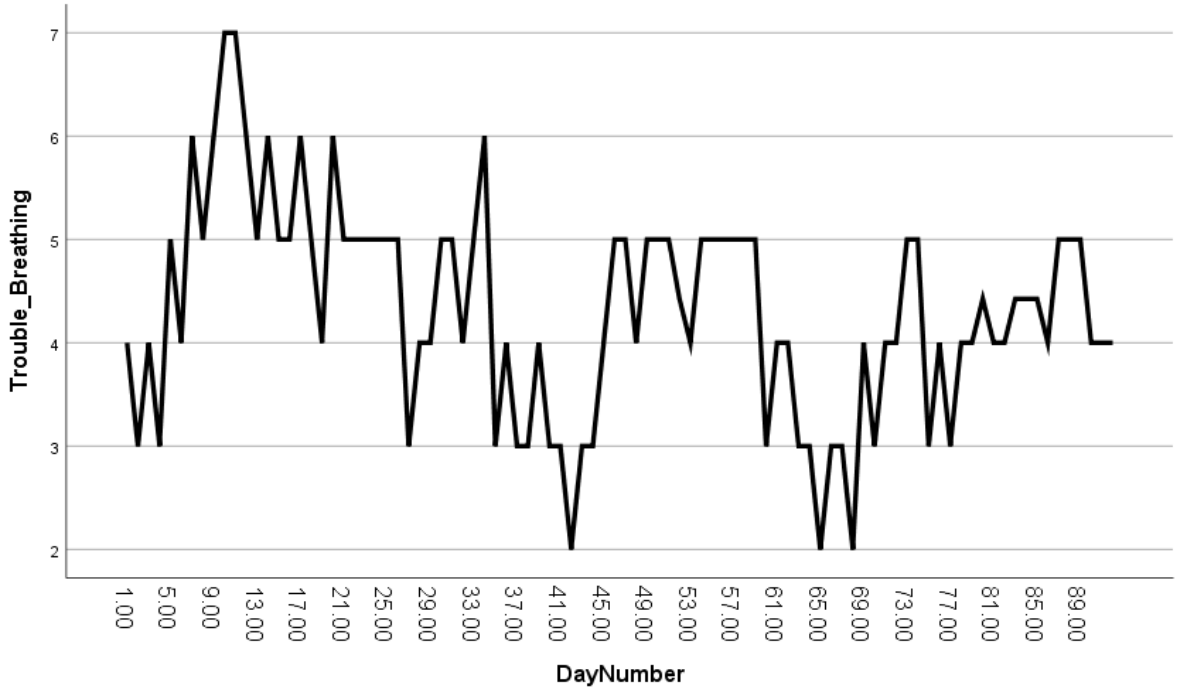
However wheeze in unable to predict adherence in 4 days time.

Day number is also unable to predict adherence for this participant.

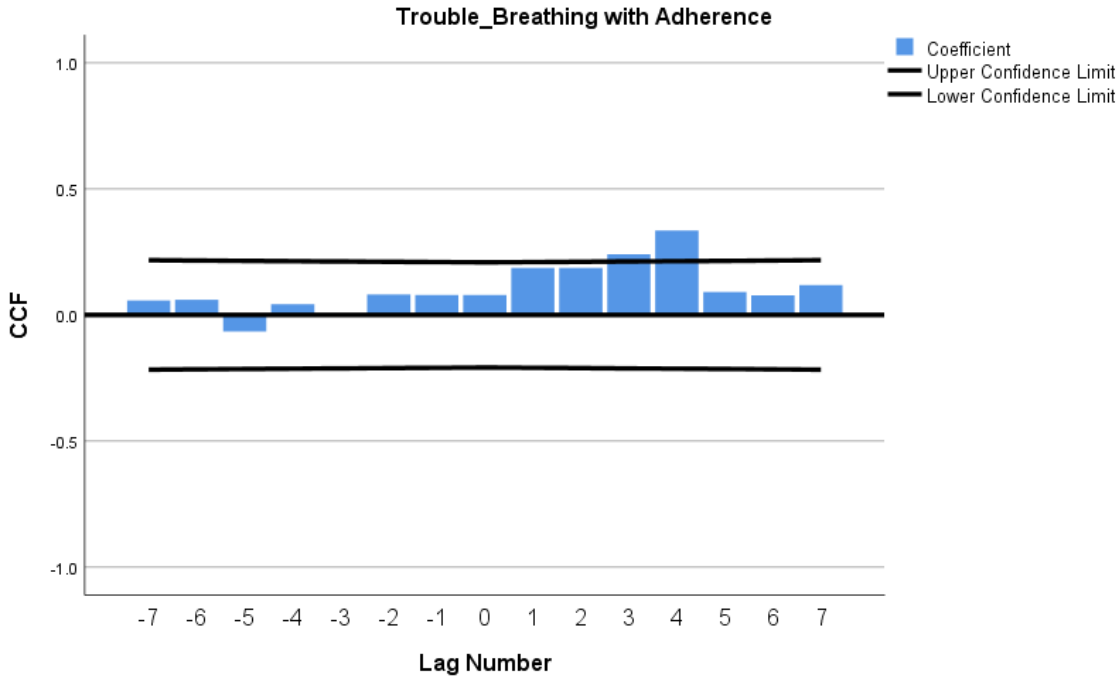
10. Report results
Please see results report in section 6.4 of chapter 6.

Trouble breathing

3. **Plot the data**
   Sequence charts was produced for trouble breathing to allow for the visual inspection of the data across the study period. The sequence charts are not used for any form of the inferential analysis.



- **Pre-analysis exploration of temporal relationships between adherence and symptom variable.** This will be explored using cross-correlation charts. The outcome variable will be determined based on the results of the cross-correlation chart. This will determine which variable should be subject to autocorrelation analysis (if the data passes the confidence interval on more than one day the findings from the highest day are used). According to McDonald et al (2020) the outcome variable should have autocorrelation explored. If the cross-correlation chart shows no evidence of a relationship at the point no further analysis is undertaken.



This cross correlation chart shows that high difficulty breathing could possibly predict high adherence in four days time.

Therefore:
Difficulty breathing is the predictor variable
Adherence is the outcome variable

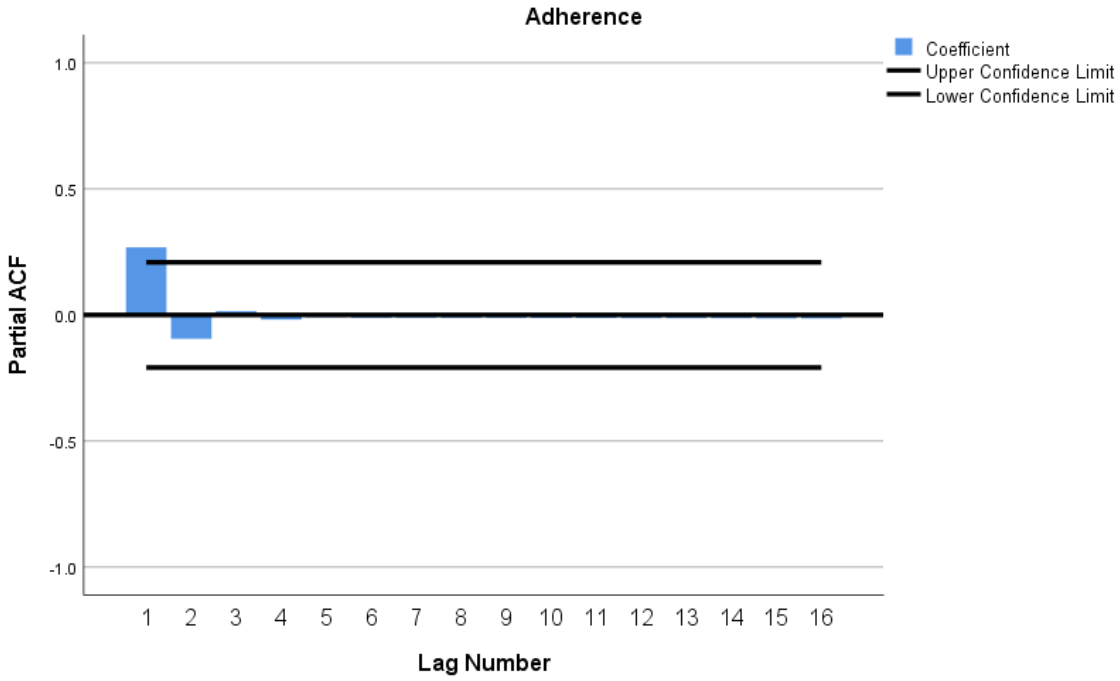
The hypothesis for this is:
Does trouble breathing on day 0 predict adherence four days later?

4.Assess the stationarity of the data on outcome variable

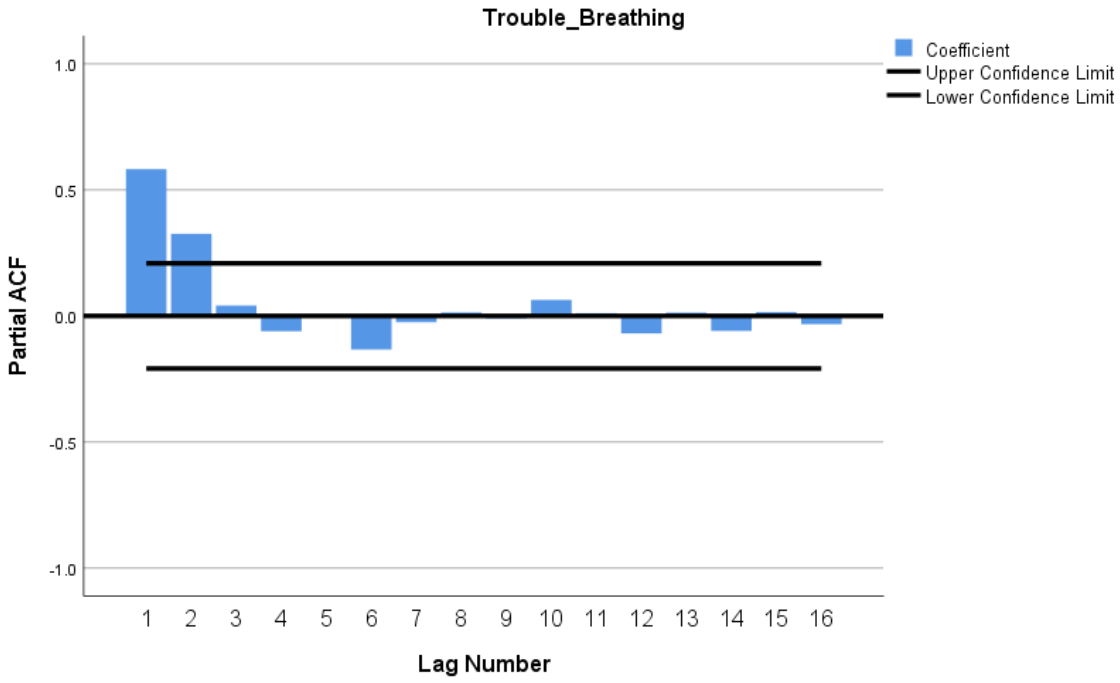
The same as above (see analysis notes for wheeze) as the outcome variable is the same (adherence).

5.Check for autocorrelation in the outcome variable.

The autocorrelation chart for adherence shows that there is evidence of autocorrelation at day 1.



As an extra precaution autocorrelation was also checked in the predictor variable (difficulty breathing), the chart shows that there is evidence of autocorrelation at day 1 and day 2 therefore this should be taken into account when interpreting the final regression.



6. Create lagged variables (within the outcome variable)

As above.

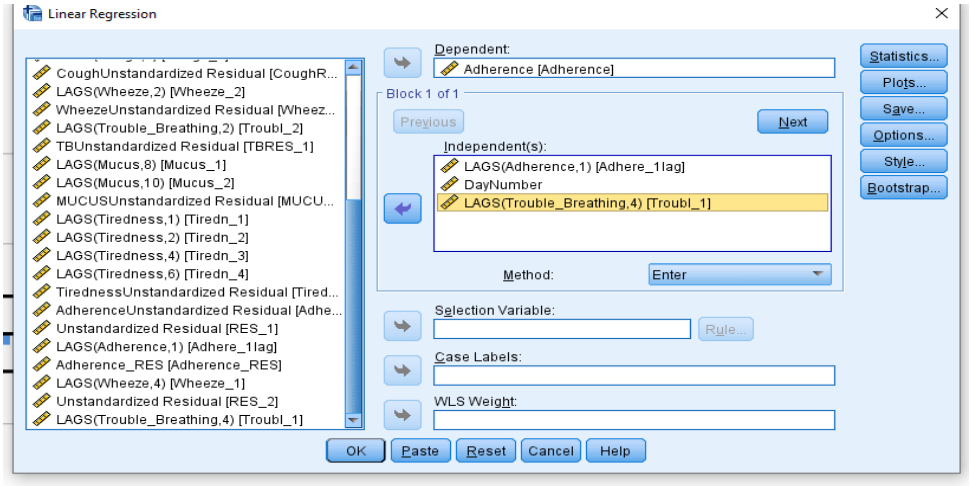
7. Confirm autocorrelation has been adequately specified

As above.

8. Conduct the dynamic regression.

Based on this analysis the following variables should be included in the final regression:

Outcome variable:
Adherence
Predictor variables:
Difficulty breathing lagged by four days (as shown on the cross-correlation chart)
Adherence lagged by one day (as shown on the auto-correlation chart)
Day number (time-trends)



9. Interpret the regression output

Model Summary[b]

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	.390[a]	.152	.122	9.42417%

a. Predictors: (Constant), LAGS(Trouble_Breathing,4), LAGS(Adherence,1), DayNumber

b. Dependent Variable: Adherence

ANOVA[a]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	1341.004	3	447.001	5.033	.003[b]
	Residual	7460.451	84	88.815		
	Total	8801.455	87			

a. Dependent Variable: Adherence

b. Predictors: (Constant), LAGS(Trouble_Breathing,4), LAGS(Adherence,1), DayNumber

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
		B	Std. Error	Beta			Lower Bound	Upper Bound
1	(Constant)	65.675	10.670		6.155	.000	44.455	86.894
	LAGS(Adherence,1)	.198	.104	.198	1.910	.060	-.008	.404
	DayNumber	.021	.042	.053	.495	.622	-.063	.104
	LAGS(Trouble_Breathing,4)	2.900	1.039	.306	2.791	.007	.834	4.966

a. Dependent Variable: Adherence

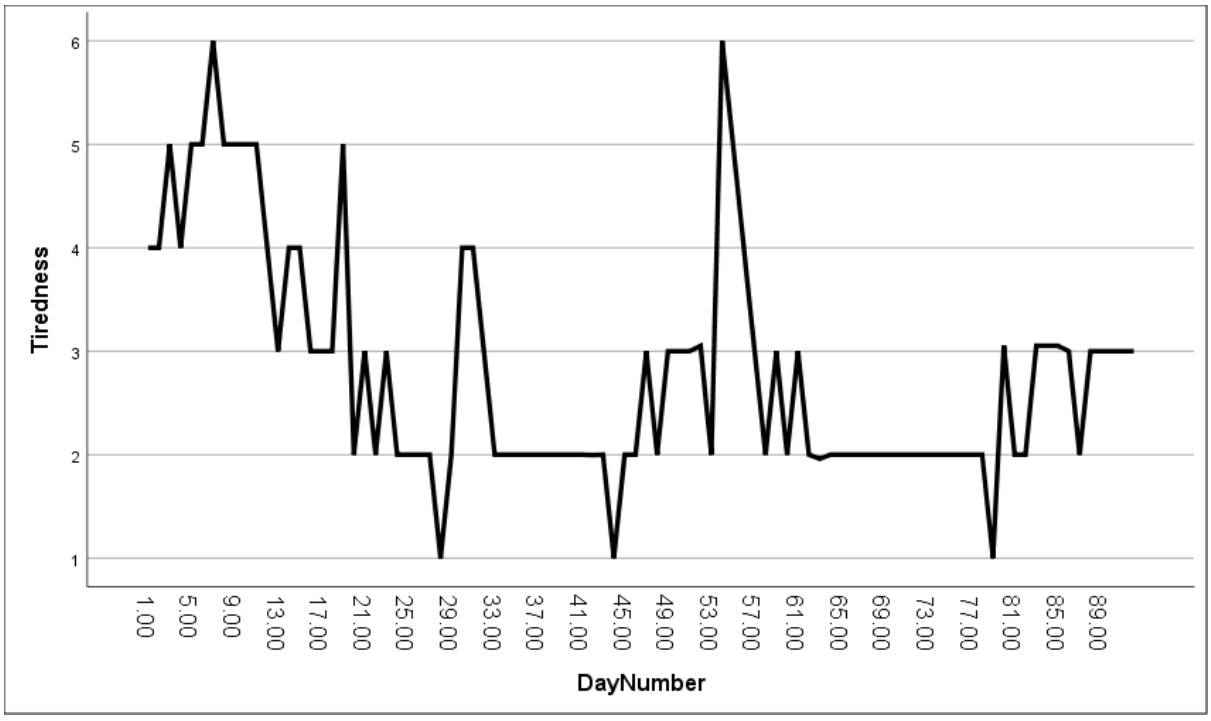
This regression shows that trouble breathing predicts adherence in 4 days times for this participant and supports the hypothesis.

However adherence at one day is unable to predict adherence the next and day number is also unable to predict adherence.

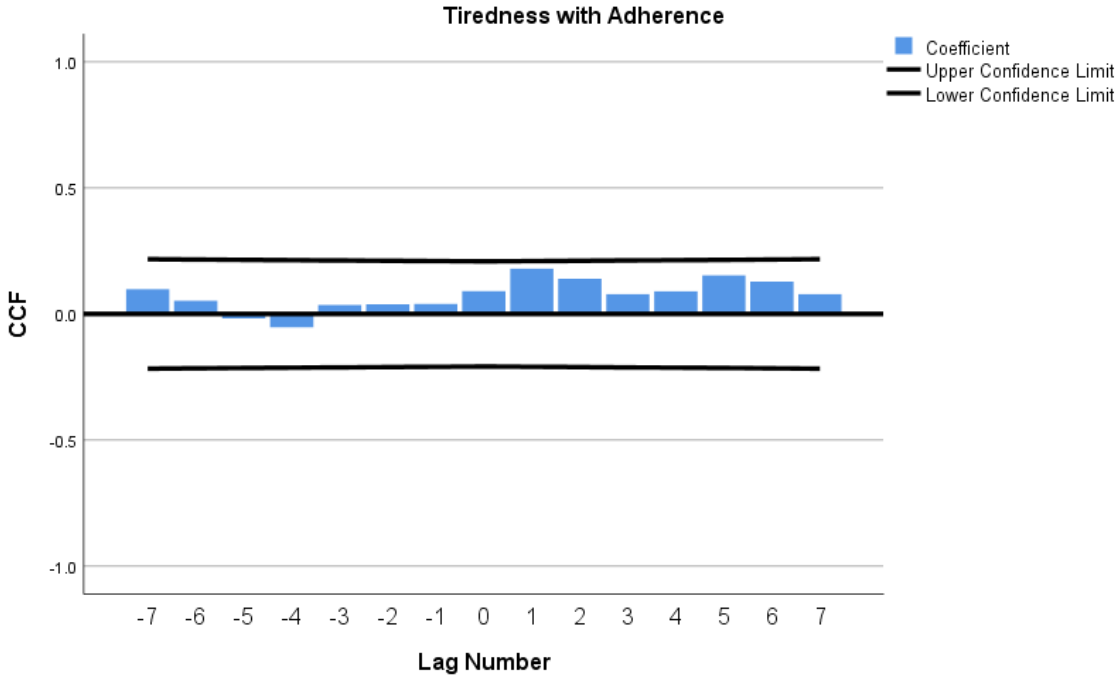
Tiredness

3. **Plot the data**

   Sequence charts was produced for tiredness to allow for the visual inspection of the data across the study period. The sequence charts are not used for any form of the inferential analysis.



- **Pre-analysis exploration of temporal relationships between adherence and symptom variable.** This will be explored using cross-correlation charts. The outcome variable will be determined based on the results of the cross-correlation chart. This will determine which variable should be subject to autocorrelation analysis (if the data passes the confidence interval on more than one day the findings from the highest day are used). According to McDonald et al (2020) the outcome variable should have autocorrelation explored. If the cross-correlation chart shows no evidence of a relationship at the point no further analysis is undertaken.

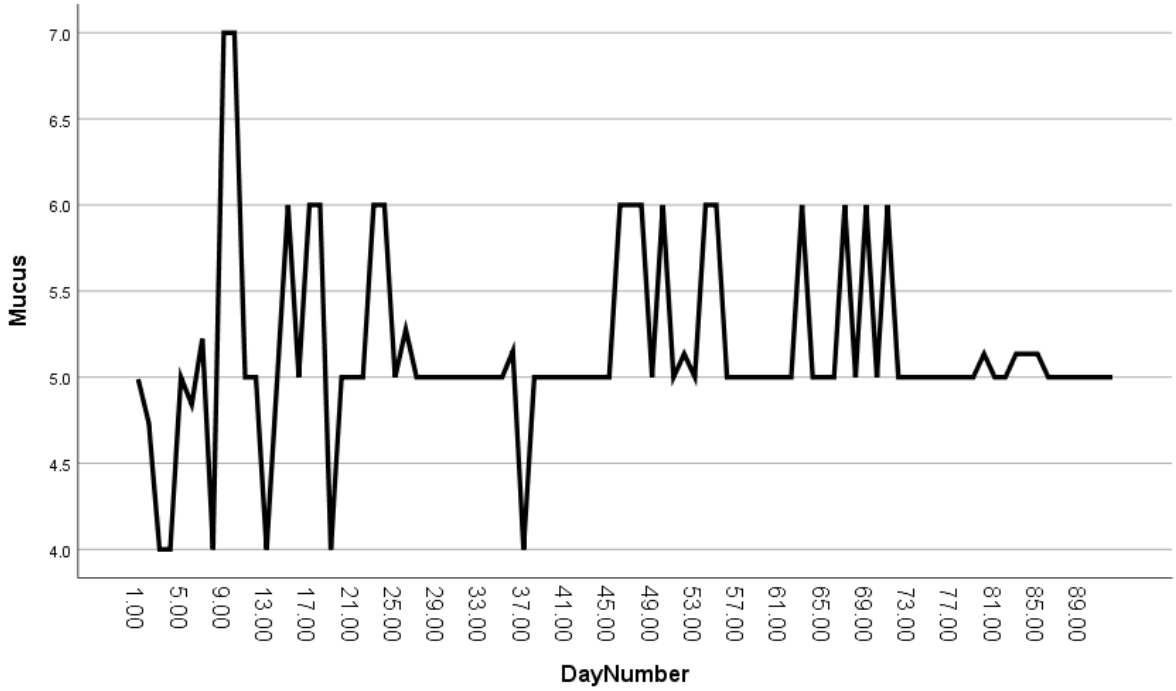


Therefore no further analysis was undertaken for tiredness and adherence for this participant as the confidence interval is not clearly passed.

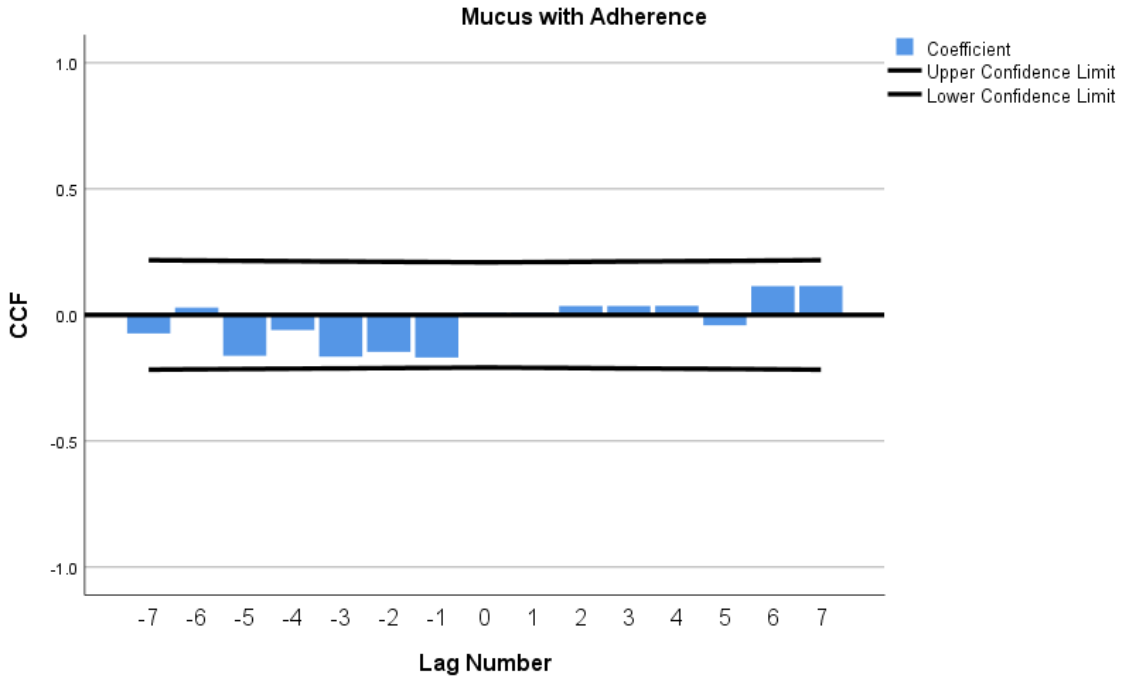
Mucus

3. **Plot the data**

   Sequence charts was produced for mucus to allow for the visual inspection of the data across the study period. The sequence charts are not used for any form of the inferential analysis.



- **Pre-analysis exploration of temporal relationships between adherence and symptom variable.** This will be explored using cross-correlation charts. The outcome variable will be determined based on the results of the cross-correlation chart. This will determine which variable should be subject to autocorrelation analysis (if the data passes the confidence interval on more than one day the findings from the highest day are used). According to McDonald et al (2020) the outcome variable should have autocorrelation explored. If the cross-correlation chart shows no evidence of a relationship at the point no further analysis is undertaken.

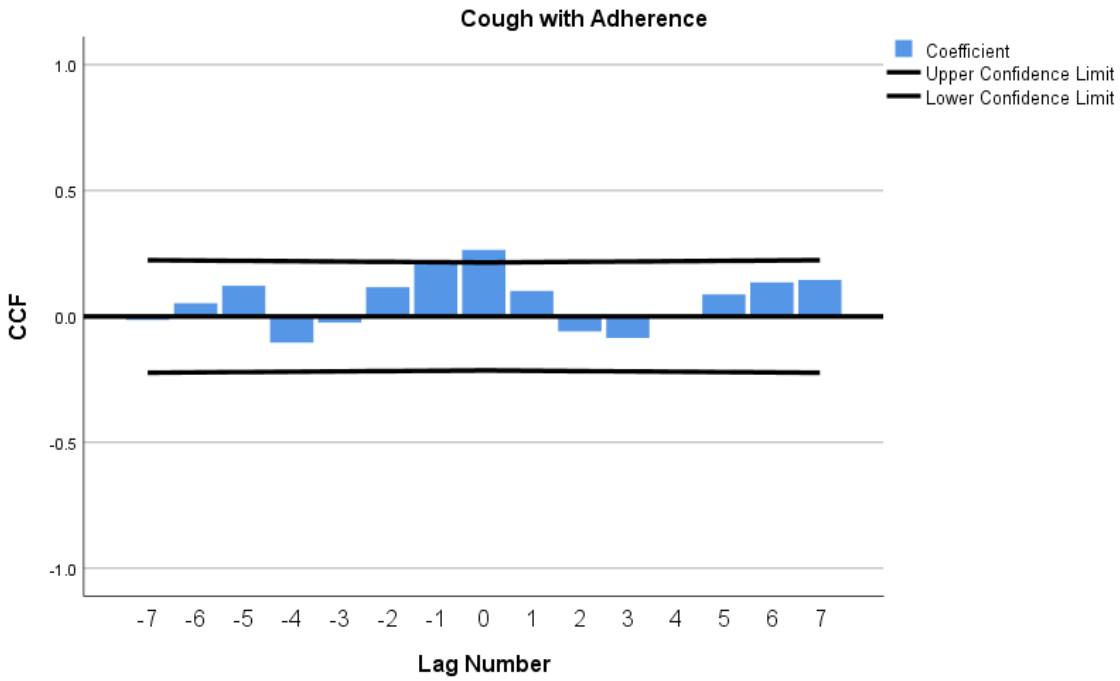


Therefore no further analysis was undertaken for mucus and adherence for this participant as the confidence interval is not clearly passed.

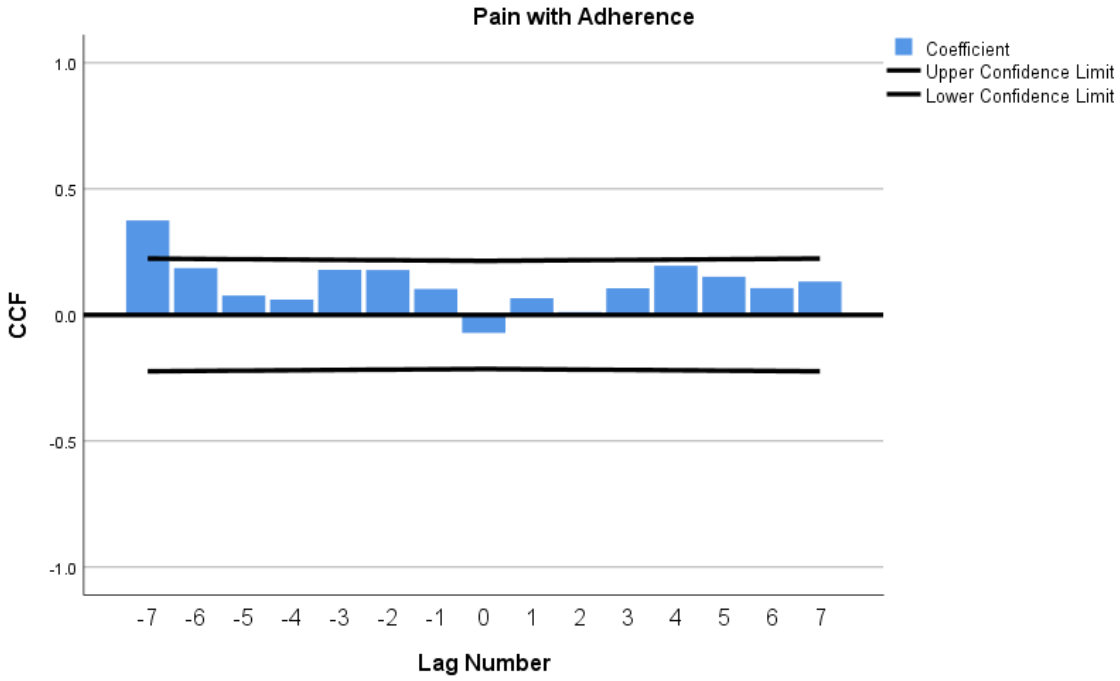
Appendix H: Cross correlation charts N-of-1 main study (chapter 5)

Participant 8

Cough

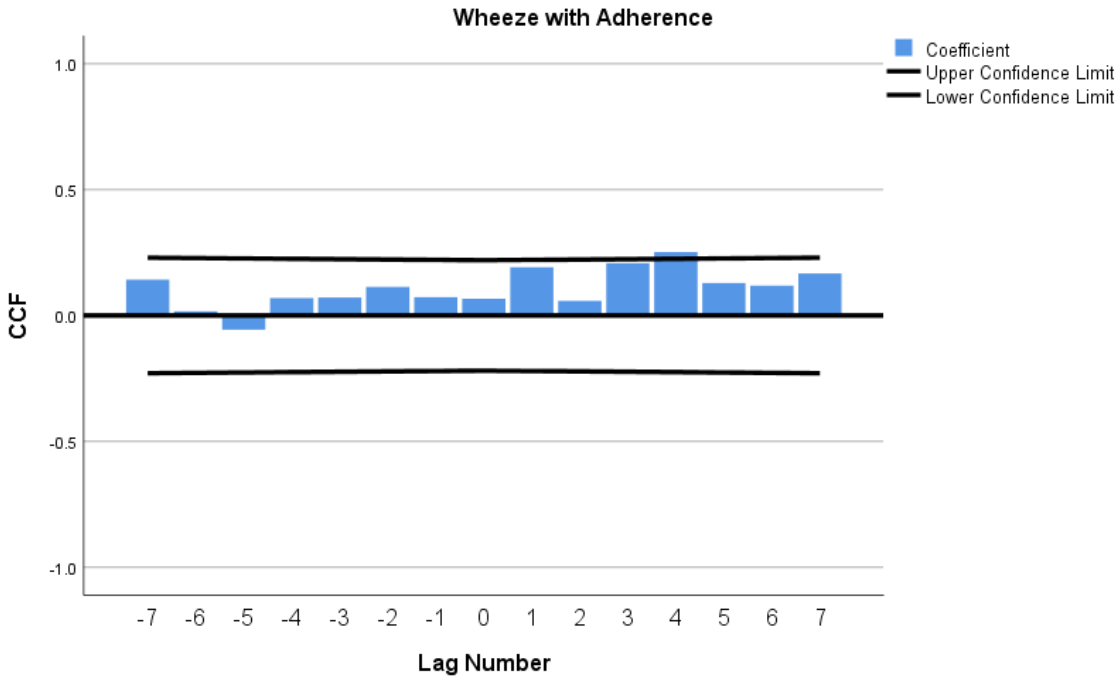


Pain

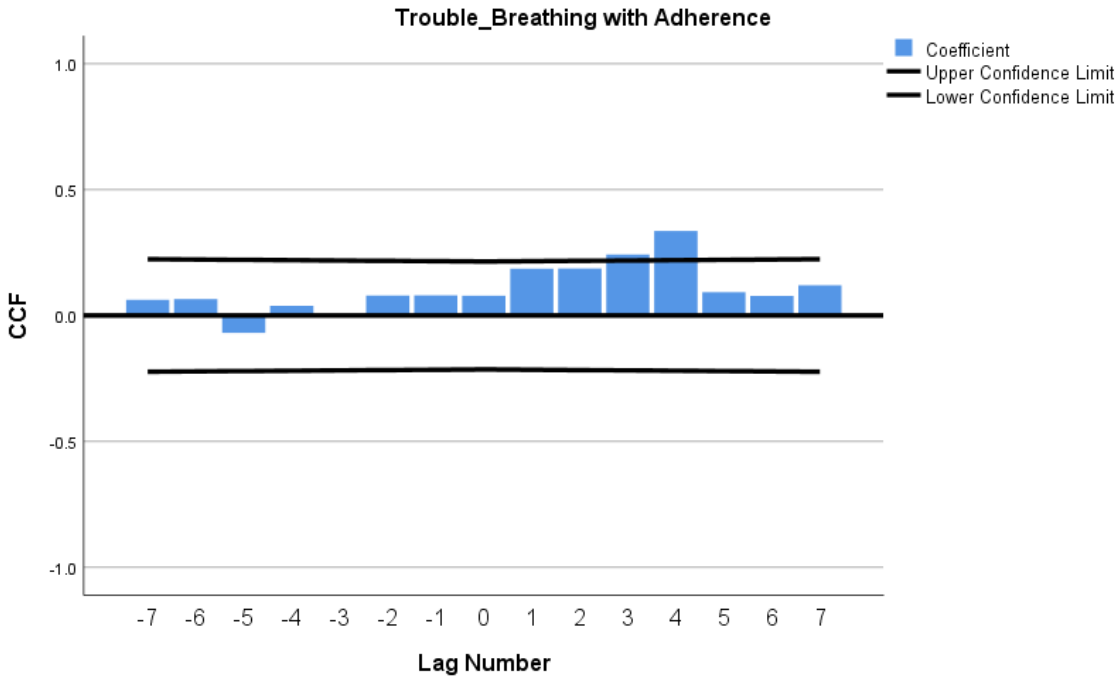


Participant 9

Wheeze

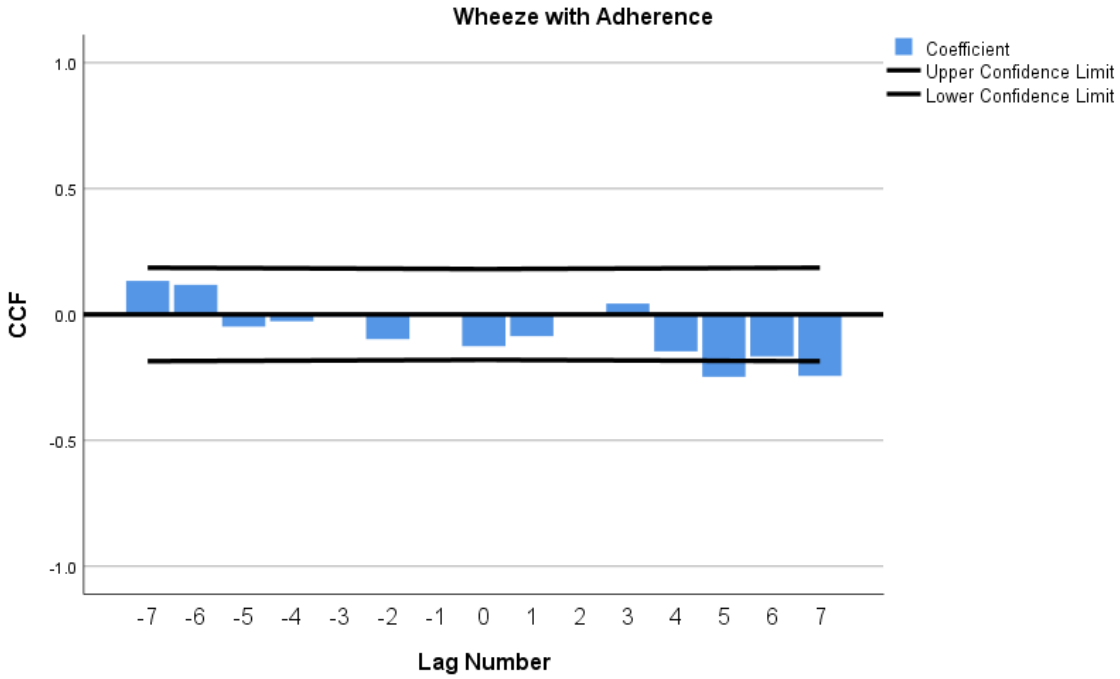


Difficulty breathing

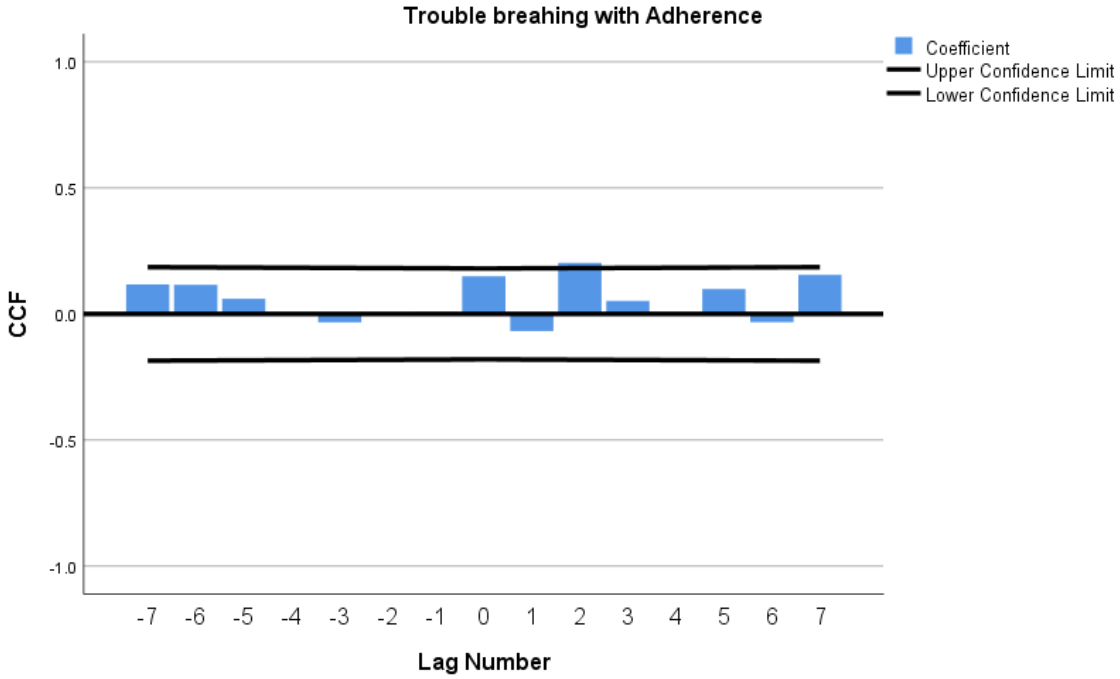


Participant 11

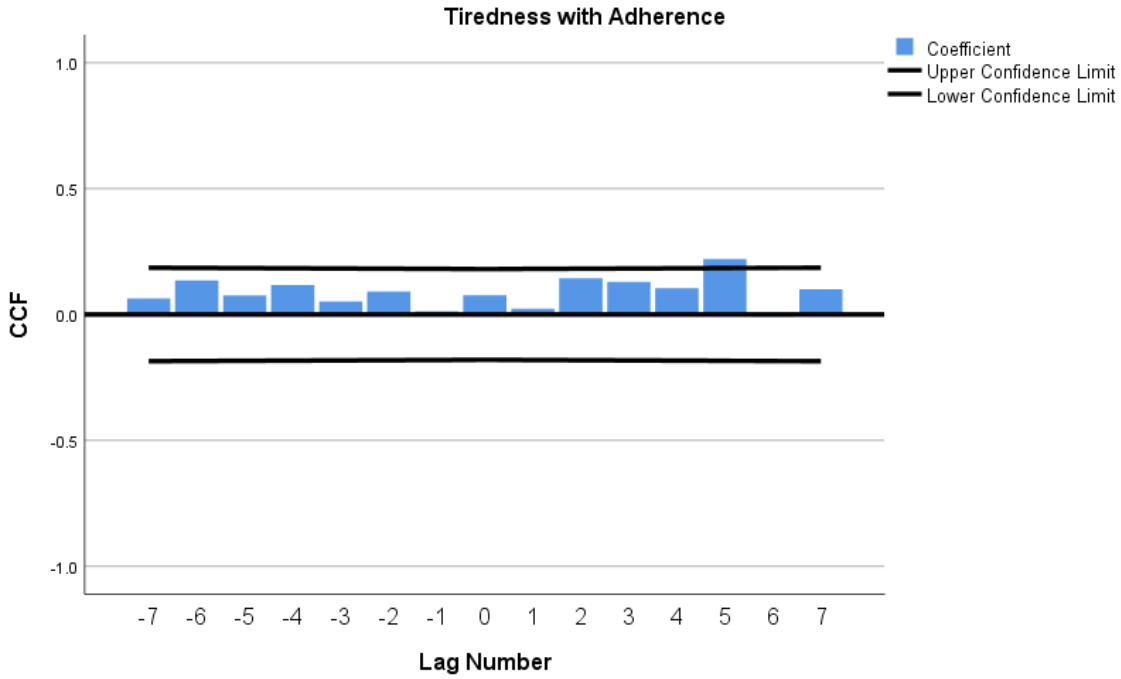
Wheeze



Difficulty breathing

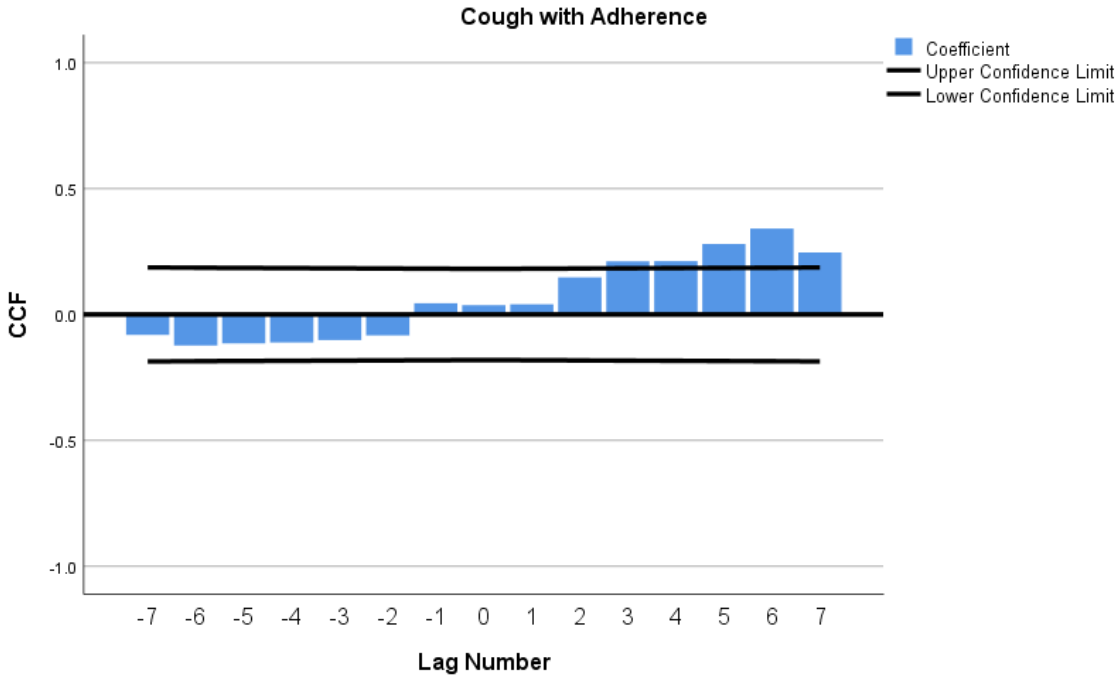


Tiredness

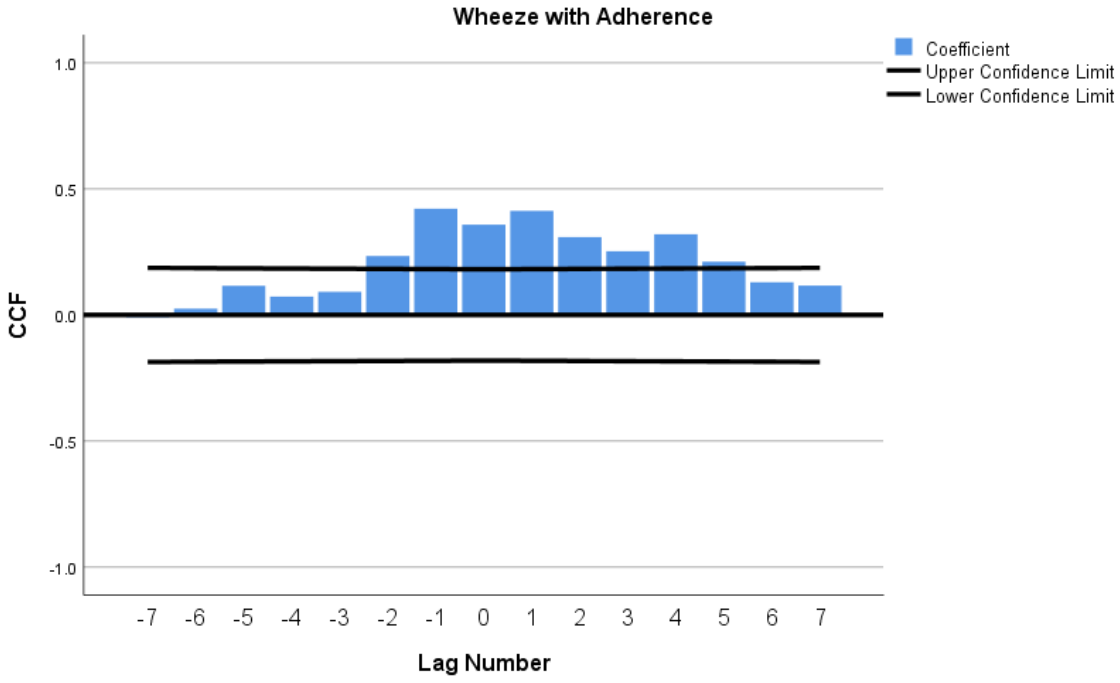

Tiredness with Adherence
Coefficient
Upper Confidence Limit
Lower Confidence Limit
CCF
1.0
0.5
0.0
-0.5
-1.0
-7 -6 -5 -4 -3 -2 -1 0 1 2 3 4 5 6 7
Lag Number

Participant 12

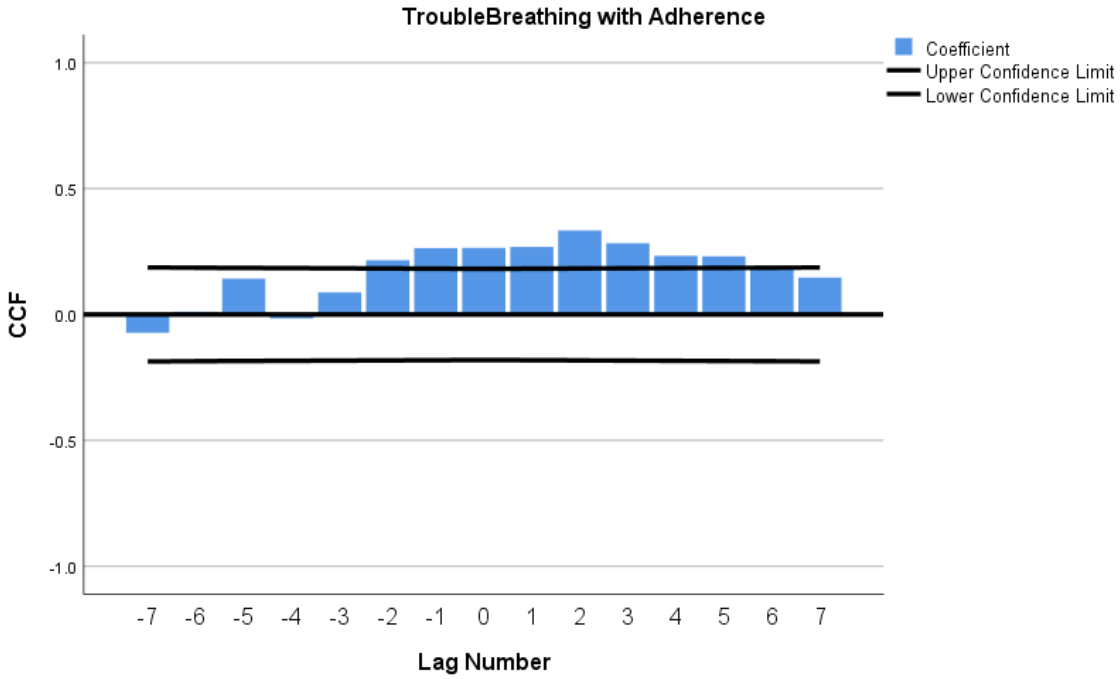
Cough



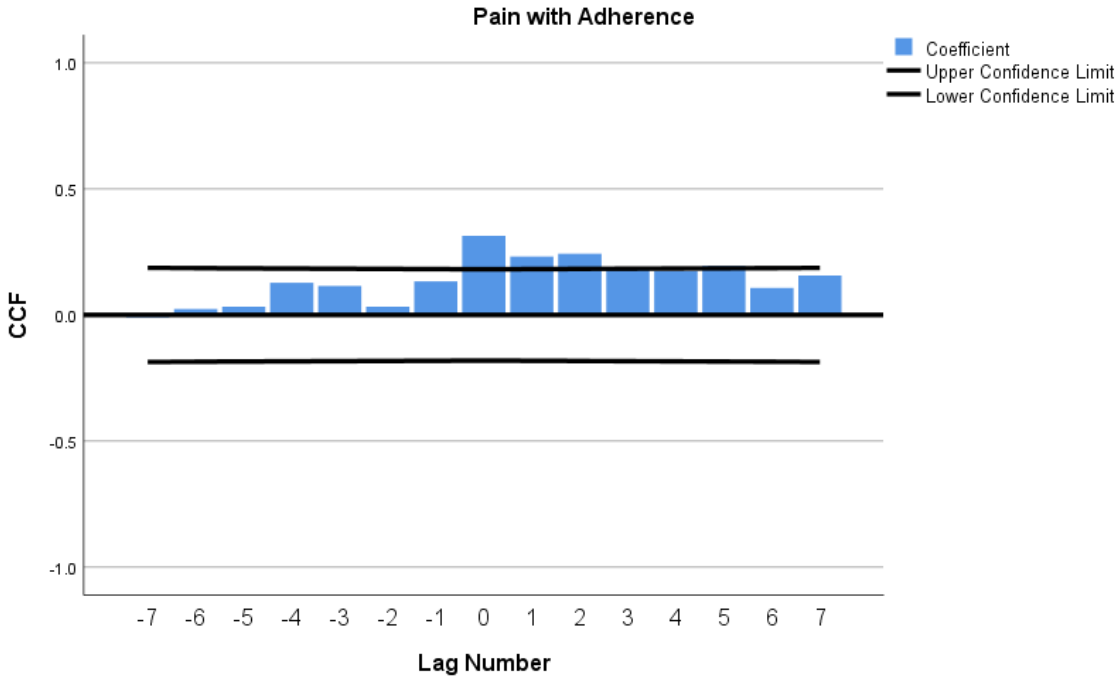
Wheeze



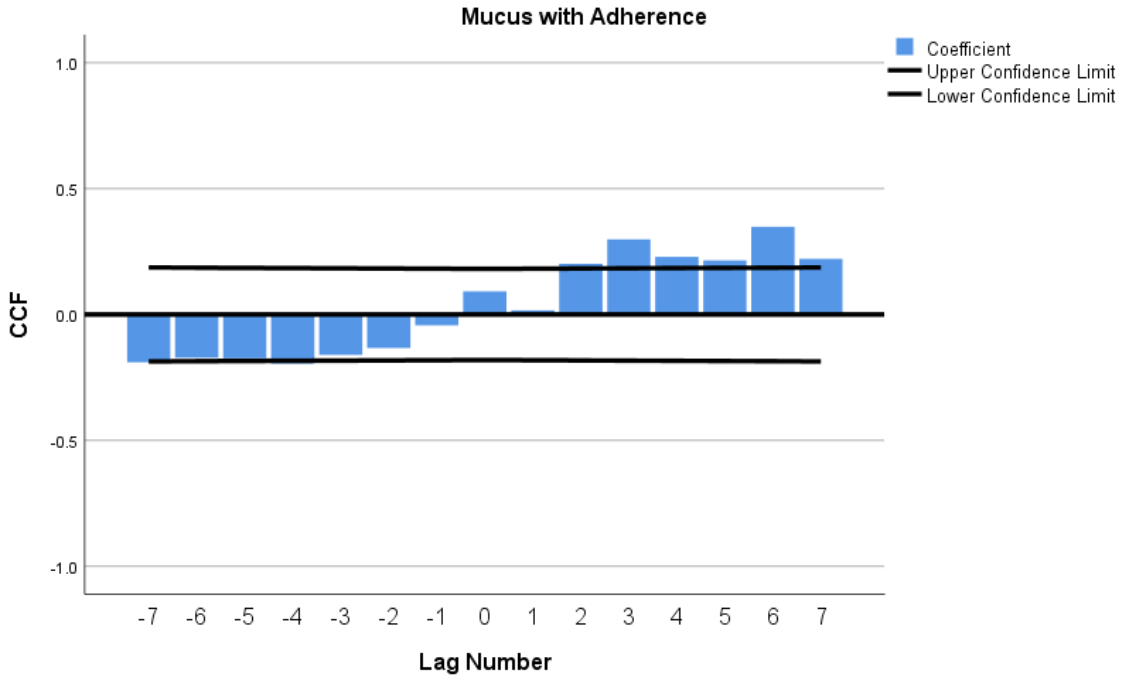
Difficulty breathing


TroubleBreathing with Adherence
Coefficient
Upper Confidence Limit
Lower Confidence Limit
CCF
1.0
0.5
0.0
-0.5
-1.0
-7 -6 -5 -4 -3 -2 -1 0 1 2 3 4 5 6 7
Lag Number

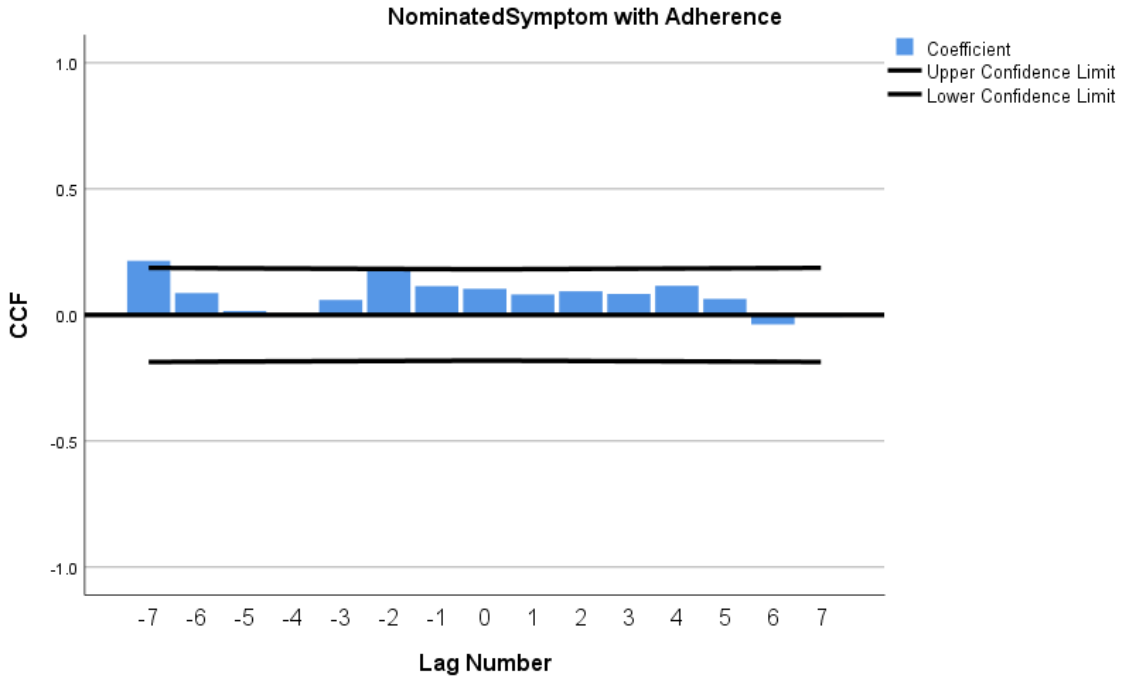
Pain


Pain with Adherence
Coefficient
Upper Confidence Limit
Lower Confidence Limit
CCF
1.0
0.5
0.0
-0.5
-1.0
-7 -6 -5 -4 -3 -2 -1 0 1 2 3 4 5 6 7
Lag Number

Mucus

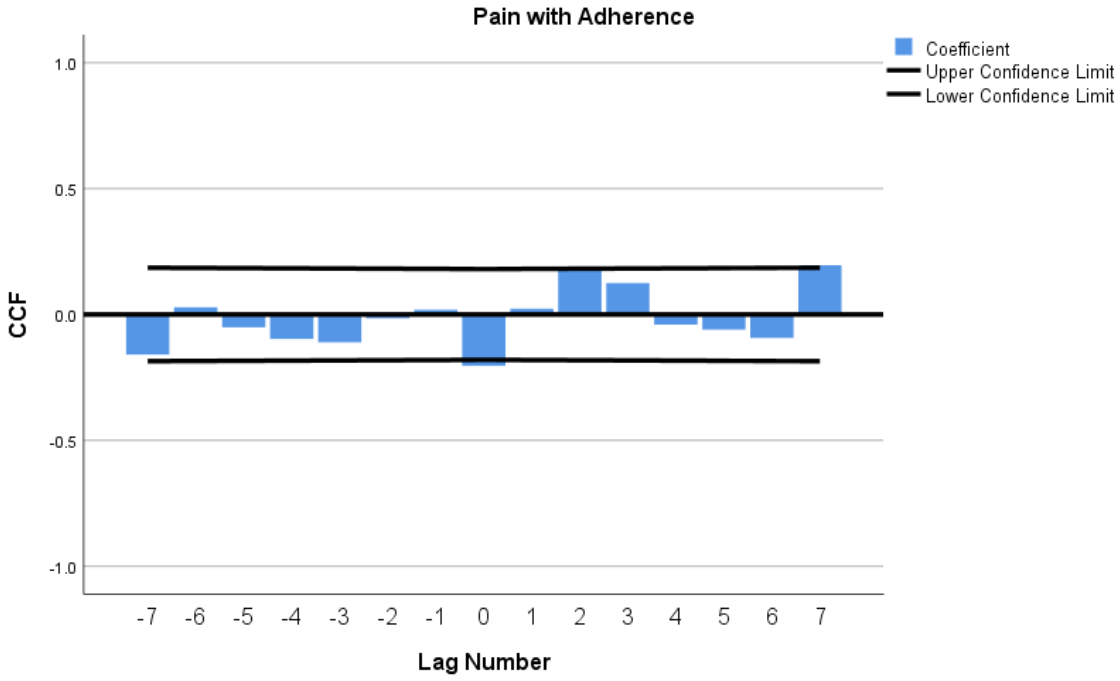


Nominated symptom

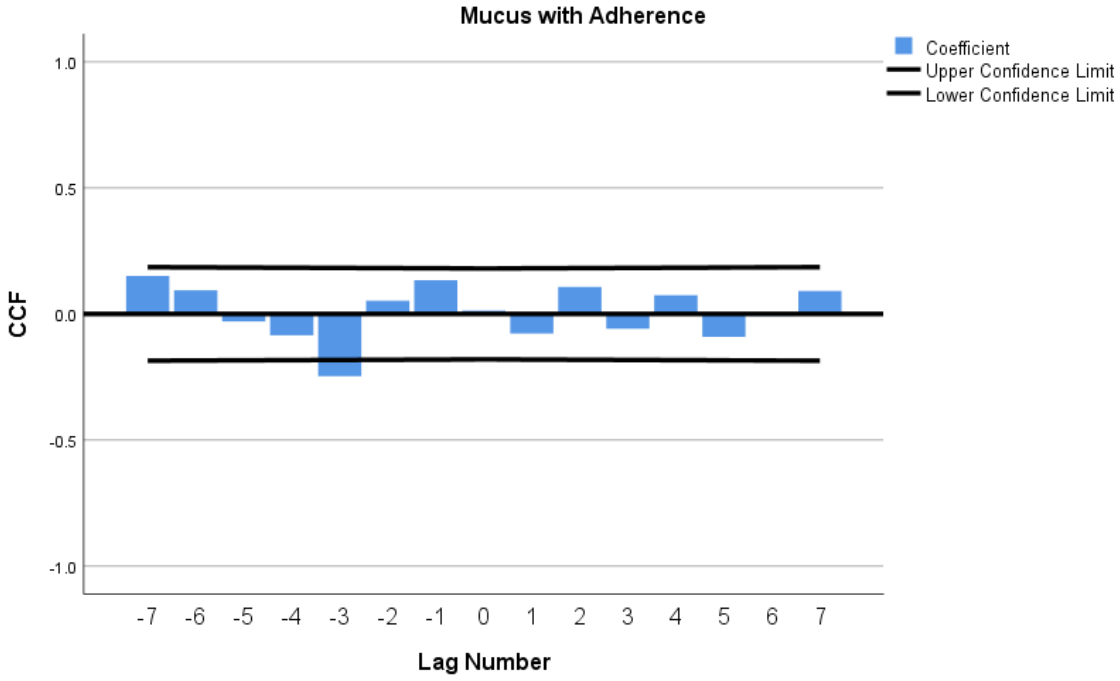


Participant 13

Pain

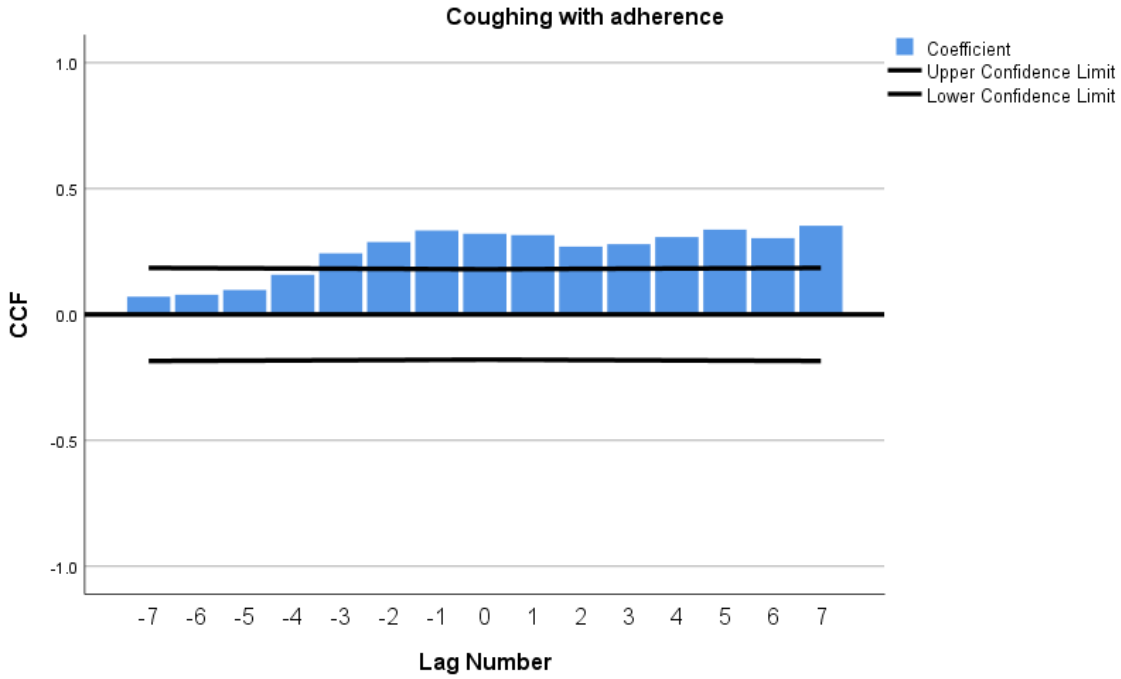


Mucus

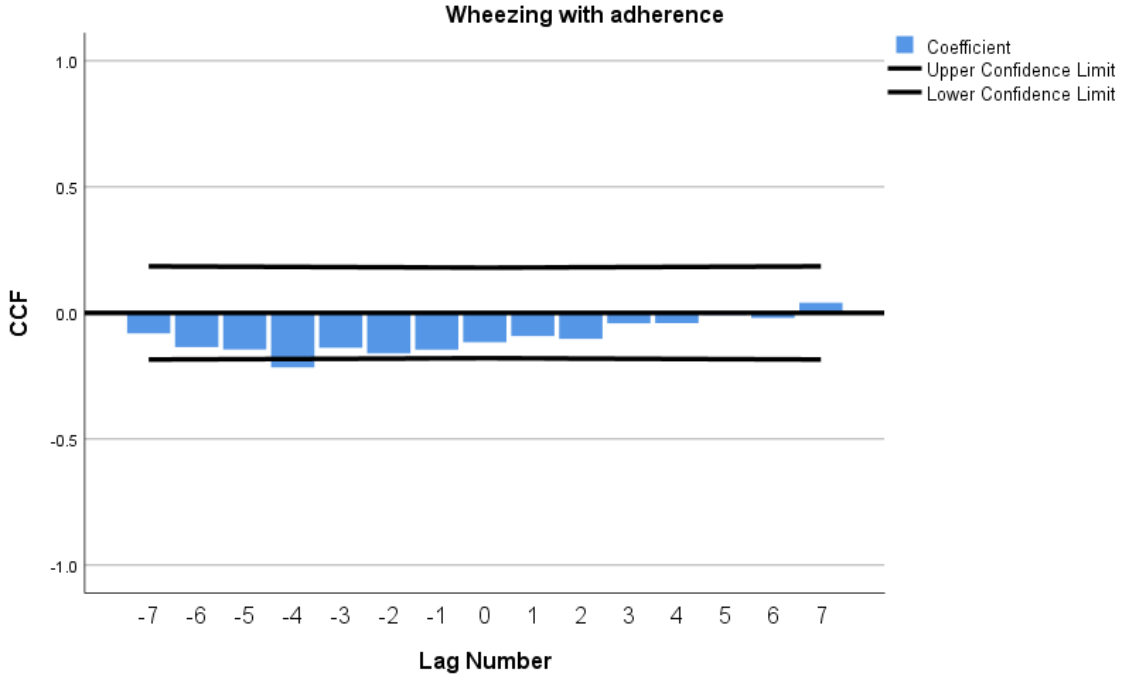


Participant 14

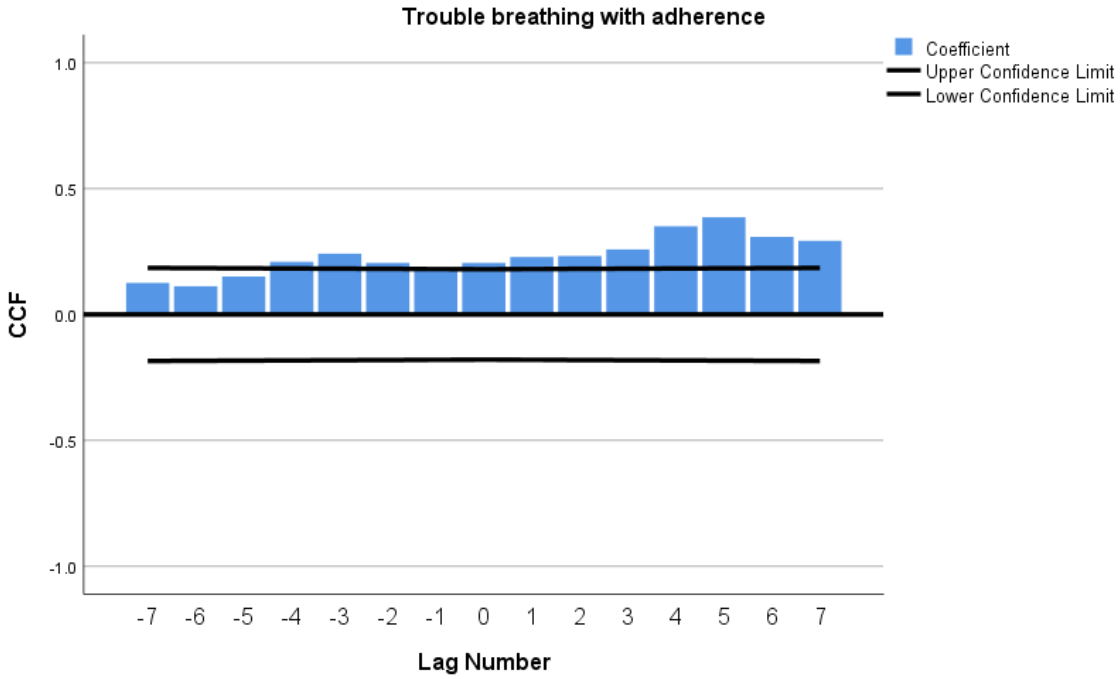
Cough



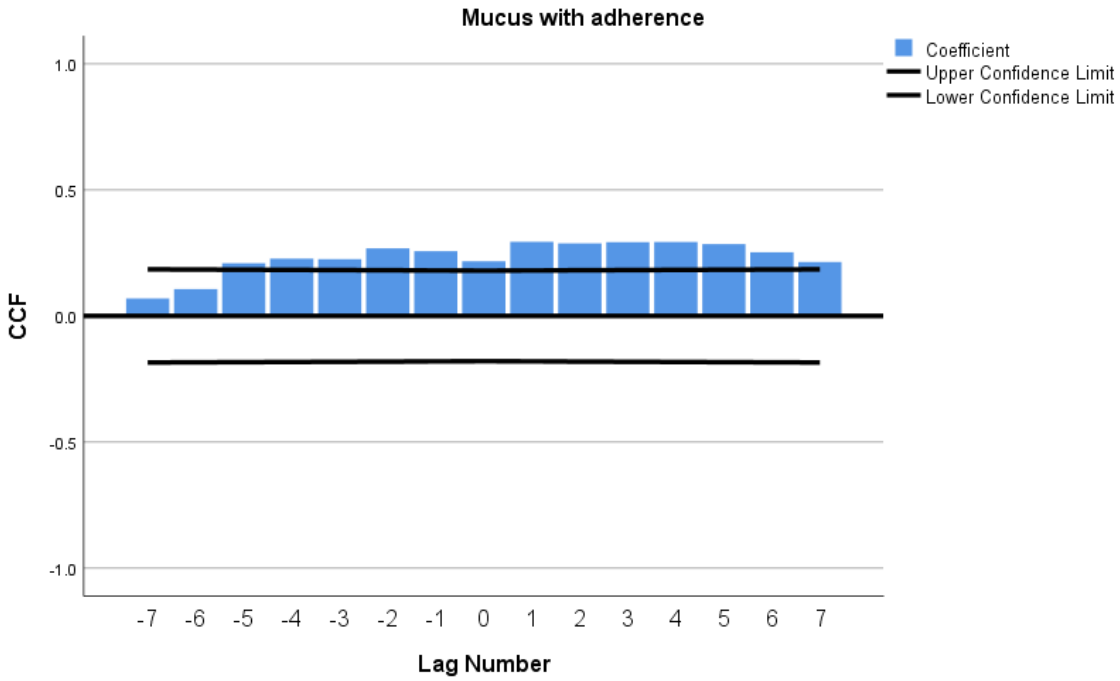
Wheeze



Difficulty breathing

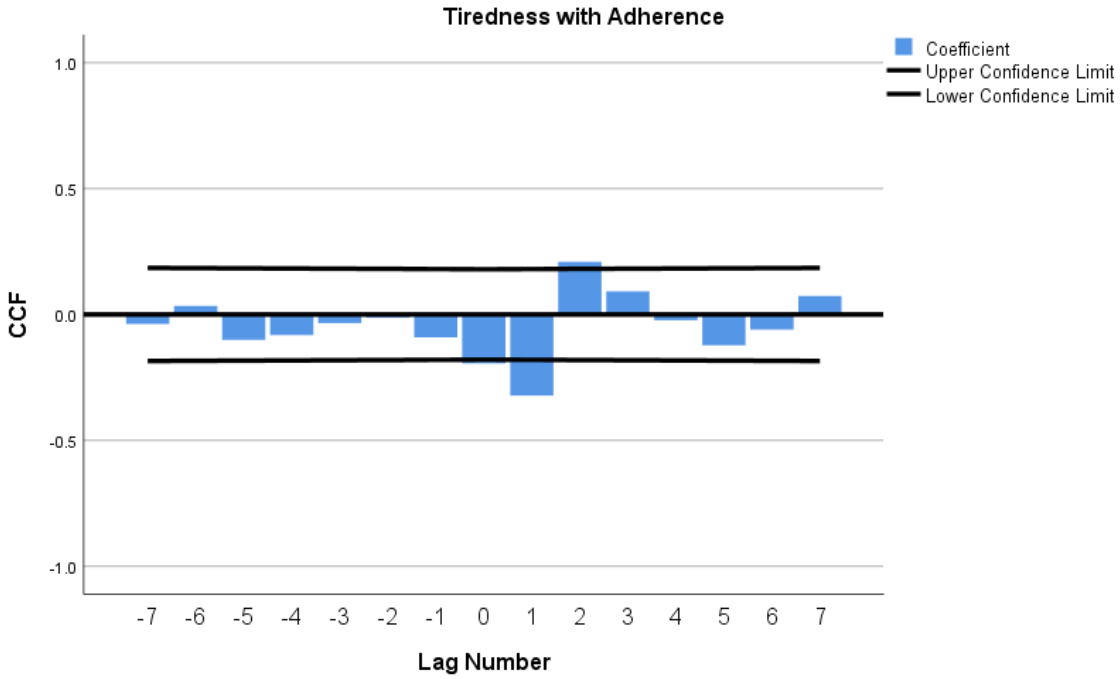


Mucus



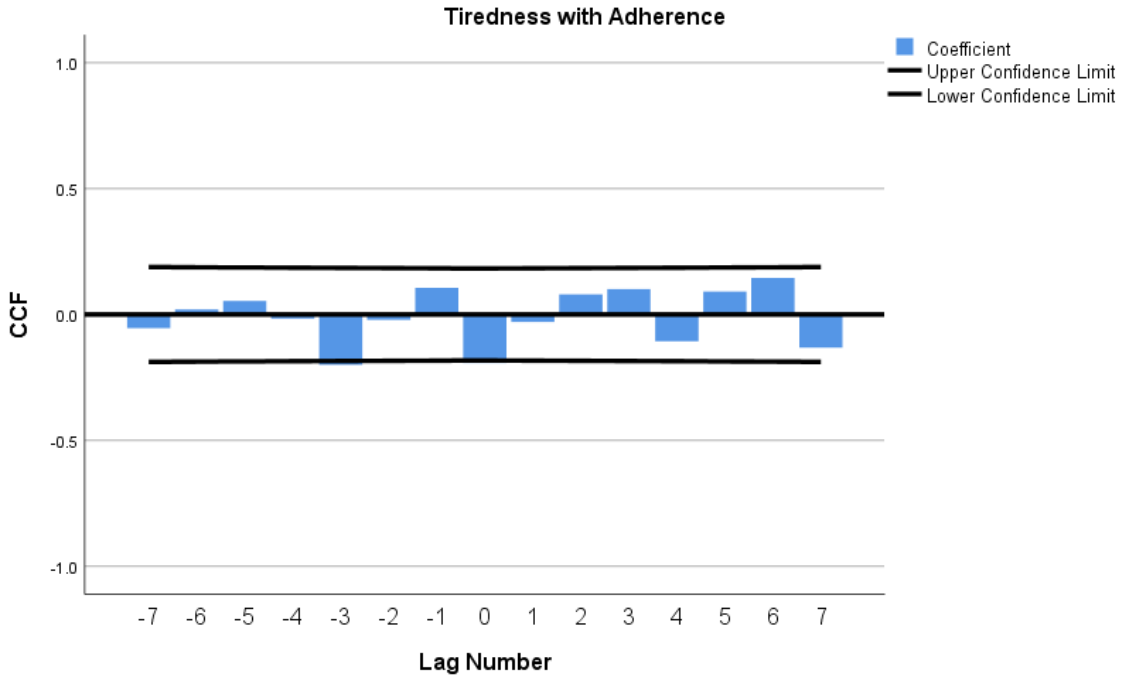
Participant 15

Tiredness


Tiredness with Adherence
Coefficient
Upper Confidence Limit
Lower Confidence Limit
CCF
1.0
0.5
0.0
-0.5
-1.0
-7 -6 -5 -4 -3 -2 -1 0 1 2 3 4 5 6 7
Lag Number

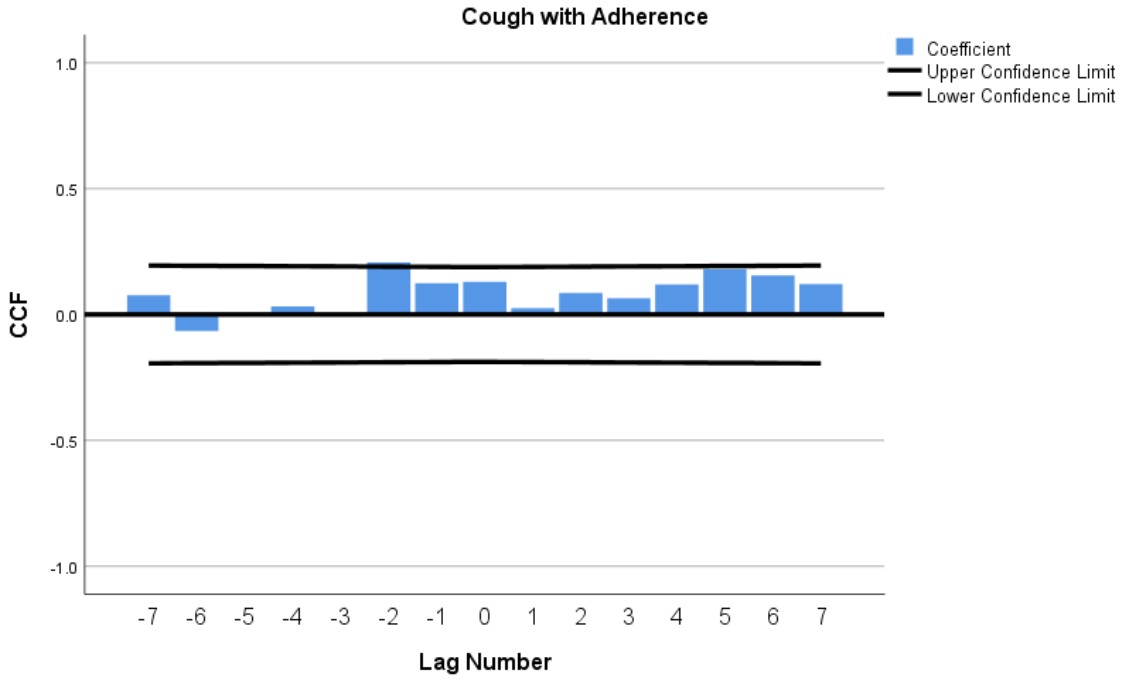
Participant 16

Tiredness



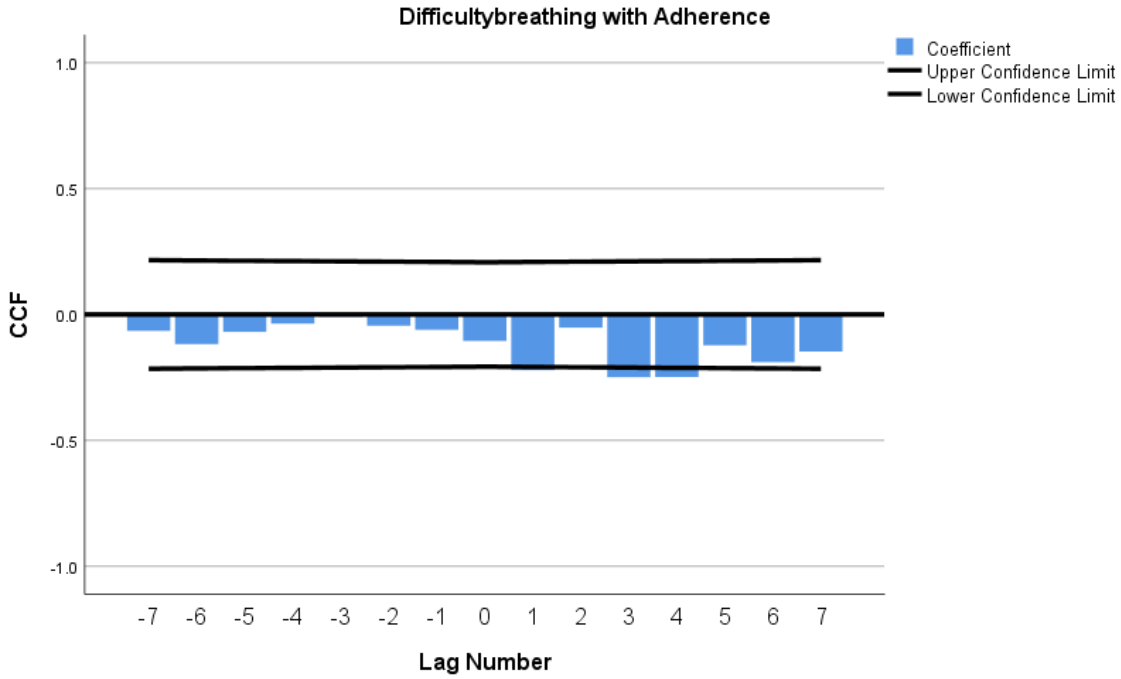
Participant 17

Cough

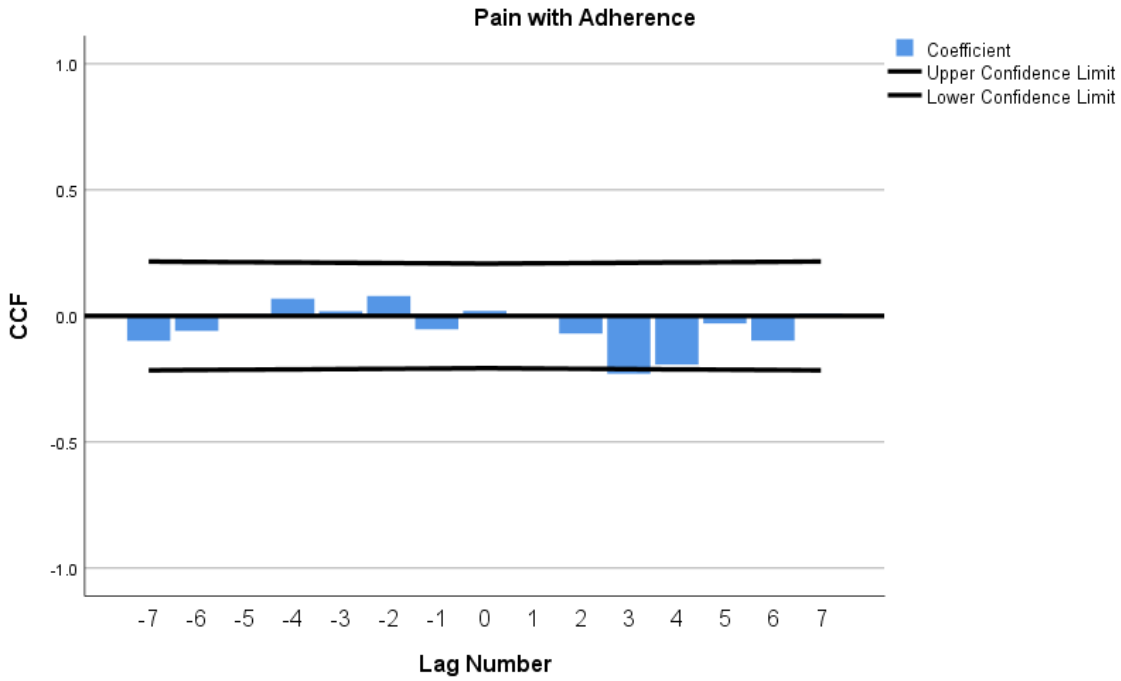


Participant 18

Difficulty breathing

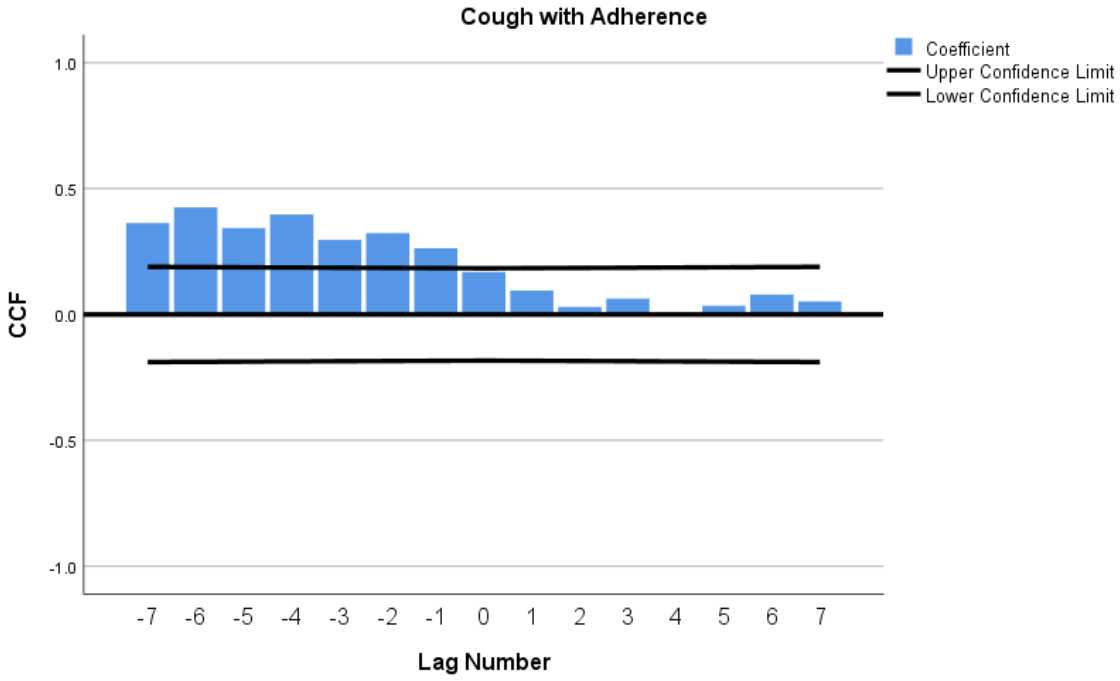


Pain

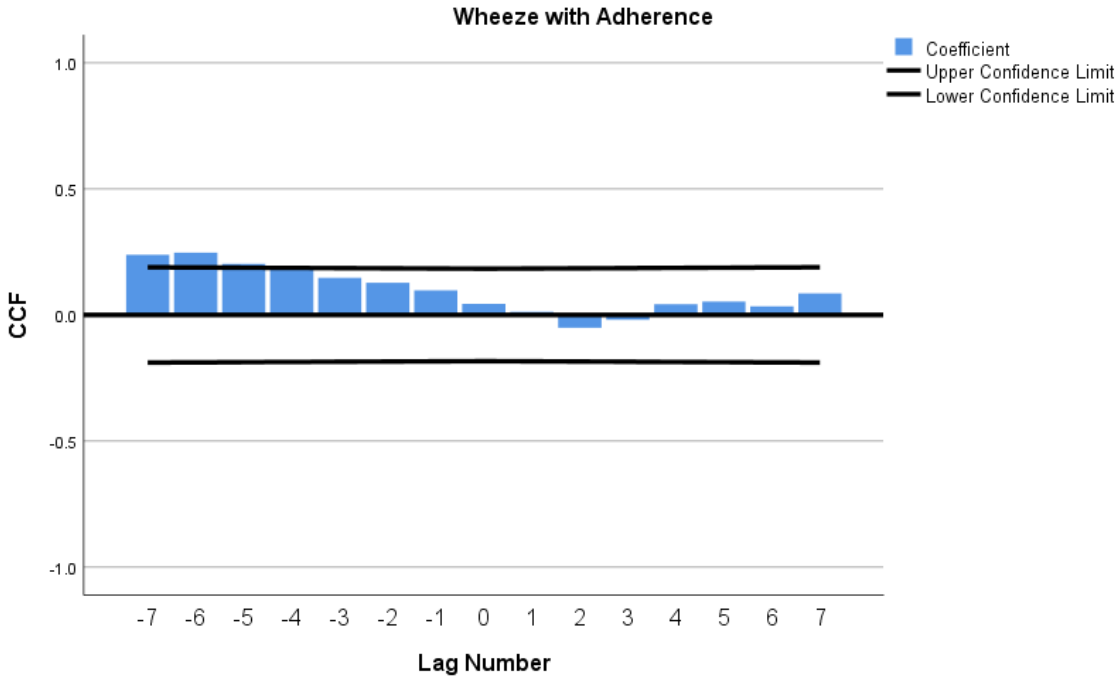


Participant 19

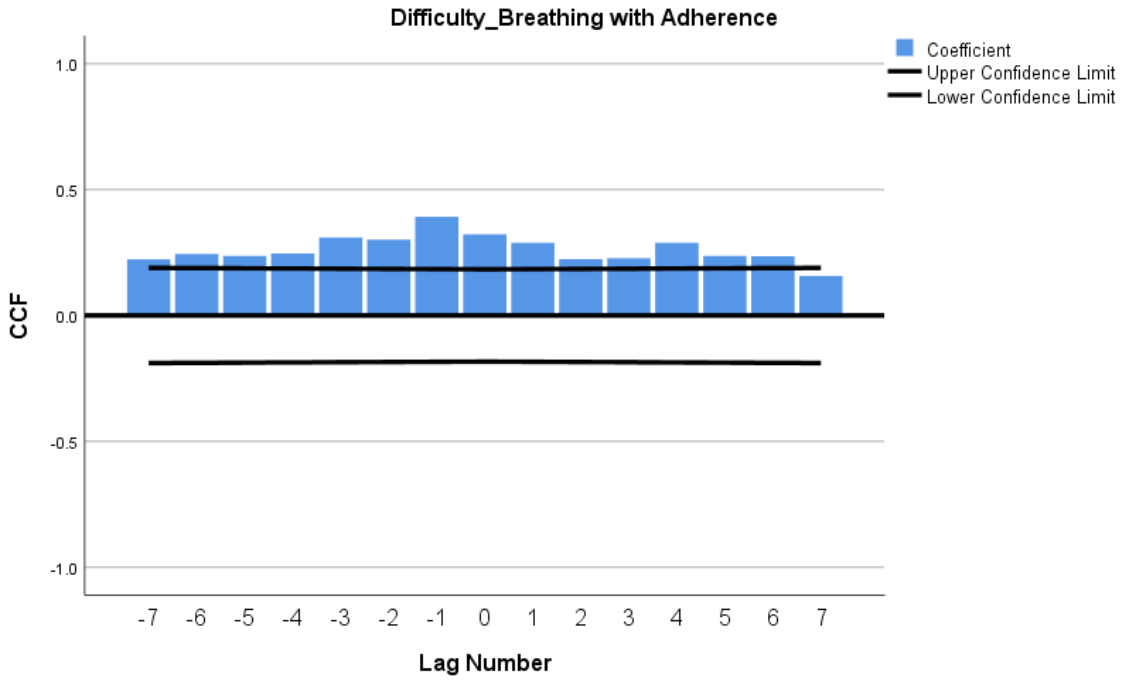
Cough



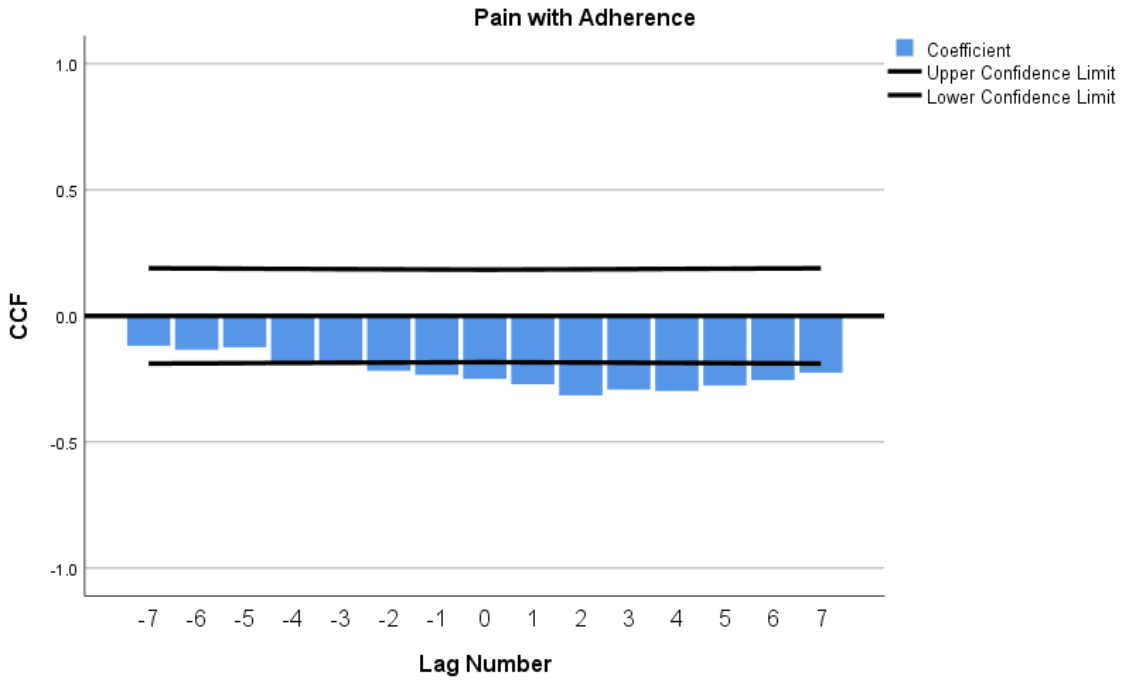
Wheeze



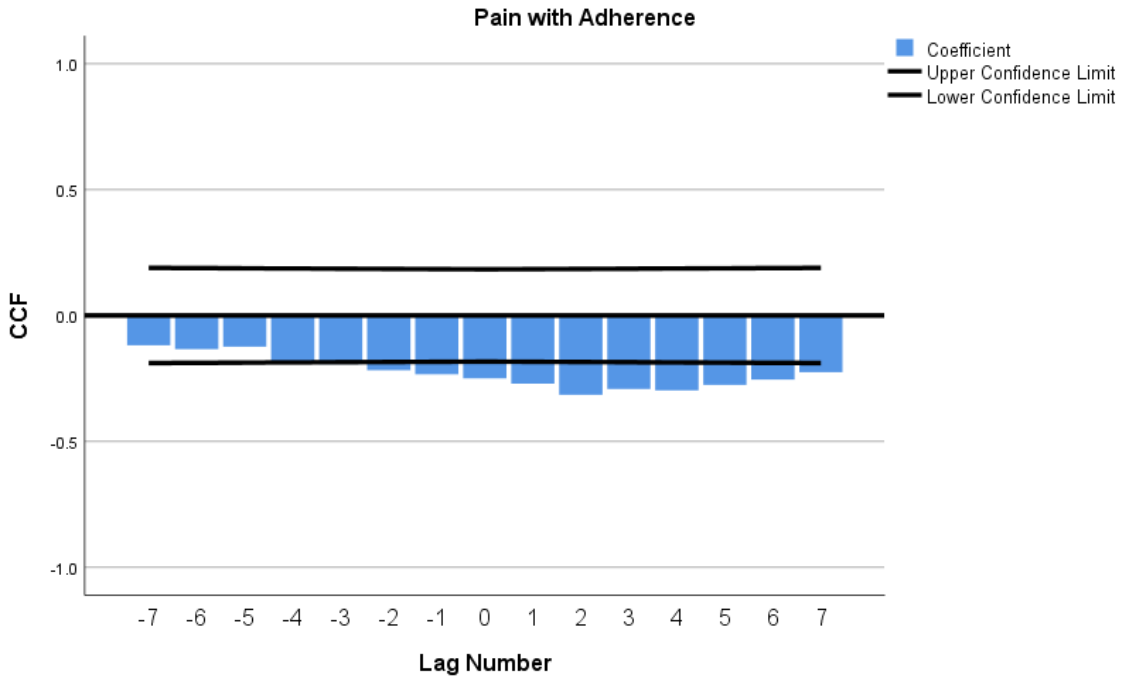
Difficulty breathing



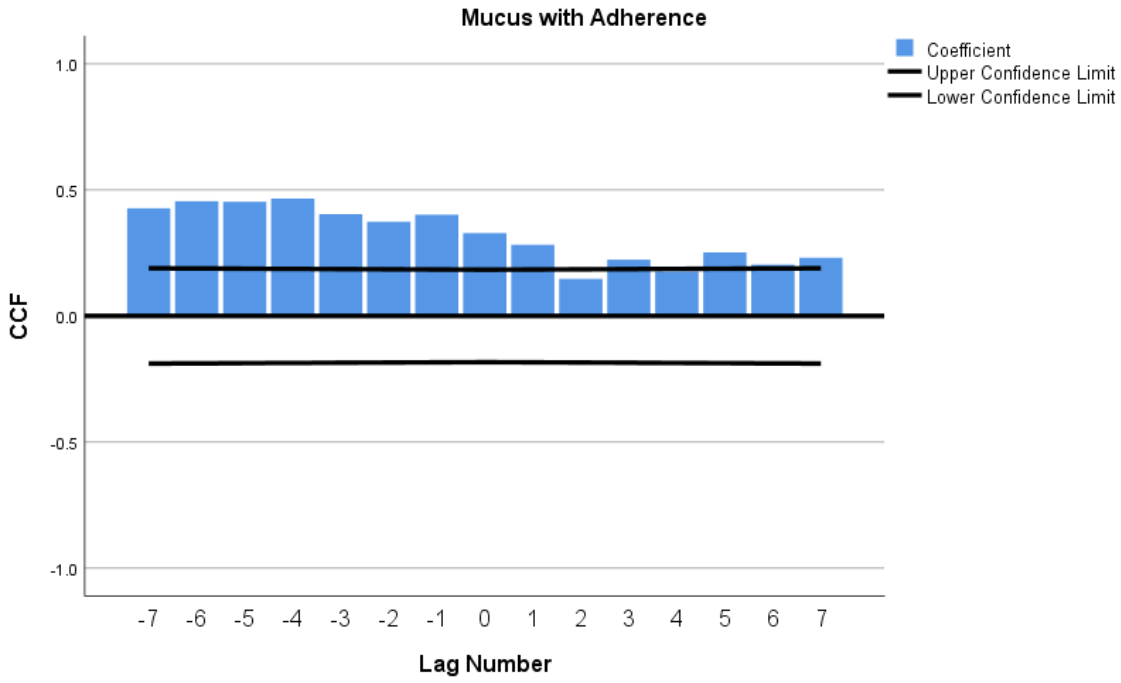
Pain



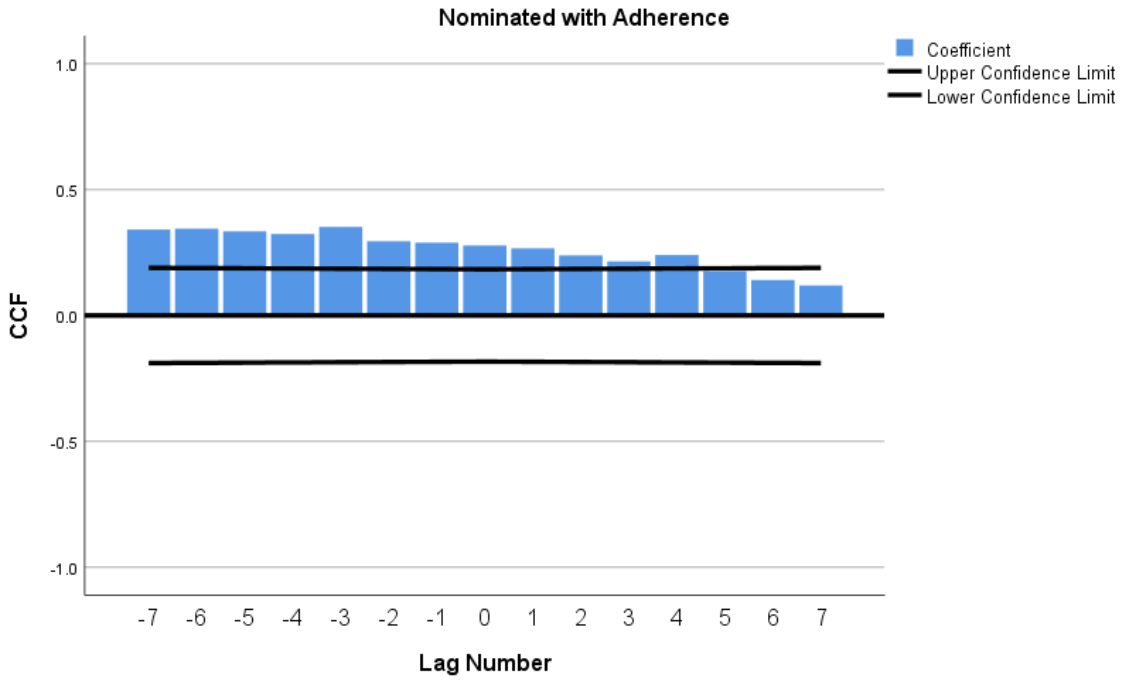
Tiredness



Mucus

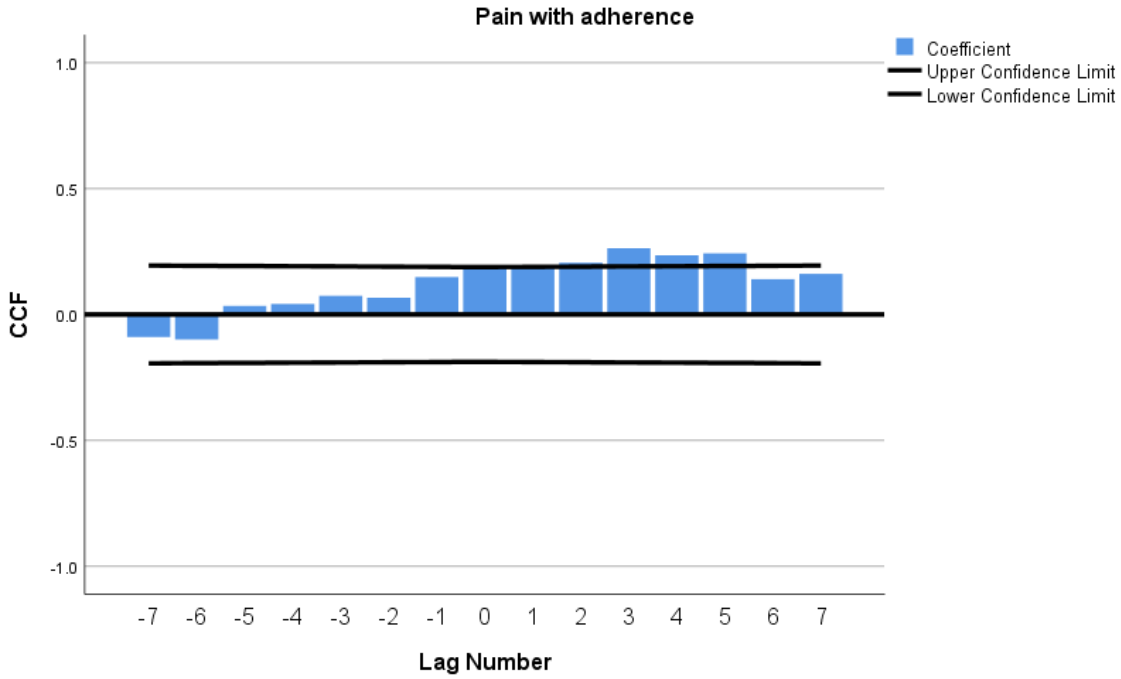


Nominated symptom

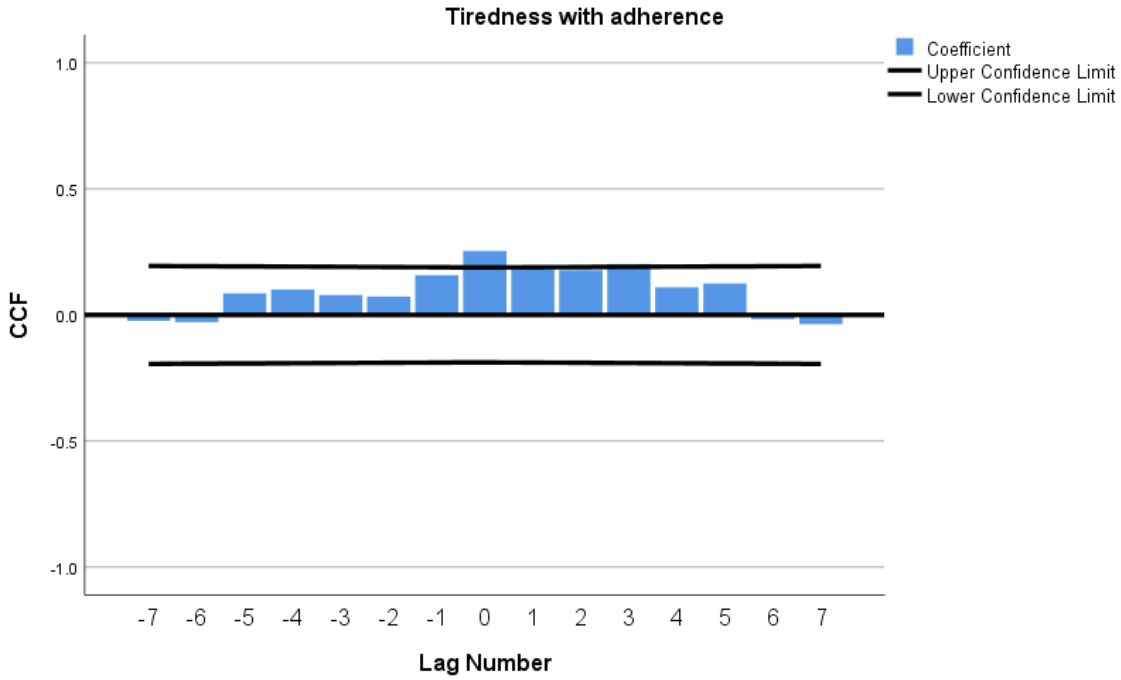


Participant 20

Pain

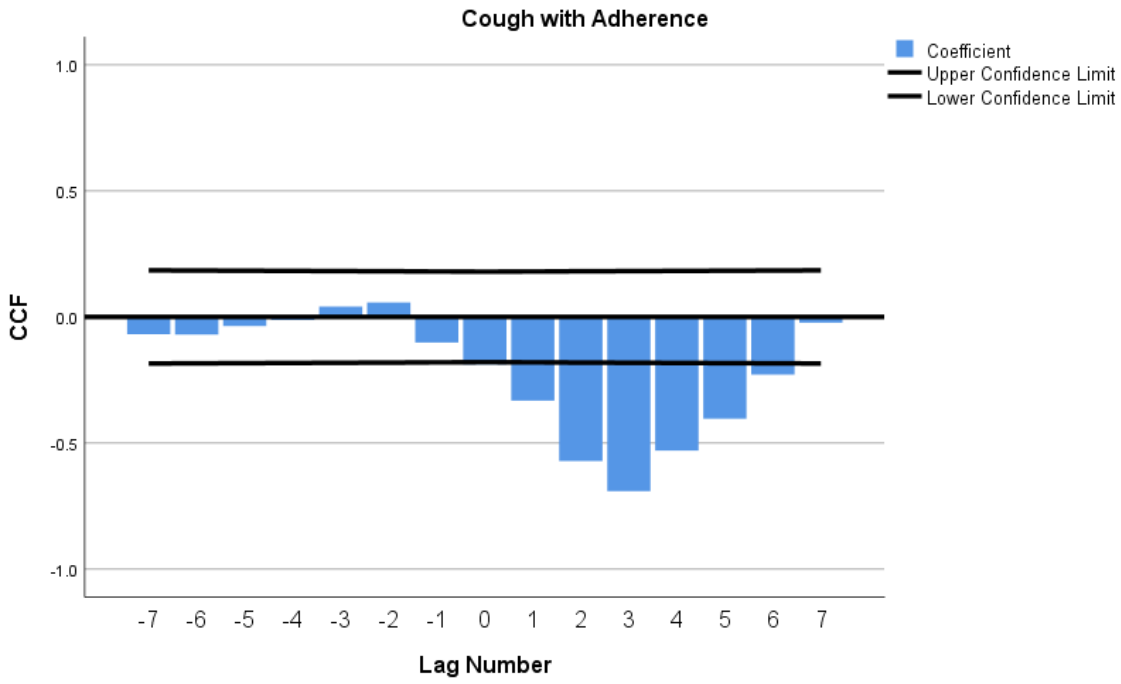


Tiredness

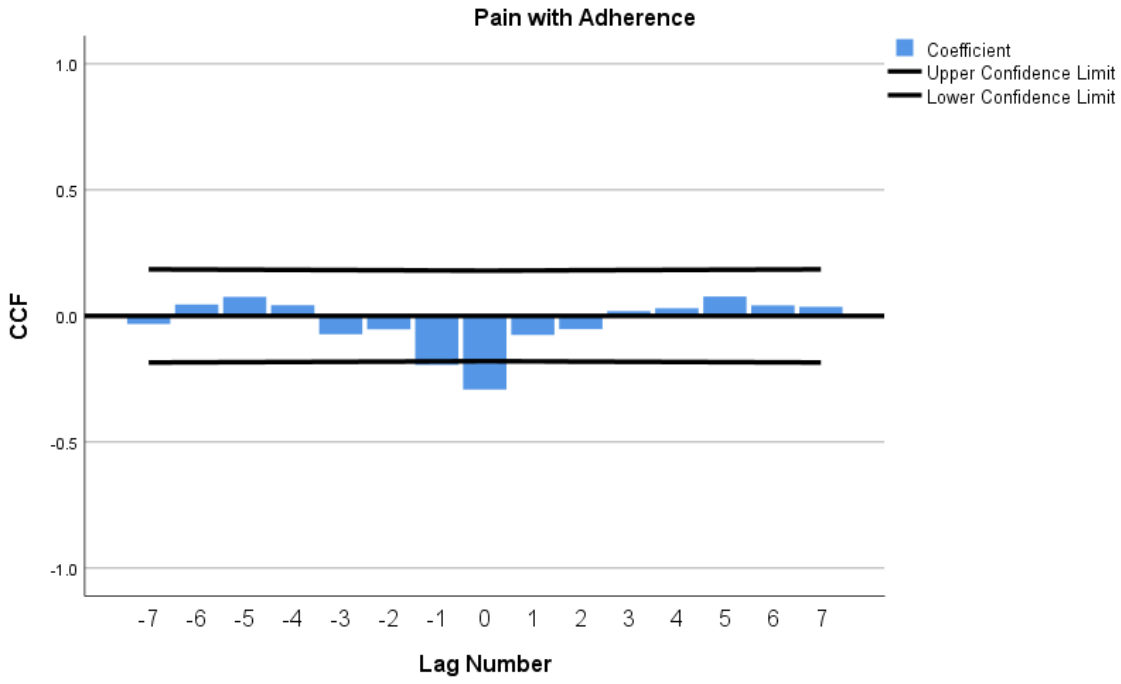


Participant 21

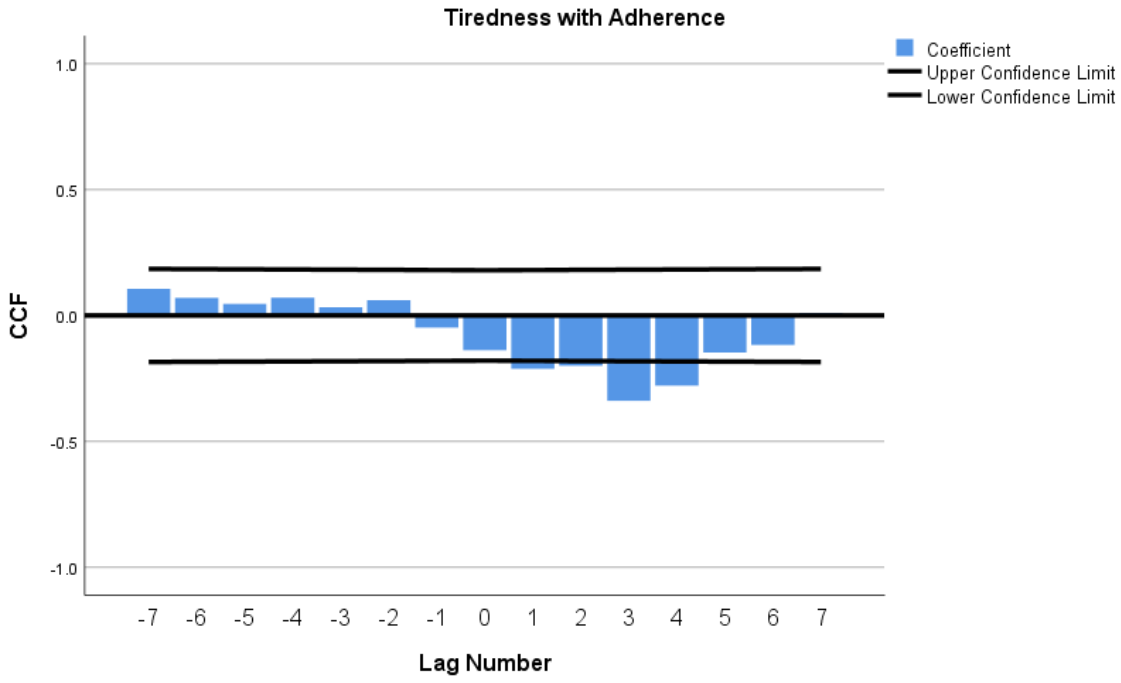
Cough



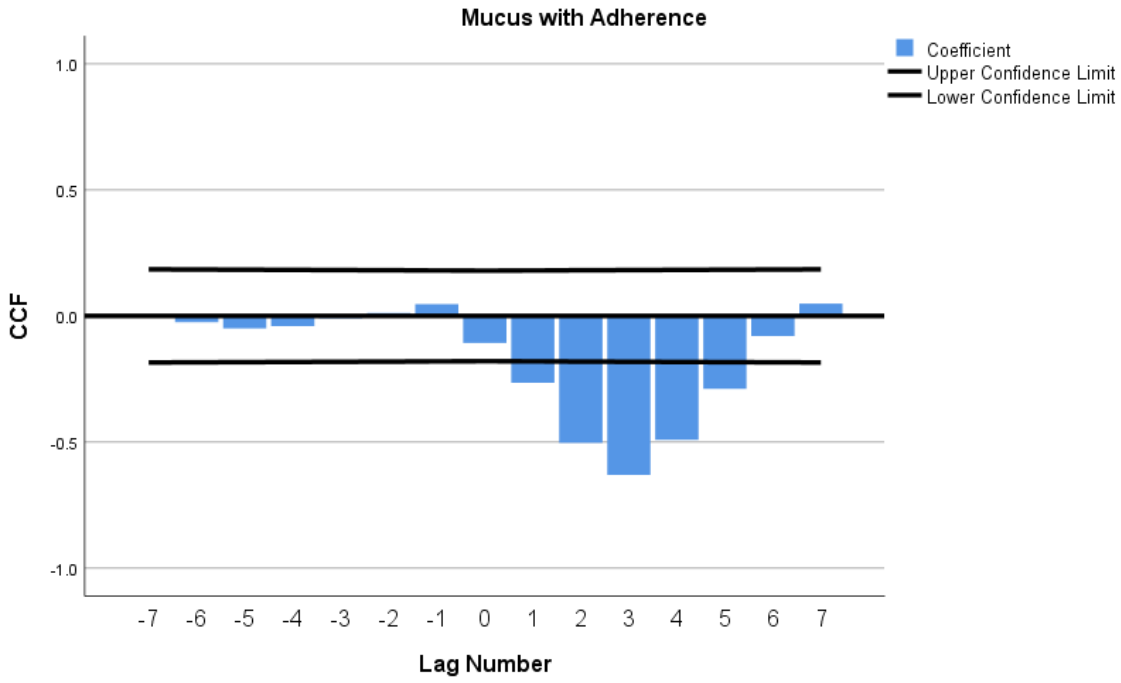
Pain



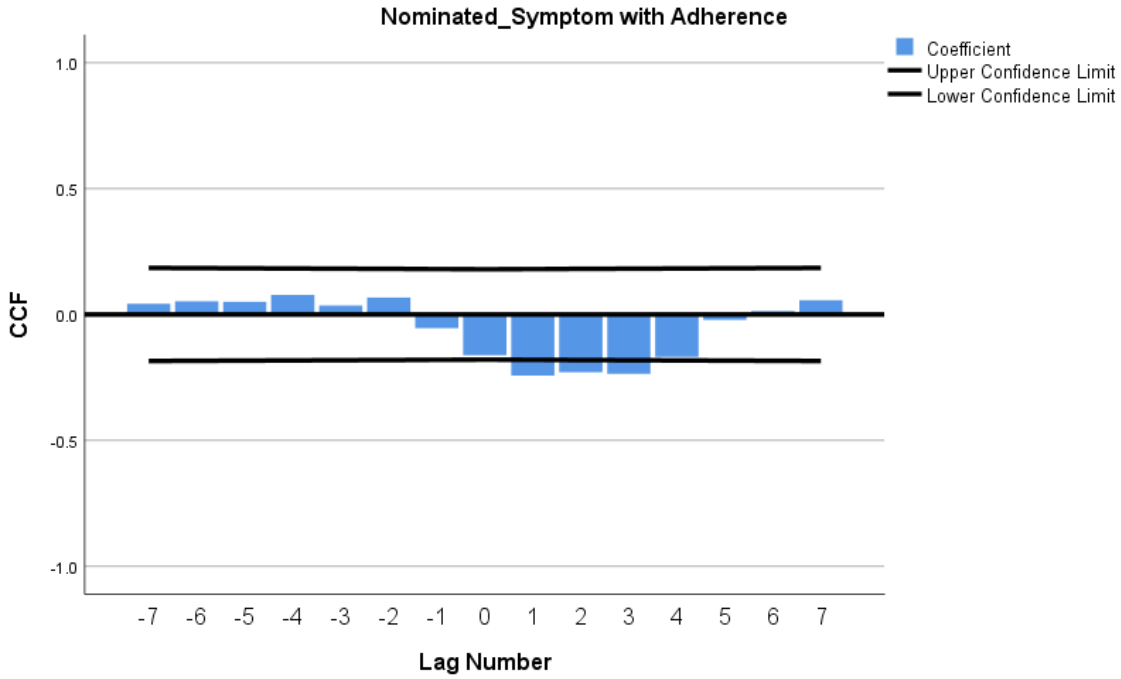
Tiredness



Mucus

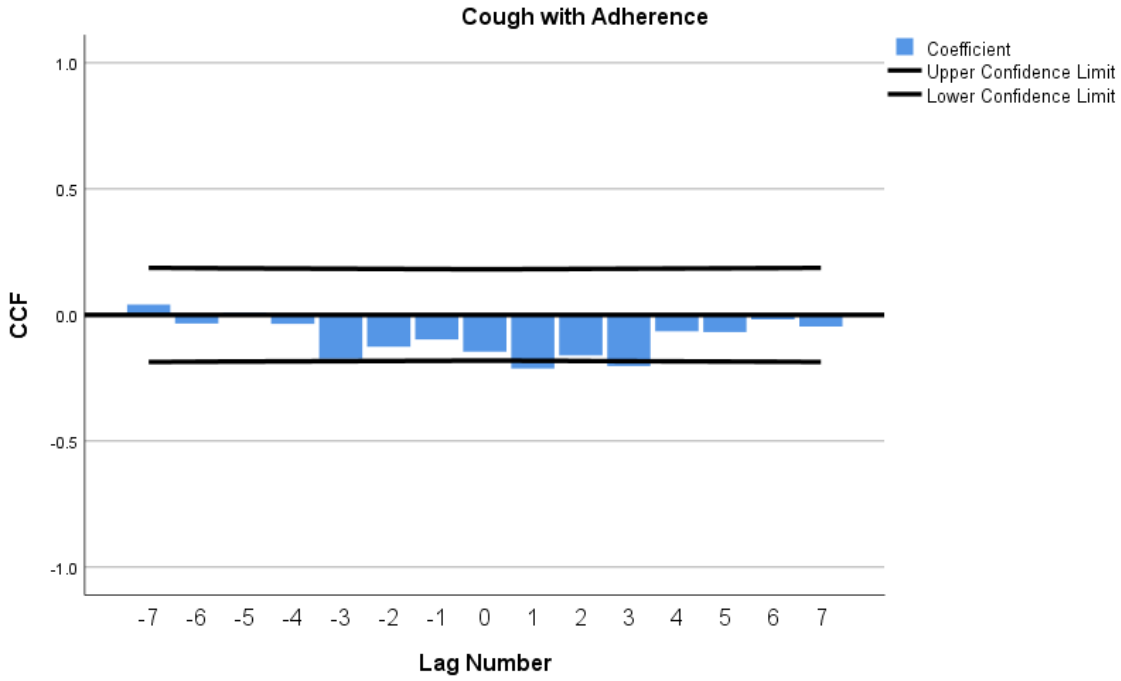


Nominated symptom



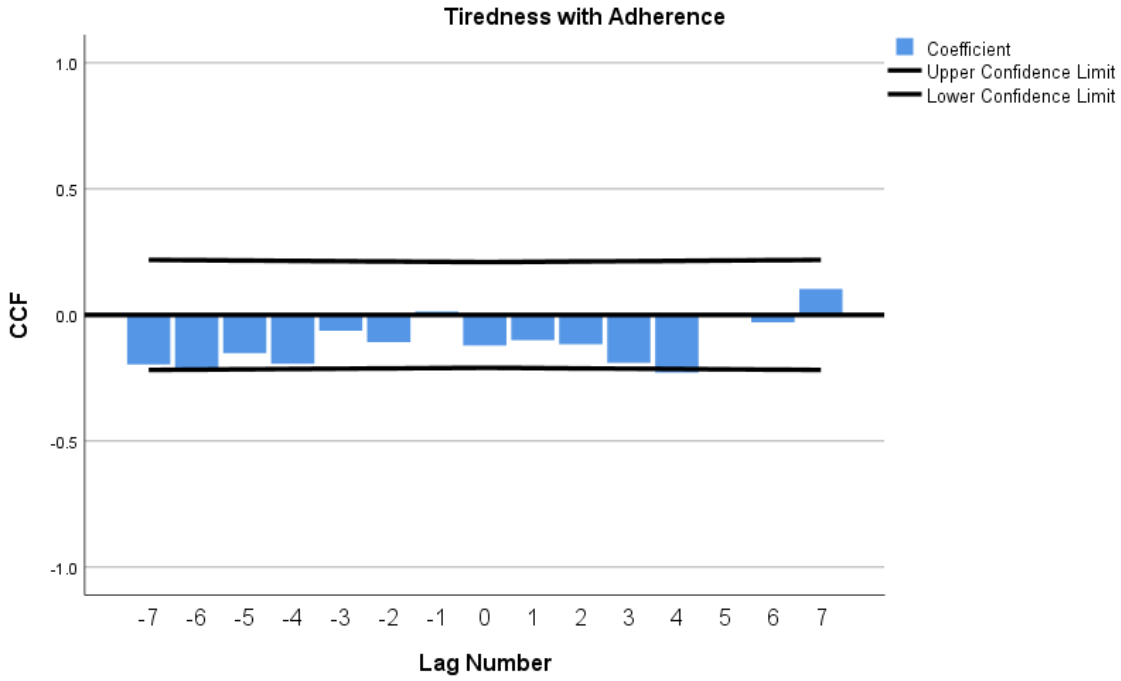
Participant 22

Cough



Participant 25

Tiredness



Appendix I: Autocorrelation table N-of-1 main study (chapter 5)

Symptom	P8	P9	P10	P11	P12	P13	P14	P15	P16	P17	P18	P19	P20	P21
Nominated Symptom	No analysis	No analysis	No analysis	No analysis	**Outcome:** Nominated symptom 10 days ***Predictor:** Adherence 1 days	No analysis	No analysis	No analysis	No analysis	No analysis	No analysis	***Outcome:** Nominated symptom 1 day ***Predictor:** Adherence 2 days	No analysis	***Outcome:** Adherence 1 day ***Predictor:** Nominated symptom 1 day
Cough	**Outcome:** Cough 1 day ***Predictor:** Adherence 1 day	No analysis	No analysis	No analysis	***Outcome:** Adherence 1 day ***Predictor:** Cough 1 day	No analysis	**Outcome:** Adherence1 day ***Predictor:** Cough 1 day	No analysis	No analysis	***Outcome:** Cough 1 day ***Predictor**: Adherence 3 days	No analysis	**Outcome:** Cough 1 day ***Predictor:** Adherence 2 days	No analysis	***Outcome:** Adherence 1 day ***Predictor:** Cough 3 days
Wheeze	No analysis	**Outcome:** Adherence 1 day ***Predictor:** Wheeze 1 day	No analysis	**Outcome:** *****Adherence 1 day **Predictor:** Wheeze	**Outcome:** Wheeze 1 day ***Predictor:** Adherence 1 day	No analysis	***Outcome:** Wheeze 16 days ***Predictor:** Adherence 1 day	No analysis	No analysis	No analysis	No analysis	***Outcome:** Wheeze 1 day ***Predictor:** Adherence 2 days	No analysis	No analysis
Difficulty breathing	No analysis	**Outcome:** Adherence 1 day ***Predictor:** Difficulty	No analysis	**Outcome:** *****Adherence 1 day **Predictor:** Difficulty breathing	***Outcome:** Adherence ***Predictor:** Difficulty breathing	No analysis	***Outcome:** Adherence 1 day ***Predictor:** Trouble	No analysis	No analysis	No analysis	**Outcome:** Adherence 9 days ***Predictor:** Difficulty	**Outcome:** Difficulty breathing 2 days	No analysis	No analysis

		breathing 1 day					breathing 2 days				breathing 1 day	***Predictor:** Adherence 2 days		
Pain	**Outcome:** ***Pain 1 day** ***Predictor:** Adherence 1 day	No analysis	No analysis	No evidence	***Outcome:** Adherence ***Predictor:** Pain	**Outcome:** Adherence 8 days **Predictor:** Pain 10 days	No analysis	No analysis	No analysis	No analysis	**Outcome:** Adherence 9 days **Predictor:** Pain 1 day	**Outcome:** Adherence 2 days ***Predictor:** Pain 1 day	**Outcome:** Adherence 1 day **Predictor:** *Pain 1 day	***Outcome:** Pain 2 days ***Predictor:** Adherence 1 day
Tiredness	No analysis	No analysis	No analysis	**Outcome:** *Adherence 1 day **Predictor:** ***Tiredness** 8 days	**No analysis**	No analysis	No analysis	**Outcome:** Adherence (no evidence of AC) **Predictor:** Tiredness (no evidence of AC)	***Outcome:** Tiredness 1 day **Predictor**: Adherence (no evidence of AC)	No analysis	No analysis	***Outcome:** Tiredness 2 days ***Predictor:** Adherence 2 days	**Outcome:** Adherence 1 day **Predictor:** Tiredness 1 day	***Outcome:** Adherence 1 day ***Predictor:** Tiredness 2 days
Mucus	No analysis	No analysis	No analysis	No analysis	***Outcome:** Adherence ***Predictor:** Mucus	**Outcome:** Mucus (no evidence of AC) ***Predictor**: Adherence 8 days	***Outcome:** Adherence 1 day ***Predictor:** Mucus 1 day	No analysis	No analysis	No analysis	No analysis	***Outcome:** Mucus 2 days ***Predictor:** Adherence 2 days	No analysis	***Outcome:** Adherence 1 day **Predictor:** Mucus 1 day

* Still evidence of AC within this variable, these results should be interpreted with caution.

Appendix J: Interview topic guide (chapter 6)

Interview Schedule

Opening

I will ask you a series of questions relating to the daily diary you have used to track your symptoms of Cystic Fibrosis and how this relates to your adherence charts. If you would like to withdraw from the study you can do so at any time.

Participation

Note for researcher: The following questions will address the RQ 'How valuable was the experience of self-monitoring?

How did you find recording symptoms on a daily basis?

Prompt: What did you like?

Prompt: Was there any barriers?

Prompt: Did you stop or continue after the study?

Prompt: Would you continue if you had the resources?

Were there any symptoms which you preferred tracking?

Probe: *Could you tell me why this was?*

Could you talk me through examples of when it was easier or more difficult?

How did symptom tracking change your awareness of your condition?

Prompt: Is this positive or negative?

How aware are you of your medication adherence?

Prompt: How do you know if you have adhered?

How do you tell that your treatment is working?

Could you give any examples of how your nebuliser causes change in symptoms?

Are there any specific symptoms which change?

Prompt:-At what stage do you receive this change in symptoms? E.g After a week? After a day?

How do you know if you are developing infections?

Prompt: Do you feel symptom tracking could help with monitoring future infections?

Are there any times you may take more treatment?

Prompt :For example when you feel you may be getting an infection.

Could you explain any patterns you may have noticed when tracking your symptoms?

Closing questions

The following questions will address the RQ 'how valuable did participants find symptom tracking?'

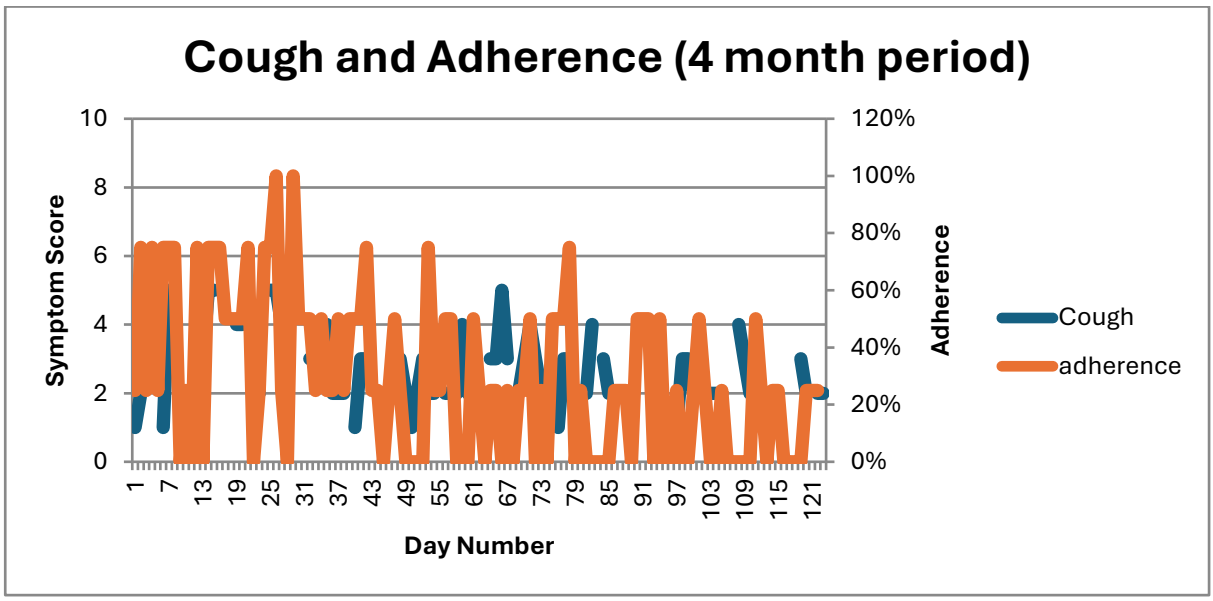
How would you feel about using symptom tracking as a long-term tool to help manage your condition?

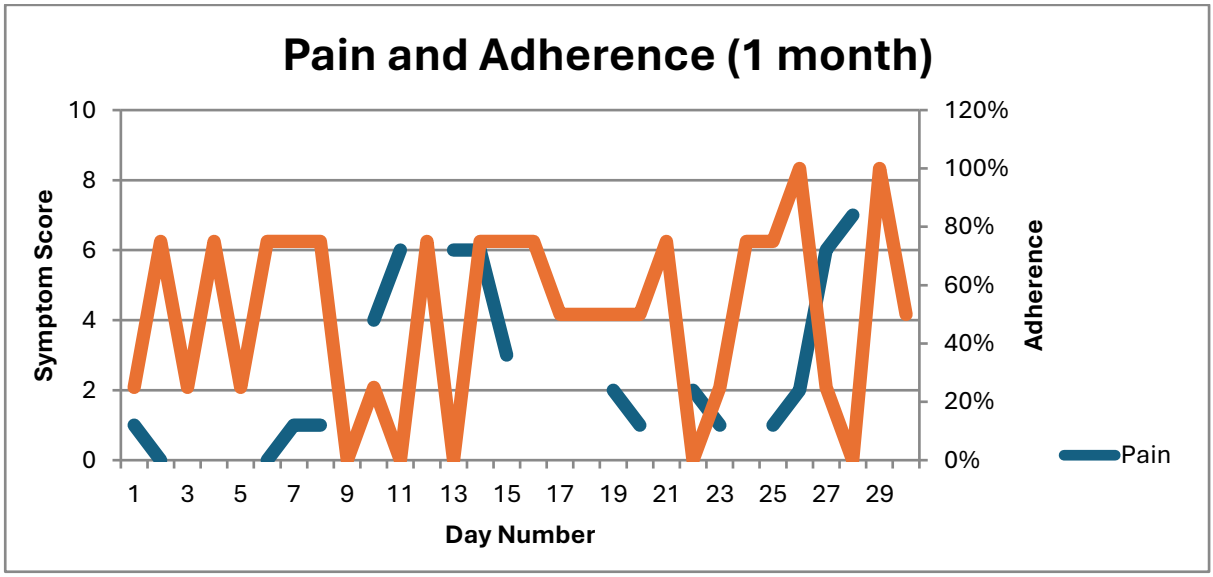
How would you like your symptom tracking to be used in the future?

Is there anything you would like to add?

Thank participant

Appendix K: Graph examples used in interviews in chapter 6





Appendix L- Participant facing documents from chapter 7

Understanding Healthcare Professional's (HCP's) perceptions of the factors which influence adherence to nebuliser treatments in patients with Cystic Fibrosis

Thank you for taking the time to read this information sheet, this document contains information relating to a research study. The study aims to further understand Healthcare Professional's (HCP's) perception of the factors which influence adherence to nebuliser treatments in patients with Cystic Fibrosis (CF), and how HCP's understanding of this influences symptom experience and management.

Why have you asked me to take part? You have been asked to take part in this project as you are a Health Care Professional and currently work with patients with CF.

Do I have to take part? It is up to you to decide if you want to take part. A copy of the information provided here is yours to keep, along with the consent form if you do decide to take part. You can still decide to withdraw at any time without giving a reason, or you can decide not to answer a particular question. You can withdraw your data up to 7 days after the interview.

What will I be required to do? You will be required to take part in a one-off interview online with Rosie Martin, in which you will be asked questions which relate to medication adherence to nebulised treatments in patients with CF. During this interview you will be presented with findings from a recent study with CF patients and asked to comment on the implication of these findings for clinical practice.

Where will this take place? The interviews will take place online, you will be sent a Teams link to your staff email.

How often will I have to take part, and for how long? Your participation in the study is one-off, you will be asked to participate in a one-off interview which will last between 40 minutes to one hour.

Are there any possible risks or disadvantages associated with taking part? It is not anticipated that there are any risks associated with taking part in the study. However, if you feel uncomfortable answering any of the questions you do not have to do so, and of course can withdraw at any point during the interview.

What are the possible benefits of taking part? This study will provide you an opportunity to discuss medication adherence to nebuliser treatments in patients with CF and contribute to the research about how best to do this effectively with patients. However, it is unlikely that there are any benefits which will impact you directly.

When will I have the opportunity to discuss my participation? You can contact Rosie (see details below) if you have any questions prior to or after your participation. You will be provided with a debrief after your participation which will provide you with the researchers details and also details of support services.

Will anyone be able to connect me with what is recorded and reported?

Your interview will be audio-recorded via Teams, following this it will be transcribed and any identifiable information will be removed or replaced with pseudonyms. This

is to ensure that chances of identification are as limited as possible. Each participant will be provided with a unique code, if you would like to withdraw you have up to 7 days and must provide this code. Following this your data will be fully anonymised and therefore it is not possible to withdraw. All consent forms will be stored securely and separately to interview data.

Who will be responsible for all of the information when this study is over? Rosie Martin will be responsible for the ensuring the data is stored securely once the study is over.

Who will have access to it? Only members of the research team will have access to raw data and consent forms. The information you provide in this study is confidential, this confidentiality would only be breached if a safeguarding issue arises (for example you state you are going to harm yourself or somebody else).

What will happen to the information when this study is over? Raw data (the interview recording) will be anonymised during the transcription process, the audio files will then be deleted. Electronic consent forms will be retained, they will be stored securely on a University One Drive Account and this information will be stored for as long as journals require.

If you consent to this on the consent form, your redacted data may be shared with students for teaching and learning purposes, however you are able to participate in the study but decline to share your data if you wish. There is no requirement or obligation to do so.

How will you use what you find out? The findings of this study will be written up for a doctoral thesis. It is also anticipated that the findings will be published in academic journals and presented at research conferences. Quotes from interview maybe used within dissemination, however all information will be anonymised. Finally data collected may be used for teaching purposes and analysed by students for their dissertation (only if you consent to this). Students will only have access to anonymised data.

How long is the whole study likely to last? Your participation in the study will last between 40-60 minutes, the participation is one-off.

How can I find out about the results of the study? If you would like to receive a summary of the results of this study please contact Rosie Martin (details below) after August 2024 and this will be provided.

Thank you for taking the time to read this.

Please contact Rosie Martin if you have any questions or concerns about this study.

Research Team Details:

Rosie Martin- rosie.martin@shu.ac.uk

Prof Maddy Arden- m.arden@shu.ac.uk

Dr Jenny Porritt- j.porritt@shu.ac.uk

Legal basis for research for studies.

The University undertakes research as part of its function for the community under its legal status. Data protection allows us to use personal data for research with appropriate safeguards in place under the legal basis of **public tasks that are in the public interest.** A full statement of your rights can be found at: www.shu.ac.uk/about-this-website/privacy-policy/privacy-notices/privacy-notice-for-research. However, all University research is reviewed to ensure that

participants are treated appropriately and their rights respected. This study was approved by the University's Research Ethics Committee with reference number **AA64736224** . Further information at: www.shu.ac.uk/research/excellence/ethics-and-integrity

You should contact the Data Protection Officer if:	**You should contact the Head of Research Ethics (Dr Mayur Ranchordas) if:**
• you have a query about how your data is used by the University • you would like to report a data security breach (e.g. if you think your personal data has been lost or disclosed inappropriately) • you would like to complain about how the University has used your personal data DPO@shu.ac.uk	• you have concerns with how the research was undertaken or how you were treated ethicssupport@shu.ac.uk
Postal address: Sheffield Hallam University, Howard Street, Sheffield S1 1WBT Telephone: 0114 225 5555	

HRA Information

In this research study we will use information from you. We will only use information that we need for the research study. We will let very few people know your name or contact details, and only if they really need it for this study.

Everyone involved in this study will keep your data safe and secure. We will also follow all privacy rules.

At the end of the study we will save some of the data in case we need to check it
We will make sure no-one can work out who you are from the reports we write.

The information pack tells you more about this.

How will we use information about you?

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

People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead.

We will keep all information about you safe and secure.

Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study.

What are your choices about how your information is used?

- You can stop being part of the study at any time, without giving a reason, you have up to 7 days after participation to withdraw data.
- We need to manage your records in specific ways for the research to be reliable. This means that we won't be able to let you see or change the data we hold about you.

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

You can find out more about how we use your information

- at www.hra.nhs.uk/information-about-patients/
- our leaflet available from **www.hra.nhs.uk/patientdataandresearch**
- by asking one of the research team
- by sending an email to ethicssupport@shu.ac.uk, or
- by ringing us on 0114 225 5555

PARTICIPANT INFORMED CONSENT FORM

Understanding Healthcare Professional's (HCP's) perceptions of the factors which influence adherence to nebuliser treatments in patients with Cystic Fibrosis

Participant's Unique ID:

Please answer the following questions by initialling the boxes which apply:

INITIAL

9. I have read the Information Sheet (V4 02.10.2024) for this study and have had details of the study explained to me.

10. My questions about the study have been answered to my satisfaction and I understand that I may ask further questions at any point.

11. I understand that I am free to withdraw from the study for 7 days after your participation, without giving a reason for my withdrawal or to decline to answer any particular questions in the study without any consequences to my future treatment by the researcher.

12. I understand the interview will be audio-recorded using Microsoft Teams.

13. I agree to provide information about medication adherence in patients with Cystic Fibrosis to the researchers under the conditions of confidentiality set out in the Information Sheet.

14. I consent to the information collected for the purposes of this research study, once anonymised (so that I cannot be identified), to be used for any other research purposes and included in the write-up of this study.

15. I consent to my redacted data being used as teaching materials and shared with students.

Participant's Signature: _____ Date: _____

Participant's Name (Printed): _____

Contact details:

_____

_____
_

Researcher's Signature: _____ Date: _____

Researcher's Name (Printed): _____
Researcher's Name: Rosie Martin
Researcher's contact details: rosie.martin@shu.ac.uk
Please keep your copy of the consent form and the information sheet together.

Debrief: Understanding Healthcare Professional's (HCP's) perceptions of the factors which influence adherence to nebuliser treatments in patients with Cystic Fibrosis

Thank you for participating in this research study, the aim of this study was to further understand Healthcare Professional's (HCP's) perception of the factors which influence adherence to nebuliser treatments in patients with Cystic Fibrosis (CF), and how HCP's understanding of this influences, symptom experience and management.

If you would like to withdraw the data, you have provided during your interview please contact the researcher within a week of your interview and provide your unique code.

If you would like to receive a summary of the study findings, please contact Rosie Martin (details below), Rosie will provide you with this information once the study has been completed.

If you feel you need to access support based on anything we have discussed today, please consider contacting:

Support for NHS Staff: https://www.england.nhs.uk/supporting-our-nhs-people/support-now/staff-mental-health-and-wellbeing-hubs/

General Advice: https://www.nhs.uk/nhs-services/mental-health-services/

Please also contact your GP if you would like to discuss your mental health further.

Thank you for taking the time to read this.

Please contact Rosie Martin if you have any questions or concerns about this study.

Research Team Details:
Rosie Martin- rosie.martin@shu.ac.uk
Prof Maddy Arden- m.arden@shu.ac.uk

Dr Jenny Porritt- j.porritt@shu.ac.uk

You should contact the Data Protection Officer if:	**You should contact the Head of Research Ethics (Dr Mayur Ranchordas) if:**
• you have a query about how your data is used by the University • you would like to report a data security breach (e.g. if you think your personal data has been lost or disclosed inappropriately) • you would like to complain about how the University has used your personal data DPO@shu.ac.uk	• you have concerns with how the research was undertaken or how you were treated ethicssupport@shu.ac.uk

Legal basis for research for studies.
The University undertakes research as part of its function for the community under its legal status. Data protection allows us to use personal data for research with appropriate safeguards in place under the legal basis of **public tasks that are in the public interest.** A full statement of your rights can be found at: www.shu.ac.uk/about-this-website/privacy-policy/privacy-notices/privacy-notice-for-research. However, all University research is reviewed to ensure that participants are treated appropriately and their rights respected. This study was approved by the University's Research Ethics Committee with reference number ER65284159. Further information at: www.shu.ac.uk/research/excellence/ethics-and-integrity

Appendix M- Interview schedule from chapter 7

Interview Schedule

This interview schedule may be subject to minor changes

Introduction Questions

What is your job role within the NHS?

How long have you worked with patients with CF?

How much experience do you have in your past or current role of managing adherence?

How often do you discuss adherence to nebuliser treatments with adults with CF?

Could you tell me a little about how you managed medication adherence in your role?

The following questions will address the research question '*To further understand HCP's perception of the factors which influence adherence to nebuliser treatment in CF patients and their understanding of how treatment influences symptom experience and management'*

What factors do you think influence adherence in your CF patients?

Do your patients notice improvements in their symptoms (i.e. cough, wheeze, difficulty breathing) as a result of taking their medication?

What symptoms do you think they will notice changes in as a result of taking their treatment?

What symptoms do you think they will NOT notice changes in as a result of taking their treatment?

How long do you think patients have to be taking treatment prior to noticing improvements in their symptoms?

Are there any symptoms that might prompt increased adherence? What are they and why?

How do you currently discuss adherence with patients?

What are the barriers to you discussing medication adherence with patients?

Prompt: Time, difficult conversations, patients not willing to discuss this.

What strategies/ways do you currently use to try and increase treatment adherence?

What would you say are the main barriers to adherence?

The following questions will address the research question *'To explore the implications of the findings from study 2 (Nof1) and study 3 (qualitative interviews with CF patients) for how healthcare professionals understand the relationship between symptom experiences and treatment adherence in CF patients and the management of adherence in the clinical setting'*

Do you think there would be any benefits to using individualised patient data such as the data I have shown you (Nof1 data) with patients to better understand their condition?

How you think this data could be used to help improve adherence for some patients?

Have the findings discussed influenced how you understand the impact treatment has on people's experiences of symptoms associated with CF?

Do these findings support your experiences of working with patients with CF?

The following questions will address research question 2: How feasible is it to use self-monitoring data alongside adherence data to create individualised interventions to help care for patients with CF? (Questions informed by the COM-B)

Make it clear to participants that they are not being asked to deliver any interventions this is just hypothetical.

- What do you think the benefits and disadvantages of discussing patients' symptom and adherence data could be? (Motivation)
- How do you feel about the idea of discussing patients' symptom and adherence data with them? (motivation)
- To what extent do you feel you have the skills, understanding and/or knowledge to be able to discuss symptom and adherence data with patients in a useful way? (Capability)
- To what extent do you feel that you have the necessary resources and support to discuss symptom and adherence data with patients in a useful way? (Opportunity)
- How feasible do you think it would be to use/discuss patients' symptom and adherence data with them (either in consultations or via online platforms)? (general question)

Closing Questions

Is there anything you feel we have missed?

Is there anything you would like to add?

Thank you for taking part in this study.

Appendix N- Sample of field notes from chapter 7

Today I conducted my first interview, I felt a little nervous as I haven't collected qualitative data for a little while. However the interview went really well and the participant was very interested in symptom tracking. The interview schedule worked well and I felt there was enough questions to address the research questions for this chapter.

Participant was very enthusiastic and passionate, she has worked in CF care for a very long and knew so much about the condition. As she was so knowledgeable at times it was hard to keep on track with the schedule. However this was a very in-depth interview with lots of interesting data captured.

This participant was newer within their role in CF and had less experience of the CFHH in comparison to other HCP's I had interviewed to date. The participant was still able to discuss adherence and symptom tracking and the data is relevant and useful for the study.

My final interview today and I found this interview really enjoyable- the participant showed great interest when I discussed the findings of my PhD and the work I had conducted. I feel as though presenting this data to HCP's has been really worthwhile and completes the story of my thesis nicely.